Nutritional Neurosciences

Wael Mohamed
Firas Kobeissy *Editors*

Nutrition and Psychiatric Disorders

Springer

Nutritional Neurosciences

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This book series aims to publish volumes focusing on both basic and clinical research in the field of nutritional neuroscience with a focus on delineating the effect of nutrition on brain function and behavior. The books will examine the role of different nutrients, food agents and supplements (both macro and micro) on brain health, neurodevelopment, neurochemistry, and behaviour. The books will examine the influence of diet, including phytochemicals, antioxidants, dietary supplements, food additives, and other nutrients on the physiology and metabolism of neurons, neurotransmitters and their receptors, cognition, behavior, and hormonal regulations.

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Nutrition and Psychiatric Disorders

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In deep respect and with true love, I would like to dedicate this book to my best friend, forever and always, MYSELF.

Wael Mohamed
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To my mentor and colleague, the chair of the Department of Biochemistry and Molecular Genetics at the American University of Beirut, Professor Julnar Usta, whose honesty and knowledge touch the heart and mind of everyone working with her, I dedicate this humble work.

Firas Kobeissy
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Foreword

Our understanding of the role of nutrition in mental health continues to expand. This book stands out in describing the intricate relationship between food and the central nervous system by exploring the most recent research about the effects of nutrition on psychiatric disorders. The food we eat impacts our brain and how we feel. Nutritional patterns may improve or worsen our mood and sense of well-being. A healthy diet, particularly a traditional Mediterranean diet, appears to confer some level of protection against depression. Certain nutritional deficiencies or excesses might exacerbate psychiatric symptoms, whereas an adequate diet can help balance the adverse effects of certain medications.

The vagus nerve connects the gut and brain, acting as the main modulator of the gut-brain axis. Along with the human microbiome, the gut-brain axis provides insights into the connection between diet and disease, whether it is an organic or psychiatric illness. From this perspective, **nutritional psychiatry is a novel research area and an emerging opportunity for clinical intervention in the treatment of psychiatric disorders.**

This book brings together the work of experts in the field of psychiatry and highlights what is known about the roles of food and nutrition in mental health. The first volume elaborates on basic concepts and research, discussing the role of nutrition in brain functioning, the nutrition and modulation of cognition and emotions, how specific diets can affect the treatment of neuropsychiatric injuries, the impact of malnutrition on brain development, and how nutrition impacts neurotransmitter functioning, and lastly provides insights on nutritional omics in schizophrenia and Alzheimer's disease. The second volume of this book is clinically oriented, looking at the intersection between nutrition and specific psychiatric disorders, specifically discussing the role of zinc in depression and its treatment, nutrition and depression, nutrition and obsessive-compulsive disorder, caffeine and mental health, chocolate consumption and mental health, food addiction, nutrition and anxiety disorders, nutrition and substance use disorders, and lastly nutrition and schizophrenia. The two volumes cover both basic and translational research on nutrition and mental health.

This unique book presents a solid foundation for scholars and practitioners interested in the intertwining aspects of psychiatric disorders and nutrition. It is my great honor to be part of this work, wherein Dr. Mohamed (Menoufia University and International Islamic University) and Dr. Kobeissy (the American University of Beirut and the University of Florida) have gathered to deliver one of the most updated presentations on nutritional psychiatry. By providing a state-of-the-art summary of the role of food in brain function and mental health, this book seeks to contribute to and impact the clinical management of our patients. This book offers a timely comprehensive review for basic scientists, graduate and medical students, clinical researchers, and medical and mental health professionals with an interest in nutritional psychiatry.

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Preface

"To study the phenomenon of disease without books is to sail an uncharted sea, while to study books without patients is not to go to sea at all"
William Osler (1849–1919)

Recently, the impact of nutrition and food intake has been highly investigated to study its impact on our brain function and its development as it was shown that the diet we take will determine the outcome of certain brain disorders, such as brain injury and stroke. Along with its effects on cardiovascular diseases and cancer development, nutrition and diet have been shown to be involved in preserving our mental cognitive function and behavior. Recent studies have implicated the development or exacerbation of certain neuropsychiatric disorders to imbalance in our nutritional intake and diet, such as the development of obsessive-compulsive disorder (OCD), bipolar disorder, depression, and schizophrenia.

These findings have been driven by the revolutionary application of different "omics" fields and its application to the study of the central nervous system (CNS), which broadened our understanding of fundamental neurobiological processes and has enabled the identification of proteins and pathways related to the complex molecular mechanisms underlying various diseases of the CNS. In fact, the field of proteomics has a subdiscipline of "psychoproteomics" that evaluates the role of protein alterations in neuropsychiatric disorders. In addition, the fields of metabolomics and microbiome assessment have studied the role of the gut serotonin secretion and how its implication by "good" bacteria is contributing to our sleep cycle, moods, and pain. Surveying the literature, we have noticed that there is a huge gap in knowledge that discusses psychiatric health and the role of nutrition in modulating its development. We are not implying that changes to our daily diet may be an alternative substitute for mental health intervention, such as medication or psychoanalysis; however, what we aim from this work is to highlight the role of healthy diet and sound nutrition in alleviating certain psychiatric symptoms. Coming from the background in the areas of neuropsychiatric health research, the editors (Drs. Mohammed and Kobeissy) decided to collaborate with other colleagues with expertise in areas of psychiatric disorders and nutrition to have a comprehensive

book entitled "*Nutrition and Psychiatric Disorders*," which includes 16 chapters divided into two sections.

In the first section, entitled "*Food, Brain Function, and Behavior*," we have six chapters that describe various outcomes and effects of nutrition on brain functions (Heba Mansour) and cognitive and emotional changes (Rasoul Ghasemi) as well as describe the different kinds of diets and their cross talk to disease outcomes (Fatima Dakroub). This section continues to evaluate the effect of malnutrition on brain development (Pranshul Sethi) and how neurotransmitter changes are implicated in diet intake (Sumit Kumar). This section is concluded by discussing the role of omics and its role in assessing changes in schizophrenia and Alzheimer's disease (Sumit Kumar).

The second section of the book focuses on *nutrition-psychiatric disorder cross talk*. We are excited to have a number of chapters that dissect how nutrition imbalance, whether vitamins, caffeine, and carbs, would modulate several known neuropsychiatric disorders. In the first chapter, we discuss the zinc relation to depression levels (Samer El Hayek). In the next chapter, nutrition and depression (Ramdas Ransing) are evaluated in terms of mechanisms and interaction; this is followed by an elegant chapter by Dr. Samer El Hayek et al., where they elaborate on nutritional deficiency and its relation to obsessive-compulsive disorder. Other areas of discussion are introduced involving food addiction and craving, where Dr. Ahmed Radwan discusses the role of caffeine, mental well-being, and psychiatric disorders. Interestingly, the following chapter discusses the biopsychology of chocolate craving (Laura Orsolini) followed by another overview chapter discussing food addiction (Samer El Hayek). This section is concluded with three chapters discussing nutrition in relation to anxiety disorders (Ramli Musa), substance use disorders (Zehra Batool), and finally nutrition and schizophrenia (Heba Mansour).

Overall, this new book provides updated and novel concepts in the field of psychiatry and its relation to the food intake. The new compilation will be of high interest among researchers and clinical scientists involved in psychiatry, nutrition, and biochemistry.

Finally, we thank all the authors for their significant effort in writing such excellent chapters for this new edition. We are also sincerely grateful to each author for their patience during the compilation and final editing of this book.

Pahang, Malaysia — Wael Mohamed
Beirut, Lebanon — Firas Kobeissy

Acknowledgments

First, we would like to send a great appreciation for all the authors who contributed to this timely project. The high level of devotion and dedication between the authors and editors made writing this book an enjoyable journey. In addition, we also extend our gratefulness to the authors who are in the fields of medical psychiatry and neuropsychiatric research for delivering years of their experience and work in different areas of psychiatric disorders to deliver such an elegant piece of work. The herein discussed topics and applications are of a great value in the areas of nutrition, psychiatry, neurological disorders, and neurodegeneration. Finally, we would like to thank the encouragement of many of our friends and colleagues for their unconditional love, encouragement, and inspiration throughout the endeavor of the project. Thank you.

Wael Mohamed
Firas Kobeissy

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About the Editors

Wael Mohamed is a psychiatrist neuroscientist. He earned his medical degree from Menoufia Medical School, Egypt, and his research doctorate degree from the Penn State University, USA. Currently, he is an Assistant Professor at the IIUM, Malaysia. He has published widely in the field of Parkinson's as well as Alzheimer's dementia, with about 120 peer-reviewed journal papers with >800 citations, h-index 32. He has authored for Springer, Cambridge, and Elsevier. He is the founder and president of AfrAbia Society (AAS). He has delivered and/or participated in >200 international level lectures and expert panels. He has received many research grants from national and international organizations, namely IBRO, ISN, MJF, STDF, FRGS, and INDO-ASEAN, with a total research funding of one million US$. He is now an active partner in GP2 consortium (IPDG-Asia).

Firas Kobeissy is an Associate Professor at the American University of Beirut (AUB) in the Department of Biochemistry and Molecular Genetics. Dr. Kobeissy obtained his Ph.D. from the University of Florida in the area of neuroscience with a focus on brain injury biomarkers. He is a trained neuroscientist with extensive expertise in neurotrauma and drug abuse research utilizing neuroproteomics approaches. His research interest is focused on applications of proteomics related to brain injury models, including closed-head injuries and blast injuries. Dr. Kobeissy has authored more than 240 articles, reviews, and book chapters along with two patents. He is the Associate Director of the Center of Neuroproteomics and Biomarker Research (NNBR) at the McKnight Brain Institute at the University of Florida, Department of Emergency Medicine. He is the current President of the International Brain Research Organization (IBRO)-MENA Chapter (2020–2023).

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Part I
Food, Brain Functions, and Behavior

Chapter 1
Nutrition and Brain Functions in Health and Disease

Heba M. Mansour

Contents

Abstract Adequate food consumption of dietary nutrients is vital for normal brain functions. There is considerable proof that dietary nutrition helps in the cure and prevention of many psychiatric and neurological disorders. This chapter aims to highlight the effects of macronutrients, including fatty acids and amino acids, and micronutrients, including vitamins and minerals, on different brain functions such as neuronal functions, synaptic plasticity, memory, neuroinflammation, and neuronal signaling network. Furthermore, this chapter discusses the underpinning neuroprotective mechanisms of dietary nutrients, including antioxidant and anti-inflammatory effects, modulation of hypothalamic-pituitary-adrenal (HPA) axis, regulation of neurotransmitter synthesis, and neurotrophic functions. The highlighted relationships of dietary nutrients on brain functions in health and psychiatric diseases have revealed some of the critical mechanisms underpinning diet's effect on brain health and will aid to control how best to utilize dietary nutrients to boost neuronal resistance to injuries and promote mental health.

Keywords Nutrition · Brain functions · Amino acids · Minerals · Vitamins · Fatty acids · PUFA

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Abbreviations

BPD	Bipolar depression
CNS	Central nervous system
DHA	Docosahexaenoic acid
FAs	Fatty acids
GABA	Gamma-aminobutyric acid
HPA axis	Hypothalamic-pituitary-adrenal axis
IL	Interleukin
MCFAs	Medium-chain fatty acids
MDD	Major depressive disorder
NGFs	Nerve growth factors
NMDA	N-methyl-D-aspartate
PUFAs	Polyunsaturated fatty acids
SCFAs	Short-chain fatty acids
SCZ	Schizophrenia
TNF-α	Tumor necrosis factor-alpha

1.1 Introduction

There is growing evidence from the discipline of nutritional psychiatry that nutrition is important for psychological health across the lifetime. Nutrition has lately emerged as a pivotal element in modifying brain functions and plasticity, since there is a nexus between poor nutrition during childhood and a higher risk of developing psychiatric disorders later in life (Schwarzenberg and Georgieff 2018). For instance, prenatal and postnatal deficiency of folic acid has detrimental neurodevelopmental effects and increases the risk of developing psychiatric disorders during later life (Enderami et al. 2018). Proteins and amino acids obtained from food can affect sleep quality and duration by influencing the production of neurotransmitters and neuromodulators (Glenn et al. 2019). For instance, tryptophan is vital for sleep because it is a precursor of melatonin and serotonin (Friedman 2018). Glycine may enhance sleep quality by modulating glutamate and glycine receptors (Bannai and Kawai 2012). L-ornithine may relieve stress by inhibiting the hypothalamic-pituitary-adrenal (HPA) axis and lowering corticosterone concentration (Kurata et al. 2012).

Fatty acids (FAs), including eicosapentaenoic acid and docosahexaenoic acid (DHA), exert vital functions on brain cells. DHA is an important structural component of the cellular membrane's stability, fluidity, and functions. Eicosapentaenoic acid exerts anti-inflammatory effects due to the suppression of leukotrienes, prostaglandins, and thromboxanes. Furthermore, it is thought to positively affect both metabolic and immunological functions. On the contrary, omega-6 polyunsaturated fatty acid is the major source of arachidonic acid and has been known as a pro-inflammatory marker. Omega-3 polyunsaturated fatty acids have been shown to influence the neuroendocrine signaling of dopaminergic and serotoninergic

neurons, regulate protein kinases, enhance signal transduction, suppress P-glycoprotein, regulate many enzymes, increase glutamatergic receptors, and modulate the HPA axis (Godos et al. 2020). Omega-3 FAs are essential for the integrity of cell membranes; to regulate multiple pathways in the CNS, such as neurogenesis, gene expression, neuronal survival, and neurotransmission; and to exert anti-inflammatory and antioxidant effects. Omega-3 FAs are effective in ADHD, MDD, and bipolar depression (BPD) (Mischoulon and Freeman 2013). Moreover, monounsaturated FAs have been proven to affect brain functions and sleep rhythm, presumably through influencing glucose metabolism (Sartorius et al. 2012). Consumption of fibers from fruits, vegetables, legumes, and grains may exert anti-inflammatory effects via the production of SCFAs by gut microorganisms (Ceppa et al. 2019).

Vitamin B complex is a micronutrient that enhances cognitive and memory functions by reducing homocysteine levels (Smith and Refsum 2016). In addition, vitamin B3 may be an adjunctive therapy in the treatment of schizophrenia (SCZ) (Hoffer and Prousky 2008). Vitamin D may be protective against psychiatric disorders. Vitamin E protects neuronal cells from oxidative damage (Cui et al. 2007; Manosso et al. 2020). Among micronutrients, minerals such as manganese, copper, and zinc contribute to enzymatic pathways protecting cells from oxidative damage. Iron has various functions in respiration, energy supply, myelin synthesis, as well as neurotransmitter production, and potassium, calcium, and magnesium control sleep through the modulation of ion channel functions (Zeng et al. 2014).

Disrupted levels of amino acids and minerals have been reported in many psychiatric disorders. For instance, tryptophan, tyrosine, methionine, and phenylalanine were lower in patients with MDD relative to control (Islam et al. 2020). Reduction in the levels of zinc, magnesium, and copper was found in patients with ADHD relative to control (Skalny et al. 2020). Lower levels of zinc, iron, calcium, sodium, selenium, and potassium were detected in the patient with BPD compared with control (Chowdhury et al. 2017).

According to reports, increased consumption of fresh fruits and vegetables has improved mental health. Flavonoids present in vegetables, fruits, and tea have antioxidant and anti-inflammatory properties. Vegetables and fruits are rich in selenium, zinc, iron, magnesium, as well as vitamins, including lime, orange, lemon, tangerine, grape, guava, mango, banana, pineapple, avocado, apple, dates, tomatoes, cucumbers, ginger beets, onion, and garlic (Offor et al. 2021). The aforementioned micronutrients may reduce the suitability of psychiatric disorders like depression through the increase of serotonin, modulation of the HPA axis, alterations in the glutamatergic pathways, suppression of inflammation, and oxidative stress (Wang et al. 2018). Several nutrients affect psychiatric diseases in different ways. Flavonoids, omega-3 FAs, vitamins, probiotics, and green tea may affect psychiatric disorders through numerous mechanisms such as modulation of hippocampal neurogenesis, production of monoamine neurotransmitters, regulation of the HPA axis, alterations of gut microbiota, and exertion of antioxidant and anti-inflammatory protective effects, increasing the levels of brain-derived neurotrophic factor (Offor et al. 2021). The major dietary origins of some macro- and micronutrients are summarized in Fig. 1.1.

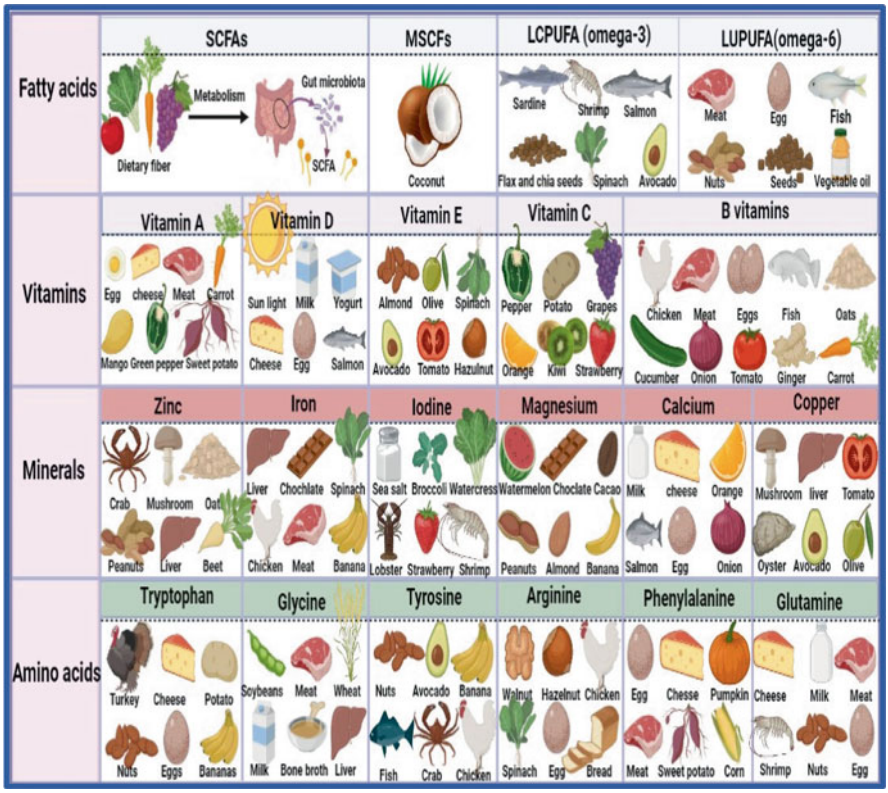

Fig. 1.1 Main food sources of macro- and micronutrients

This chapter discusses the effects of macronutrients, including amino acids and fatty acids, and micronutrients, including vitamins and minerals, on brain functions such as synaptic plasticity, neuroinflammation, neuronal network signaling, and others. Further, this chapter sheds light on the underpinning neuroprotective mechanisms of different dietary nutrients such as modulation of neurotransmitter level, antioxidant and anti-inflammatory properties, neurotrophic mechanisms, alteration of HPA axis, as well as modulation of the composition of gut microbiota.

1.2 Macronutrients and Brain Functions

Balanced nutrition is required for normal brain functions. Balanced nutrition includes macronutrients such as amino acids and fatty acids. The World Health Organization recommends a protein diet of 10–15% and a fat consumption of 15–30%. Insufficient macronutrient consumption jeopardizes the normal brain functioning (Muth and Park 2021). There is significant proof that appropriate consumption of dietary amino acids such as tryptophan, methionine, and serine is essential for

brain function (Maugard et al. 2021). For instance, consumption of tryptophan-free drink in Alzheimer's patients worsens their cognitive symptoms as compared to control group (Porter et al. 2000). The effects of fatty acids (FAs) on brain functions are heavily influenced by fat type and consumption. FAs are key physical regulators in the CNS for preserving energy homeostasis. Diets high in polyunsaturated fatty acids (PUFAs) were correlated with better discriminating abilities than most of those high in saturated fat (Dye et al. 2000).

1.2.1 Amino Acids and Brain Functions

All nutrients are necessary for brain development and functions, but macronutrients that promote energy, such as proteins, carbohydrates, and fats, are particularly critical. Proteins play substantial structural, functional, and biological roles. Proteins (amino acids) are the constructing elements of the body. Our bodies produce 12 amino acids, whereas the other 8 amino acids must be taken from our diet. The major sources of protein are plants such as nuts, legumes, and grains, followed by proteins derived from animal origins like dairy products, meat, and eggs, and small amounts of proteins may be obtained from bacteria, fungi, and algae (Lonnie et al. 2018). In the brain, many neuronal signaling networks are related to many mental states and moods, such as sleep, arousal, awakeness, depression, pain, and perception. Neurotransmitters such as acetylcholine, serotonin, glutamate, norepinephrine, dopamine, c-aminobutyric acid (GABA), glycine, and others direct these neuronal signaling. Disturbance of neurotransmitter balance is a key therapeutic target in psychiatric diseases (Süudhof 2008). Numerous amino acids, such as glutamine, γ-aminobutyric acid, and glutamate, are the precursors of the proteins that are crucial for brain functions (Zamenhof 2010). For instance, tryptophan is critical for the formation of neurobehavioral regulators of food consumption, appetite, and sleep-wake rhythms (Heine 1999). In addition, tryptophan is the source of serotonin and dopamine. Tryptophan supplements increase the level of serotonin (Young 2007). Some amines, such as tyramine and histamine, present in fermented food are neurotransmitters (Ladero et al. 2010). Melatonin is important in many brain functions, such as sleep. Melatonin and its source, tryptophan, are present in milk, egg, meat, fish, vegetables, fruits, and cereals. Hence, nutrition may affect the level of melatonin in the brain (Peuhkuri et al. 2012).

Glycine receptors are present throughout the CNS. They regulate pain, perception, synaptic transmission, and motor control (McDearmid et al. 2006). Glycine is found in various CNS regions, including pyramidal neurons in the cerebral cortex, spinal cord, hippocampus, and limbic system. Based on its region, glycine can serve as an excitatory or inhibitory neurotransmitter. It is the main inhibitory neurotransmitter in the brain stem, spinal cord, sensorimotor, and locomotor brain areas. Moreover, glycine works as a co-agonist of NMDA receptors and modulates dopamine release (de Bartolomeis et al. 2020). L-Arginine is a source of nitric oxide. It regulates levels of glutamate, GABA, and dopamine in prefrontal cortex region (Bernstein et al. 2005). L-Histidine is the precursor of histamine, which is a

neurotransmitter in the brain. The total number of histaminergic neurons in the CNS is believed to be around 60,000 (Haas et al. 2008). Because of its prevalence, neuronal histamine plays a variety of physiologic roles, including the sleep-wake cycle, anxiety, stress response, sedation, monoamine neurotransmitter synthesis, social memory, and hunger control (Panula and Nuutinen 2013). Consequently, sufficient release of histamine is vital for brain functions (Yoshikawa et al. 2014). Lysine is another AA. It is vital for brain functions. It has the potential to influence cell proliferation and differentiation through regulatory mechanisms (Severyanova et al. 2019). Furthermore, it is incorporated in some neurotransmitter synthesis such as glutamate, adrenaline, noradrenaline, and serotonin (Galili et al. 2001). Valine deficiency results in motor incoordination due to damage of midbrain structures that regulate motor activity in rats (Hutchison et al. 1983).

Leucine, isoleucine, and valine are branched-chain amino acids. Since the brain metabolizes branched-chain amino acids to CO_2, they are regarded as fuel in the CNS. In addition, branched-chain amino acids have a favorable effect on cognitive function retrieval after traumatic brain injury (Sharma et al. 2018). Leucine-rich proteins are present abundantly in the hippocampus, cerebral cortex, paleocortex, and brain stem nuclei, where it regulates behavior, emotions, and learning (Severyanova et al. 2019). The leucine is converted into β-hydroxybutyrate and acetoacetate. Consequently, leucine can be regarded as the origin of ketone bodies that can serve as an alternative for glucose as a fuel source (Morris 2005). L-Leucine regulates some neurotransmitters such as glutamate (García-Espinosa et al. 2007). Leucine regulates the hypothalamic mammalian target of rapamycin (mTOR), which controls food intake (Smith et al. 1987). Intracerebroventricular injection of leucine to animals decreases food intake (Laeger et al. 2014). Valine metabolism is vital in glutamate translocation between neurons and astrocytes during glutamatergic signaling (Murín et al. 2009).

Methionine has a significant impact on the synthesis of S-adenosylmethionine, generating some neurotransmitters in the brain (Maurizi 1990). It is also vital for glutathione production. Thus, reduction in methionine causes oxidative stress (Dash et al. 2016). Tyrosine and phenylalanine are precursors of serotonin, dopamine, epinephrine, and norepinephrine (Lakhan and Vieira 2008). Tyrosine supplements increase cognitive performance (Jongkees et al. 2015). β-Alanine is a natural neuromodulator AA present in the CNS (Tiedje et al. 2010). L-Arginine is important in synaptic plasticity, neurotransmitter formation, learning and memory, and neuroprotection (Fleszar et al. 2019). The brain is dependent on de novo synthesis of asparagine, which is a precursor of L-aspartate (Jaeken et al. 2016). D-Aspartic acid is an endogenous neurotransmitter. Furthermore, it is involved in the adult neurogenesis and synthesis of dopamine and gamma-aminobutyric acid (GABA) (D'Aniello et al. 2011). Glutamine is found extensively in the brain. It is a precursor of aspartate, glutamate, and GABA (Albrecht et al. 2010). L-Proline is produced from ornithine or glutamate (Wyse and Netto 2011). L-Serine is formed in the astrocytes. It is important for neurotransmission. L-Serine is the origin of glycine and D-serine that regulate the excitatory glutamatergic transmission (Maugard et al. 2021). Collectively, amino acids are crucial for brain functions. Nonetheless, the role of some amino acids such as β-alanine, methionine, phenylalanine, cysteine, and isoleucine in different brain functions still requires greater clarification.

1.2.2 Fatty Acids and Brain Functions

Lipids make up 50% of the brain's mass and play important roles in ion flux control, vesicle formation, formation of microenvironments for the cellular network, and signaling pathways (Frost et al. 2014). FAs are a type of carboxylic acid with hydrocarbon chains. They are classified based on the length of the hydrocarbon side chain into short, medium, and long FAs. They are further categorized depending on the existence of double bonds into saturated FAs and unsaturated FAs. Nutritional sources of FAs, mainly omega-3, include fish oil, mackerel, and salmon. FAs are the main structural constituents of cell membranes and are important for tissue formation. Accordingly, dietary consumption of FAs is vital for brain functions (Middleton et al. 2018). The effects of FAs on brain functions are fundamentally reliant on fat type and amount. FAs maintain energy homeostasis (Lei et al. 2016).

1.2.2.1 Short-Chain Fatty Acids (SCFAs)

Short-chain fatty acids consist of 2–5 hydrocarbon chains. Acetic acid, butyric acid, and propionic acid are derived from the metabolism of indigestible dietary fibers by gut microbiota (Lunn and Buttriss 2007). SCFAs have a pivotal role in maintaining blood-brain barrier integrity, which is closely related to the controlled transport of nutrients from the bloodstream to the brain, exerting important functions in the maintenance of CNS homeostasis. SCFAs are vital in the maturation of microglia (Yang et al. 2020). SCFAs may affect neuronal functions and control the levels of neurotrophic factors and neurotransmitters. Acetate, for example, has been shown to increase the expression of appetite neuropeptide and modulate neurotransmitters' levels like glutamate, GABA, and glutamine in the hypothalamus (Frost et al. 2014). Propionate and butyrate have an impact on cytoplasmic potassium levels, implying that SCFAs play a role in the cell signaling network (Oleskin and Shenderov 2016). Moreover, propionate and butyrate alter the expression level of tryptophan 5-hydroxylase 1, an enzyme essential in serotonin production, and tyrosine hydroxylase, a vital enzyme in the synthesis of dopamine, adrenaline, and noradrenaline, resulting in a change in brain neurochemistry (Silva et al. 2020). Furthermore, SCFAs have been stated to regulate glial cell line-derived neurotrophic factor and nerve growth factors (NGFs), controlling the neuronal growth and differentiation (Barichello et al. 2015). SCFAs also have an impact on various brain processes, including improving sleep and inhibiting the orexigenic neuron activation in the hypothalamus that releases neuropeptide Y (Szentirmai et al. 2019). Furthermore, SCFAs exert anti-inflammatory effects. For instance, sodium butyrate inhibits pro-inflammatory cytokines that are emitted by activated microglia in lipopolysaccharide-mediated depression in mouse models (Yamawaki et al. 2018). Similarly, acetate treatment of primary microglia and astrocytes inhibited pro-inflammatory molecules, including P38 mitogen-activated protein kinase (p38-MAPK), tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), IL-6, and nuclear factor-kappa. Suppression of histone deacetylase, which regulates

the expression of neuroinflammatory mediators, has been attributed to the anti-inflammatory effects of SCFAs (Soliman et al. 2012, 2013). Therefore, SCFAs may offer novel ways to control the dysregulation of brain immunity that underpins neurodevelopmental and psychiatric diseases. Dairy products are rich in glutathione and display antioxidant effects.

1.2.2.2 Medium-Chain Fatty Acids (MCFAs)

Medium-chain fatty acids consist of 6–12 hydrocarbon chains and are present in coconut oil, milk, as well as palm kernel oil (Huang et al. 2021). The neuroprotective effects of MCFAs are credited to their hepatic metabolism, which produces ketone bodies that act as an alternative ATP source to recompense the glucose utilization by the brain (Mett and Müller 2021). MCFAs provide energy by ketogenesis, regulate lipid and glucose metabolism, and exert anti-inflammatory and antioxidant effects (Lei et al. 2016). MCFAs enhance cognitive functions in diabetic patients. Beta-hydroxybutyrate maintains synaptic transmission in the rat hippocampus during hypoglycemic circumstances, while C8 combined with the beta-hydroxybutyrate improves synaptic recovery once glucose levels are restored (Page et al. 2009). MCFA decanoic acid inhibits oxidative stress in neuroblastoma cell lines by suppressing H_2O_2 release, upregulating catalase enzyme, and promoting neuronal health (Mett and Müller 2021). A recent study has found that C8 and C10 are broken down in astrocytes, stimulating mitochondrial respiration and ATP production. Surprisingly, glutamine yielded from C8 and C10 is used for GABA production (Andersen et al. 2021). Because MCFAs are involved in several metabolic pathways, it is crucial to understand how adding MCFAs to a normal diet impacts brain health in the long term.

1.2.2.3 Long-Chain Polyunsaturated Fatty Acids

Long-chain fatty acids consist of 13–22 hydrocarbon chains and are present in the form of omega-3 FAs and omega-6 FAs. DHA is the most studied type of omega-3 (Lei et al. 2016). Long-chain polyunsaturated fatty acids have been demonstrated to contribute to neurogenesis, neuronal wiring, and synaptic plasticity in preclinical and clinical studies (Bordeleau et al. 2021). LC-n3-FA exerted positive effects on gray matter size in temporal, parietal, limbic, and frontal areas, as well as white matter microstructural integrity (Witte et al. 2014). Half of the lipids are PUFAs. The PUFAs are present in certain vegetables, nuts, and seeds. DHA present in PUFAs regulates glutamatergic synapses that are associated with cognitive ability and plasticity, affects gene expression, and enhances neuronal differentiation (Piomelli et al. 2007). Long-chain polyunsaturated fatty acids such as DHA have beneficial effects on cerebral circulation by increasing cerebral acetylcholine, choline, and nitric oxide synthase activity with consequent production of nitric oxide (Haast and Kiliaan 2015).

1.3 Micronutrients and Brain Functions

Because the body is unable to produce micronutrients, they must be obtained from the food in sufficient quantities (Akram et al. 2020). Vitamins are categorized into fat-soluble vitamins, including vitamins K, E, D, and A, and water-soluble vitamins, including vitamins B and C (Zhao et al. 2019). Vitamins are micronutrients essential for brain development and function, especially vitamin C, vitamin B9, vitamin B12, vitamin D, vitamin B6, as well as vitamin E. Deficiency of any of them leads to psychiatric disorders (Benton 2012). Interestingly, malnutrition is the most significant nongenetic factor contributing to mental retardation or irreversible changes in embryonic brain development (Galler and Barrett 2001). Impairments in the brain and behavioral development are also caused by vitamin inadequacies. Interestingly, a cohort study, which studied the nexus between vitamin and mineral consumption and mental health, revealed that a lack of four or more micronutrients could raise the chance of developing depression (Sánchez-Villegas et al. 2018). Minerals cannot be produced in the body and must be obtained through nutrition. Minerals are crucial in production of energy, maintenance of biochemical processes, and proper brain functions (Akram et al. 2020). In conclusion, vitamins and minerals strongly correlate with healthy brain functions through neurotransmitter formation, regulation of neuronal metabolism, controlling of glutamate excitability, production of myelin, and exerting of antioxidant activity. Hence, early detection and restoration of nutritional deficiencies are vital for brain development.

1.3.1 Vitamins

1.3.1.1 Vitamin A

Vitamin A is provided by a variety of fruits and vegetables as well as animal origins such as egg yolks, liver, and milk products (Olson and Mello 2010; Marie et al. 2021). Retinoic acid, a by-product of vitamin A, is needed for regulating multiple gene products and synaptic plasticity in embryonic life. It is also vital for neuronal survival, dopamine signaling, neurogenesis, cognitive function, and memory in postembryonic life (Olson and Mello 2010; Marie et al. 2021). The effect of retinoic acid receptor pathways on hippocampal long-term potentiation and depression, which assess neurogenesis and synaptic plasticity, has been established in an animal model (Luo et al. 2009). Agonists of the retinoic acid receptor promote the expression of acetylcholine transporter and acetylcholine transferase genes to improve cholinergic transmission (Mufson et al. 2008). Research provided the first solid proof that retinoids affect cognitive functions, revealing that retinoic acid receptor knockout mice showed impaired spatial memory as confirmed by the Morris water maze test (Chiang et al. 1998). A previous study showed that long-term consumption of beta-carotene (provitamin A) lowered the risk of cognitive impairment (Yuan

et al. 2020). Vitamin A protects against neuroinflammation by inhibiting cytokines like TNF-α, IL-1, and IL-6 (Das et al. 2019). Furthermore, vitamin A deficiency has been implicated in sleep and memory problems (Tafti and Ghyselinck 2007; Marie et al. 2021).

1.3.1.2 B Vitamins

Neurotropic B vitamins such as vitamins B1, B2, B3, B6, B9, and B12 have critical roles in the healthy CNS as coenzymes and beyond (Calderón-Ospina and Nava-Mesa 2020). Mammals are unable to produce B vitamins, so they must obtain them from their diet in appropriate quantities. Most B vitamins are derived from plants or animal origins like meat, eggs, and dairy. Only vitamin B12 is derived from an animal source. B vitamin deficiency has been associated with various neurodevelopmental disorders (Gómez-Pinilla 2008). Vitamin B1 is essential for the production of serotonin, acetylcholine, and amino acids, as well as brain energy production (Calderón-Ospina and Nava-Mesa 2020; Tardy et al. 2020). Language deficits, which are common in children with autism, could occur as a consequence of infantile vitamin B3 shortage (FATTAL-VALEVSKI et al. 2009). In addition, neuropsychiatric disorders named Korsakoff's psychosis, beriberi, and Wernicke's encephalopathy are among serious CNS complications of thiamine deficiency (E et al. 2012; Bjørklund et al. 2019). Vitamin B3 converts tryptophan to serotonin and melatonin. Vitamin B5 is important in the acetyl-CoA synthesis that is vital for neuronal development. Vitamin B6 is crucial in the synthesis of serotonin, GABA, norepinephrine, and dopamine. Vitamin B9 is engaged in brain functions like sleep, mood, and irritability (Tardy et al. 2020). Vitamin B9 deficiency has been related to an elevated level of neuroinflammation and oxidative stress (Bordeleau et al. 2021). B vitamin supplementation may have neuroprotective effects in many psychiatric disorders, including anxiety, MDD, and autism spectrum disorder (ASD) (Bjørklund et al. 2019; Calderón-Ospina and Nava-Mesa 2020). Vitamin B12 (cobalamin) is a coenzyme in various biochemical processes that are vital for a healthy CNS. Neonatal deficiency in vitamin B12 causes anorexia, irritability, lowered brain growth, and long-lasting cognitive impairment (Gómez-Pinilla 2008). Neurological symptoms of a low level of cobalamin include neuropathy, impaired cognitive function, polyneuritis, and myelopathy (Calderón-Ospina and Nava-Mesa 2020). Collectively, B vitamins are vital in different brain functions. Further research investigating the exact mechanisms of B vitamins in brain functions will offer an opportunity to use B vitamins to promote psychiatric health and prevent psychiatric disorders.

1.3.1.3 Vitamin D

Activated vitamin D (calcitriol) is a neuroactive steroid hormone produced mostly in the skin under UV light, and a little quantity is obtained from the diet (Saraff and

Shaw 2016). Due to the massive prevalence of vitamin D receptors in the CNS and its impact on brain functioning, vitamin D has been named "the neglected neurosteroid." Vitamin D receptors are vastly distributed in the brain's ventricle walls. In the brain, this is the most common location for neurogenesis (Cui et al. 2007). The expression of vitamin D receptors increases in the substantia nigra, nucleus accumbens, and caudate putamen, suggesting that vitamin D may influence the dopaminergic system (Kesby et al. 2011). Vitamin D has been demonstrated to control NGFs and glial-derived neurotrophic factors in the brain, which are essential for cell survival and proliferation in the brain (Dicou 2009). Glial-derived neurotrophic factor controls the development, resistance, and function of dopaminergic neurons (Kholodilov et al. 2004). Vitamin D receptors null mice display behavioral problems such as impaired prepulse inhibition, increased anxiety, and neophobia (Kesby et al. 2011). Also, vitamin D may influence dopamine levels. For instance, postnatal administration of a single dose of vitamin D to rats increased dopamine levels in the brain stem as well as changed dopamine metabolism in the caudate putamen and hypothalamus (Tekes et al. 2009). Also, repetitive intracerebroventricular administration of vitamin D to rats increased levels of both striatal and evoked dopamine.

Prenatal vitamin D deficiency may end with abnormal compromised brain functions, influencing the expression of neurological diseases (Levenson and Figueirôa 2008). In contrast, various evidence lines imply that vitamin D could play beneficial neuroprotective roles in many psychiatric disorders such as ASD, MDD, and SCZ. Administration of vitamin D has been reported to ameliorate neurotoxicity in many animal models through multiple mechanisms such as upregulation of neurotrophic factors, suppression of nerve growth factor depletion, inhibition of calcium-mediated excitotoxicity, sequestration of free radicals, reduction of oxidative stress, curbing of glutamate-induced cell death, and downregulation of inducible nitric synthase and nitric oxide (reviewed in DeLuca et al. 2013). Besides, the direct nexus between vitamin D and absorption of Ca^{2+} plays an important role in synaptic transmission (Gómez-Pinilla 2008). Vitamin D insufficiency has been demonstrated to influence the expression of a wide range of genes, including those associated with neuroplasticity and neurotransmission (Almeras et al. 2007; DeLuca et al. 2013). In conclusion, vitamin D is vital for proper brain function. But the interplay between vitamin D deficiency and dopamine needs further investigation.

1.3.1.4 Vitamin C

The highest level of vitamin C was detected in brain neurons (Tveden-Nyborg and Lykkesfeldt 2009). Vitamin C is a cofactor in the formation of neurotransmitters (Tardy et al. 2020). It catalyzes the conversion of dopamine to norepinephrine. Excess dopamine causes neuronal damage through the production of hydrogen peroxide (Berman et al. 1996). It also protects neurons from oxidative stress due to its redox properties (Venkataraman et al. 2007). Moreover, vitamin C prevents glutamate-mediated excitotoxicity (Miele et al. 1994). Vitamin C inhibited TNF-α

and nuclear factor kappa B (NF-κB) in human neuroblastoma (Son et al. 2004). In addition, studies on vitamin C deficiencies in guinea pigs have shown neuronal damage and oxidative stress (Burk et al. 2006).

1.3.1.5 Vitamin E

Vitamin E (α-tocopherol) is present in wheat germ oil, soybeans, rice bran, olives, and coconut. Vitamin E is vital for many neurological functions. Vitamin E regulates many genes such as genes encoding proteins vital for cell cycle regulation, apoptosis, lipoprotein receptors, neuronal development, and synaptic plasticity (Muller 2010). Vitamin E has anti-inflammatory properties. It inhibits the expression of cyclooxygenase-2 and 5-lipoxygenase (Manosso et al. 2020). In a rodent model, vitamin E suppressed lipopolysaccharide-activated nuclear factor-kappa and cytokines like IL-1β and IL-6 (Godbout et al. 2005).

1.3.2 Minerals and Brain Functions

The equilibrium of minerals is crucial for brain functions. Psychiatric disorders involve a variety of pathologic features that share metabolic dysregulation, oxidative stress, and protein aggregation, all of which are associated with mineral involvement (Wang et al. 2020). It has been established that some minerals affect brain functions. Iron, iodine, and zinc are essential minerals for the synthesis of norepinephrine, serotonin, and synaptic plasticity (Tardy et al. 2020).

1.3.2.1 Zinc

Zinc (Zn^{2+}) present in the CNS is estimated at 1.5% of the Zn^{2+} body content (Sikora and Ouagazzal 2021). Zinc is present in different brain regions such as the dentate gyrus, granular cell axons, CA3 pyramidal cells, neocortex, and hippocampus (Sandstead 2003). It plays a vital role in the regulation of signaling in the CNS (Gómez-Pinilla 2008). Zinc presents in synaptic vesicles of some neurons in the thalamus, cerebral cortex, hippocampus, and olfactory cortex (Kumar et al. 2021). Zinc affects the structure of both voltage-gated potassium channels and calcium channels (Bixby et al. 1999). In addition, zinc affects the production of biogenic amines (Sandstead 2003). The brain concentration of Zn^{2+} is about 150 μM (Wang et al. 2020). Zn^{2+} is involved in long-term potentiation in the hippocampus. It also regulates synaptic transmission and excitability by controlling NMDA, GABA, and glycine receptors. Postnatal zinc deficiency compromised DNA synthesis, impaired brain polysomes, reduced synthesis of proteins, and decreased growth of cerebellar granular cells (Dvergsten et al. 1983). Furthermore, neonatal Zn^{2+} deficiency leads to disrupted learning, memory, attention, and mood (Benton 2012). Iron, zinc,

choline, and copper affect neurotransmitter levels, receptors, and reuptake. Zinc regulates the electrophysiologic potential of neurons through maintaining healthy mitochondria with the subsequent generation of a sufficient amount of ATP (Georgieff et al. 2018). Furthermore, zinc lowers pro-inflammatory molecules like C-reactive protein, IL-6, and TNF-α (Prasad 2009).

1.3.2.2 Magnesium (Mg^{2+})

Magnesium is necessary for nerve conduction and neuromuscular coordination. It also blocks calcium channels of aspartate receptors, protecting the cell from excitotoxicity-mediated death (Tardy et al. 2020). Magnesium deficiency may cause hyperexcitability in the CNS. Magnesium deficiency increases some excitatory neurotransmitters such as catecholamines, acetylcholine, and excitatory amino acids and decreases inhibitory neurotransmitters such as adenosine, glutamine, GABA, and taurine. Furthermore, it enhances the synthesis of neuropeptides, prostanoids, and pro-inflammatory cytokines and decreases antioxidant defenses (Durlach et al. 2000). Magnesium deficiency has been associated with elevated levels of inflammatory and pro-inflammatory markers like TNF-α, vascular cell adhesion molecule-1, IL-1β, fibrinogen, complement, and plasminogen activator inhibitor-1. In addition, dietary intake of magnesium was inversely proportional to C-reactive protein level (Barbagallo et al. 2021). During the auditory stimulation, electroencephalogram alterations were seen in magnesium-deficient rats, suggesting an association between magnesium deficiency and increased excitability (Goto et al. 1993).

1.3.2.3 Iron (Fe^{3+})

Iron (Fe^{3+}) is vital for neurodevelopment. Fe^{3+} concentration in the brain is about 720 μM (Wang et al. 2020). Fe^{3+} contributes to myelination, immune functions, and neurotransmitter production such as dopamine and noradrenaline (Granero et al. 2021). Low intake of iron in infancy has been linked to impairments in motor performance, cognition, social orientation, and expressive language, while iron supplementation results in an improvement (Schmidt et al. 2014).

1.3.2.4 Calcium (Ca^{2+})

Calcium (Ca^{2+}) homeostasis is vital in controlling various neuronal functions such as action potential, neural growth and differentiation, learning and memory, and synaptic plasticity (Wang et al. 2020).

1.3.2.5 Copper (Cu^{2+})

Copper (Cu^{2+}) is important in neuronal function, neuropeptide activation, myelination, and synthesis of neurotransmitters. Cu^{2+} is present in the hippocampus, substantia nigra, and locus coeruleus (Patel and Aschner 2021; Das et al. 2021). The Cu^{2+}concentration in the cerebellum and frontal lobe is about 60–110 μM. Accumulation of Cu^{2+} in the brain due to mutations in the ATP7B gene leads to Wilson's disease, which is characterized by cognitive impairment and AD-like symptoms (Frota et al. 2009). Likewise, Menkes disease is caused by a mutation in ATP7A gene that is important for copper absorption and regulation. Symptoms of Menkes disease include neurological effects (Patel and Aschner 2021).

1.3.2.6 Iodine

Iodine is a mineral that is required for the formation of dendritogenesis, synaptogenesis, neurogenesis, and myelination in the fetus. It is important for brain development. The cerebral cortex can be disturbed by iodine deficiency, resulting in disrupted neuronal migratory patterns (Velasco et al. 2018).

1.3.2.7 Manganese

Manganese is vital for brain functions. It affects synaptic transmission in the glutamatergic neurons. Dietary deficiency of manganese may increase the risk of epilepsy. In addition, an abnormal level of manganese in the basal ganglia is associated with Parkinson's disease. Understanding the exact effects of manganese on brain functions in health and disease may be crucial to clarify the potential neuroprotective effects of manganese in different psychiatric and neurological disorders (Takeda 2003).

1.4 Summary and Conclusion

Mental well-being is a critical component of improving health, boosting productivity, lowering medical costs, and enhancing the quality of life. It is becoming conclusive that there is a nexus between the quality of nutrition consumed and mental health consequences. This book chapter reviews literature investigating the effect of macronutrients, such as amino acids and fatty acids, and micronutrients, including vitamins and minerals, on normal brain functions (Table 1.1). Future research should be conducted on determining the pathways of macronutrients and micronutrients and how they affect genes in the brain. This insight has the potential to enhance brain functions and psychiatric health. Dietary supplementation has the

Table 1.1 Role of macro- and micronutrients in brain functions

Type of nutrient	Functions	Reference
1. Macronutrients		
1.1. Amino acids		
Tryptophan	*Regulation of food consumption and appetite	Heine (1999)
	*Aids in better sleep: source of serotonin and melatonin	Young (2007)
	*Source of dopamine	Peuhkuri et al. (2012)
Glycine	*Participates in the sleep-wake cycle through modulation of glutamate and glycine receptors *It regulates pain, perception, synaptic transmission, and motor functions	McDearmid et al. (2006)
	*It is a co-agonist of NMDA receptors	de Bartolomeis et al. (2020)
L-Histidine	*Source of histamine	Hamino acids et al. (2008)
	Control of: *Anxiety *Sleep-awake cycle *Stress *Sedation *Neurotransmitter synthesis *Appetite *Social memory	Panula and Nuutinen (2013)
L-Arginine	*Source of nitric oxide *It regulates levels of glutamate, GABA, and dopamine	Bernstein et al. (2005)
	*It is important in learning, synaptic plasticity, memory, and neuroprotection	Fleszar et al. (2019)
Lysine	*Vital for cell proliferation and differentiation	Severyanova et al. (2019)
	*It is incorporated in some neurotransmitters' synthesis such as glutamate, adrenaline, noradrenaline, and serotonin	Galili et al. (2001)
Leucine	*Source of energy	Morris (2005)
	*It regulates the mammalian target of rapamycin (mTOR), which controls food intake	Laeger et al. (2014)
	*It regulates glutamate	García-Espinosa et al. (2007)
Valine	*Source of ketone bodies	Morris (2005)
	*Valine metabolism is vital in glutamate translocation between neurons and astrocytes during glutamatergic signaling	Murín et al. (2009)
Methionine	*It is vital for the production of S-adenosylmethionine, generating some neurotransmitters in the brain	Maurizi (1990)
	*Plays a role in antioxidant defense mechanism because it is vital for glutathione production	Dash et al. (2016)

(continued)

Table 1.1 (continued)

Type of nutrient	Functions	Reference
Tyrosine	*It is a source of dopamine, serotonin, norepinephrine, and epinephrine	Lakhan and Vieira (2008)
	*Enhances cognitive functions	Jongkees et al. (2015)
β-Alanine	It is a natural neuromodulator AA	Tiedje et al. (2010)
Glutamine	*It is a precursor of glutamate, aspartate, and GABA	Albrecht et al. (2010)
L-Serine	*It is important for neurotransmission; it is the source of D-serine and glycine that modulate glutamatergic transmission	Maugard et al. (2021)
1.2. Fatty acids		
Short-chain fatty acids (SCFAs)	*Play a role in preserving blood-brain barrier integrity *Maintenance of CNS homeostasis *Vital in the maturation of microglia	Chang et al. (2020)
	*They affect the levels of neurotrophic factors and neurotransmitters *Acetate increases the expression of appetite neuropeptide and the levels of GABA, glutamate, and glutamine in the hypothalamus	Frost et al. (2014)
	*Exert anti-inflammatory effects	Yamawaki et al. (2018)
	*Propionate and butyrate affect intracellular potassium levels and regulate cell signaling network	Oleskin and Shenderov (2016)
	*Propionate and butyrate alter the expression level of tryptophan 5-hydroxylase 1, an enzyme essential in serotonin synthesis, and tyrosine hydroxylase, an enzyme vital in the synthesis of dopamine, adrenaline, and noradrenaline	Silva et al. (2020)
	*Acetate and butyrate inhibit astrocyte activation and microgliosis through inhibition of TNF-α, IL-1β, and IL-6	Yamawaki et al. (2018)
Medium-chain fatty acids (MCFAs)	*They provide energy by ketogenesis, regulate lipid and glucose metabolism, and exert anti-inflammatory and antioxidant effects	Lei et al. (2016)
	*They enhance cognitive functions in diabetic patients	Page et al. (2009)
	*Decanoic acid inhibits oxidative stress in neuroblastoma cell lines by suppressing H_2O_2 release, upregulating catalase enzyme, and promoting neuronal health	Mett and Müller (2021)
	*The glutamine yielded from C8 and C10 breakdown is used for GABA synthesis	Andersen et al. (2021)
Long-chain polyunsaturated fatty acids	*LC-n3-FA exerted positive effects on gray matter size in different brain regions	Witte et al. (2014)

(continued)

Table 1.1 (continued)

Type of nutrient	Functions	Reference
	*DHA modulates glutamatergic synapses that are associated with cognitive ability and plasticity, affects gene expression, and enhances neuronal differentiation	Parrott and Greenwood (2007)
	*DHA has beneficial effects on cerebral circulation by increasing cerebral acetylcholine, choline, and nitric oxide synthase activity with consequent production of nitric oxide	Hamino acids t and Kiliaan (2015)
2. Micronutrients		
2.1. Vitamins		
Vitamin A	*It is vital for neuronal survival, dopamine signaling, neurogenesis, cognitive function, and memory in life	Olson and Mello (2010)
	*Promotes the expression of acetylcholine transporter and acetylcholine transferase genes to improve cholinergic transmission	Luo et al. (2009)
	*Exerts anti-inflammatory effects	Das et al. (2019)
Vitamin B1	*It is pivotal for the formation of serotonin, acetylcholine, and amino acids, as well as brain energy production	Calderón-Ospina and Nava-Mesa (2020).
Vitamin B3	*It converts tryptophan to serotonin and melatonin	Tardy et al. (2020)
Vitamin B5	*It is important in the acetyl-CoA synthesis that is vital for neuronal development	
Vitamin B6	*It is pivotal for the formation of serotonin, GABA, dopamine, and norepinephrine	
Vitamin B9	*It participates in brain functions such as sleep, mood, and irritability	
Vitamin B12	*It is a coenzyme in various biochemical processes that are vital for a healthy CNS	(Gómez-Pinilla 2008)
Vitamin D	*Controls nerve growth factors and glial-derived neurotrophic factors in the brain, which are crucial in neuronal survival in the CNS	Dicou (2009)
	*May have direct effects on dopamine	Tekes et al. (2009)
Vitamin C	*It is a cofactor in the formation of neurotransmitters	Tardy et al. (2020)
	*It catalyzes the conversion of dopamine to norepinephrine	Berman et al. (1996)
	*Prevents excitotoxicity, neuroinflammation, and oxidative stress	Burk et al. (2006)
Vitamin E	*It regulates many genes such as genes encoding proteins vital for cell cycle regulation, apoptosis, lipoprotein receptors, neuronal development, and synaptic plasticity	Muller (2010)
	*Anti-inflammatory and antioxidant properties	Manosso et al. (2020)

(continued)

Table 1.1 (continued)

Type of nutrient	Functions	Reference
2.1. Minerals		
Zinc	*It affects the structure of both voltage-gated potassium channels and calcium channels	Bixby et al. (1999)
	*It regulates synaptic transmission and excitability by controlling NMDA, GABA, and glycine receptors *It regulates the electrophysiologic potential of neurons through maintaining healthy mitochondria with the subsequent generation of a sufficient amount of ATP	Dvergsten et al. (1983) Georgieff et al. (2018)
	*Anti-inflammatory properties	Prasad (2009)
Magnesium	*It is important for nerve conduction and neuro-muscular coordination *It blocks calcium channels of aspartate receptors, protecting the cell from excitotoxicity-mediated death	Tardy et al. (2020)
Iron	*It contributes to myelination, immune functions, and neurotransmitter production such as dopamine and noradrenaline	Granero et al. (2021)
Calcium	*It controls various neuronal functions such as action potential, neural growth and differentiation, learning and memory, and synaptic plasticity	Wang et al. (2020)
Copper	*It is important in neuronal function, neuropeptide activation, myelination, and synthesis of neurotransmitters	Patel and Aschner (2021)
Manganese	*It affects synaptic transmission in the glutamatergic neurons	Takeda (2003)

benefit of being an inexpensive and noninvasive approach. The general population considers dietary supplements as more "natural" and perhaps free of adverse effects, bringing up new prospects for boosting brain functions.

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Chapter 2
Nutrition, Cognitive Functions, and Emotions

Pegah Javadpour, Sahar Askari, and Rasoul Ghasemi

Contents

Abstract The importance of daily consumed foods as affecting factors on cognition and emotion has been recognized more than ever. Due to the growing knowledge that dietary factors have a significant impact on neural functions, people become more enthusiastic about choosing good food in each phase of life. The purpose of this chapter is to give a broad overview of the effects of various kinds of nutrients including macronutrients (carbohydrates, proteins, and fats) and micronutrients (polyphenols, vitamins, and minerals) on children, adults, and the elderly. Moreover, this chapter aims to show how malnutrition impacts cognition and emotion.

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2.1 Nutrition and Cognition: A Two-Way Street

Following decades of research on the links between nutrition and cognition and mood, a number of nutrients that can be provided in food or dietary supplements have been proposed for improving mental function and brain health. They can modulate neuronal plasticity and function. The term nutraceutical refers to this type of product. This refers to any nutritional product with a health and medical benefit, such as preventing and treating several diseases. Nutraceuticals reach the brain via the blood-brain barrier (BBB) or via the choroid plexus, the primary transportation locus of cerebrospinal fluid, by distinct routes such as active transport or facilitated diffusion.

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The term cognition and its definition have been a subject of controversy during the history of psychology (Favela and Martin 2017). In one broad definition, cognition has been defined as:

> "Suite of interrelated conscious (and unconscious) mental activities, including: pre-attentional sensory gating; attention; learning and memory; problem solving, planning, reasoning and judgment; understanding, knowing and representing; creativity, intuition and insight; 'spontaneous' thought; introspection; as well as mental time travel, self-awareness and meta-cognition (thinking and knowledge about cognition)." (Millan et al. 2012)

Various regions in the brain are involved in the regulation of cognitive function; among them, the hippocampus as the critical region responsible for spatial cognition and episodic memory has been extensively studied. Interestingly, the hippocampus is one of the vulnerable regions to diet.

This complex process of cognition is shown to have bidirectional interactions with several other higher brain processes including emotion. Emotion is a state triggered by external or internal stimuli. Also, in another definition, conscious or unconscious assessment of events is related to emotion. Emotions include states of anger, fear, sadness, happiness, and pride (Pessoa 2008). The mood is a low-intensity kind of emotional state, which persists in the absence of initiating stimulus. Evidently, the experience of an emotional state, as well as the perception of an emotionally salient stimulus, intensely changes cognition (Okon-Singer et al.

2015). Emotion can either strengthen or weaken cognitive processes. For example, attention can be strongly affected by emotionally salient cues such as spiders or snakes, or for another example, working memory is disrupted by anxiety. Conversely, anxiety increases vigilance and potentiates cortical responses to safe environmental stimuli that help to detect emotionally salient data (Okon-Singer et al. 2015). Furthermore, the structure and function of the hippocampus are shown to be affected in depressed patients. Also, food-seeking and consumption behaviors based on food-related cues are modulated by the hippocampus.

Numerous studies have shown that cognition and emotion are affected by several internal and external factors. One of the important factors is what we eat generally. Furthermore, emotional and cognitive components of eating can also affect our eating habits. For example, eating in response to a definite emotional cue such as stress may result in weight gain. Also, for example, we can reduce our food intake cautiously due to controlling body weight as an example of the cognitive component of eating (Constant et al. 2020).

There is precious coordination between feeding behavior and cognitive modulating centers in the brain. The effect of food on cognition and emotion starts before eating when the olfactory bulb and visual receptors are stimulated via sensory inputs of foods. In the second stage, ingestion of foods leads to the release of peptides and hormones such as insulin and glucagon-like peptide 1 (GLP1) into circulation, which reach the hippocampus and hypothalamus and cause activation of signal transductions that are involved in learning and memory. Also, chemical messages from adipose tissue, through leptin, activate specific receptors in the hippocampus and hypothalamus and thereby influence learning and memory. Furthermore, the gut parasympathetic innervation (vagus) is a precious link between the brain and digestive system. Activation of the vagus nerve enables the gut to affect emotion. In turn, emotions can also impact the digestive system by stimulating parasympathetic efferents in the vagus nerve. Vagal nerve stimulation is being used as a therapeutic target for treating chronic depression (Gómez-Pinilla 2008).

Given that cognitive abilities emerge from the formation of new neurons and synapses (neurogenesis and synaptogenesis) and that these processes require adequate metabolites, it is quite predictable that nutrition and diet quality play a crucial role in the development of cognitive capabilities, particularly in the early stages of brain development. Furthermore, cognition and emotion are ongoing dynamic processes throughout life, and nutrition can either positively or negatively influence these processes and may even cause diseases.

We will explore the effects of some important food ingredients on cognition and emotion in the following sections.

2.2 Macronutrients

Macronutrients include carbohydrates, proteins, and fats. They supply the body's demand for glucose, amino acids, and fatty acids. In the same way as other dietary compounds, inadequate macronutrient intake is associated with psychological and mental disorders, such as depression, dementia, and cognitive problems (Muth and Park 2021). On the other hand, cognitive function will be improved by manipulation of dietary composition, for example altering the ratio of carbohydrates to protein in a meal.

2.2.1 Carbohydrates

Carbohydrates are sugar molecules, which are the main energy source for brain tissue, and a constant supply of them (particularly glucose) is the prerequisite for normal brain functions including higher brain functions like cognition and mood.

Several studies clearly refute the idea believing that individual cognitive abilities expressed as intelligence and educational scores are predetermined by genetic factors and indicated that early-life nutrition is a determining factor in cognitive performance not only in childhood but also in adolescence. For instance, teenagers who were breastfed for a longer period had better cognitive and academic performance (Horwood and Fergusson 1998; Nyaradi et al. 2015). In this regard, more detailed investigations have shown that consumption of micro- and/or macronutrients is directly involved in the development of cognitive abilities.

As mentioned, carbohydrates (particularly glucose) are the most important macronutrients for brain development and function. While it is estimated that the brain consumes almost one-quarter of glucose in resting conditions, this ratio is even bigger in developing brains, and it is conceivable to assume that any perturbation in glucose homeostasis during early-life stages may negatively affect brain development and cognition development. In alignment with this, there is evidence that sugar and fiber affect cognitive development. For example, excessive sugar consumption during pregnancy or childhood may compromise brain development (Cohen et al. 2018). Additionally, added sugar consumption and dietary fiber intake both result in negative effects on cognitive performance (reported as hippocampal dependent creativity) in children (Hassevoort et al. 2020). Moreover, any neglect in glucose management in diabetic pregnant women may have adverse effects on a child's cognitive development (Knorr et al. 2015).

We heard repeatedly in our life that consuming more sugar (simple carbohydrates) threats our healthy life. Our different aspects of cognition such as working memory, visual-spatial processing, and attention are negatively associated with sugar consumption. Conversely, a higher intake of fiber (complex carbohydrates driven from plants) boosts the resistance of our brain to cognitive impairment and depressive disorders. The effect of carbohydrates on memory performance is

somewhat mediated by glucoregulation mechanism. As we know, memory is a glucose-dependent process. Glucoregulation has a negative correlation with age. Therefore, elderly adults are more sensitive to carbohydrate intake (Muth and Park 2021). In addition to age, another risk factor that mediates the impact of carbohydrates on memory and attention is having the epsilon allele (ε4) on the cholesterol-regulating gene apolipoprotein E (APOE). APOE ε4 genotype is a known risk factor for Alzheimer's disease (AD). Evidently, people with this genotype have much more cognitive decline per year compared to others (van de Rest et al. 2016).

2.2.2 Dietary Fatty Acids

There are four categories of dietary fats: saturated, trans, monounsaturated, and polyunsaturated fats (respectively, referred to as MUFA and PUFA). Processed foods contain trans unsaturated fats. Olive oil, avocados, vegetable seed oils, and nuts all contain MUFAs and PUFAs. Dairy products, eggs, and meat contain dietary cholesterol, which is an unsaturated alcohol. While the brain is capable of synthesizing SFAs and MUFAs, PUFAs are mainly sourced from the blood. Therefore, our body constantly needs to be supplied with PUFAs from the diet. Two of the most important PUFAs in the brain are omega-3 docosahexaenoic acid (DHA) and omega-6 arachidonic acid (ARA).

Several lines of evidence have shown that long-chain PUFAs have a positive correlation with the development of cognitive abilities, to such an extent that even when pregnant mothers take higher amounts of seafood containing high levels of fatty acids (omega-3 fatty acids), the offspring had higher cognitive performance later in the life (Daniels et al. 2004; Hibbeln et al. 2007; Oken et al. 2008). Furthermore, even consumption of long-chain PUFAs by lactating mothers may also enhance cognitive development in children (Eilander et al. 2007), a finding that may explain why breastfed babies have higher brain development and cognitive scores than formula-fed infants, who receive lower long-chain PUFAs in the formula (Isaacs et al. 2010). It is noteworthy that despite the positive effects of long-chain PUFAs on cognitive development, there is doubt as to whether supplementing infant's milk with these fatty acids could fill the abovementioned gap (Simmer 2001), suggesting that the cognitive difference between breastfed and formula-fed is not entirely due to the abovementioned fatty acids and other micronutrients/factors present in the mother milk may contribute to this difference (Isaacs et al. 2010).

PUFAs with omega-3 and omega-6 essential fatty acids have a beneficial impact on different kinds and stages of the learning and memory process. For instance, faster speed in psychomotor processing and improvement in short-term memory and recall, as well as spatial memory and learning, have been reported after consumption of omega-3 and omega-6 (Horwood and Fergusson 1998). Also, omega-3 PUFAs have antidepressant effects; this valuable property can be explained by its modulatory effect on endocannabinoid metabolism, neuroinflammation, and hypothalamus-pituitary-adrenal axis, all of which are implicated in depressive disorders (Nyaradi

et al. 2015). In this regard, there are promising results about the beneficial impact of fish oil supplementation on cognitive and mood disorders. However, more studies are needed. On the flip side, habitual intake of SFAs and trans fats results in poor cognitive performance. In this regard, worsening of visuospatial learning and verbal memory performance in adults has been detected (Muth and Park 2021). Long-chain SFAs can directly enter the hypothalamus and trigger the neuroinflammatory processes via activation of Toll-Like Receptors (TLRs), which finally leads to cognitive disruption (Spencer et al. 2017).

MUFAs' and cholesterol's effect on the cognitive process is controversial; both improving and deteriorating effects on cognitive function have been reported. Of note, a previous finding that we should consider in our life is having physical activity. Exercise leads to adipose tissue reduction and increases the metabolism of fats. Exercise can fight the destructive effect of SFAs on cognition (Muth and Park 2021). So, having a healthy diet along with physical activity jointly improves mood and cognition. However, as aging progresses, physical activity would be limited, so the importance of a healthy diet is dominant.

2.2.3 Proteins

Proteins are critical constituents of blood, skin, muscle, and bones. Most of our hormones as well as neurotransmitters basically are made from amino acids. During the digestion process in the body, proteins are broken down into their residues, amino acids. Amino acids are used as an energy source for cell growth, regeneration, repair, and survival. About 22 amino acids have been known up to now; among them, 9 amino acids are "essential" or "indispensable" and cannot be synthesized endogenously from the metabolic intermediates in the body. So, they should be supplied from the diet. Moreover, there are limited intracellular deposits of amino acids in the body, and its acquired level should be supplied by daily meals.

Protein demand in the body is generally supplied by two types of sources: either animals or plants. Accordingly, animal-based sources (supplied by products such as dairy and egg) include all the essential amino acids adequately; however, different plant-based sources should be combined appropriately to substitute to a certain extent animal-based amino acids.

Protein malnutrition during pregnancy, like a lack of other essential nutrients, can lead to the development of psychopathologies and cognitive defects in children that are manifested during adolescence and adulthood (Belluscio et al. 2014). Besides avoiding protein malnutrition during the pregnancy period, infant breastfeeding is so important for supplying the needed amount and kind of proteins. It is noteworthy that the composition of macronutrients in human milk is continuously changing to prepare for the need of infants during development and growth. Human milk is rich in not only highly glycosylated proteins but also endogenous peptides which are derived from proteins in the mammary gland. Lactoferrin and proteins of the milk fat globule membrane (MFGM) seem to be so vital for the cognitive development of

infants. In this regard, a randomized controlled trial (RCT) study has shown that breastfed groups such as those who received supplemented MFGM containing 4% protein have higher mean cognitive scores compared to the standard formula based on Bayley Scales of Infant and Toddler Development (Zhu and Dingess 2019). There is also evidence that severe protein malnutrition in the first 2 years results in adverse cognitive development measured by indices such as impaired attention and learning, language, and reasoning skills in late childhood (Mendez and Adair 1999; Berkman et al. 2002; Laus et al. 2011).

In addition, nutrition epidemiologic studies have emphasized the importance of sufficient protein intake for the proper brain function certainly in elderly people. Given that amino acids are critical for proper brain function, protein malnutrition may lead to impairment in normal brain function. Repeatedly, the positive association between higher protein intake and decreased risk of cognitive impairment has been demonstrated in elderly adults. Evidently, adequate protein intake improves episodic and working memory. Despite the fact that protein deficiency is rare in developing countries, however, when switching to a vegetarian diet or training as an athlete, high protein requirements should be met (Modlinska and Pisula 2018).

One of the important roles of amino acids is being the precursor of neurotransmitters in the brain. Tryptophan and tyrosine, two amino acids, are common elements of protein-rich foods. They play a vital role in cognitive function and mood in the brain. As they are precursors for neurotransmitters, their shortage may induce cognitive behavior disorders. Tryptophan, an essential amino acid, passes the BBB and is converted to serotonin (5-hydroxytryptophan (5-HT)). This neurotransmitter is essential for regulating sleep and emotion. Serotonin also serves as a bridge between appetite and mood. So, there is no doubt that poor tryptophan intake influences the brain's serotonin levels. Furthermore, in chronic stress conditions, the release of pro-inflammatory cytokines and glucocorticoids increases the activity of tryptophan-metabolizing enzymes resulting in a decrease in serotonin production in the raphe nuclei and a rise in quinolinic acid production. Quinolinic acid is a potentially neurotoxic metabolite. Therefore, stress and low intake of dietary tryptophan increase the risk of depression, which may manifest itself by signs and symptoms such as anxiety and obsessions (Ekong and Iniodu 2021). Evidence also shows that tryptophan deficiencies lead to impaired consolidation of episodic memory (Mendelsohn et al. 2009).

Similarly, tyrosine, the other important amino acid, is a nonessential amino acid that is obtained from diets or through hydroxylation of phenylalanine by tyrosine hydroxylase. Tyrosine crosses the BBB and serves as a precursor for dopamine and noradrenaline. Tyrosine deficiency results in lower levels of dopamine and noradrenaline. Among its many functions, dopamine is crucial for cognitive functions including working/spatial memory, learning, reward processing, and aging (Harrison et al. 2004). Additionally, acute elevations in plasma concentrations of tyrosine and phenylalanine are related to faster reaction times during complicated attention tasks. Researchers hypothesize that tyrosine and phenylalanine are effective at improving cognitive performance because they inhibit monoamine oxidase, which breaks down dopamine (Jakobsen et al. 2011). Generally, as older people have reduced dopamine

receptors and transporter binding, they are vulnerable to inadequate protein consumption (Spencer et al. 2017). It is noteworthy to consider that excessive protein intake may also be detrimental, particularly among the elderly. In connection with this, elderly people with high tyrosine intake have been reported to have impaired working memory. The decline in performance may be caused by elevated dopamine synthesis capacity in older individuals (Muth and Park 2021).

2.3 Micronutrients

Micronutrients are food elements required in low amounts for the homeostasis of the body. Trace elements, vitamins, and minerals are examples of micronutrients, which are necessary for healthy development, energy metabolism, cellular growth, and disease prevention (Gernand et al. 2016). It has been demonstrated that various micronutrients can affect cognition and mood over the course of a lifetime.

2.3.1 Polyphenols

Polyphenols are a family of bioactive phytochemicals that are rich in plants such as tea, fruits, and berries. Polyphenols are generally categorized into two groups: flavonoids and non-flavonoids. Flavonoids are further subdivided into multiple groups based on their structures: flavones, flavonols, isoflavonoids, neoflavonoids, flavanols (flavan-3-ols or catechins), anthocyanins, and chalcones. Positive association between consumption of these natural substances with cognitive function and mood disorders has been found recently. In the developmental period of life, consumption of flavonoids seems hopeful for cognitive performance. In this regard, it has been demonstrated that consumption of flavonoid-rich wild blueberry drink (equivalent to 240 g or 1½ cups of fresh blueberries), after 2 h, manifests acute cognitive benefits in children (Barfoot et al. 2019). Moreover, in children and young adults, regular intake of flavonoids improves positive mood and decreases the risk of depression (Carrillo et al. 2019; Khalid et al. 2017). Regular intake of substances rich in flavonoids such as citrus fruits, cocoa, tea, and berries can prevent or delay age-related cognitive decline and dementia. They attenuate the formation of amyloid plaques and tau hyperphosphorylation in the brain. Also, they enhance cognitive recovery in ischemic stroke patients (Bellone et al. 2019). Furthermore, the antidepressant potency of flavonoids in the old population has been reported (Singh et al. 2021).

Flavonoids have a great antioxidant potential, as they act as scavengers of reactive oxygen species (ROS), expression inhibitors of pro-oxidative nitric oxide synthase (NOS) and monoamine oxidase B, as well as stimulators for the expression of antioxidant enzymes such as glutathione reductase and glutathione peroxidase. They have anti-apoptotic potency and modulate the expression of genes involved in

cell cycle progression, cellular communication, growth factor signaling, and apoptosis. They can activate α7 nicotinic receptors and their downstream molecules P13K and AKT. In this way, flavonoids not only inhibit the downregulation of the anti-apoptotic molecule, Bcl-2, but also induce the expression of CREB and CREB-regulated genes such as Brain-Derived Neurotrophic Factor (BDNF), which are associated with neurogenesis, long-term memory formation, and Long Term Potentiation (LTP). They can also decrease the activity of β- and γ-secretase. Some of them such as isoflavones are a rich source of phytoestrogens, which can improve cognition because of imitating the estrogen effect in the brain (Singh et al. 2021). Other classes of polyphenols which belong to a non-flavonoid category are stilbenes, tyrosol, curcuminoids, and phenolic acids.

Resveratrol is a polyphenol belonging to stilbenes group. Resveratrol is mainly found in grapes, berries, peanuts, and wines. Numerous beneficial effects have been described for the intake of resveratrol. This compound has been viewed as an anti-inflammatory, antioxidant, anti-apoptotic, and neuroprotective agent. Human clinical trials are limited for this agent; however, there are hopeful results about the effectiveness of resveratrol on cognitive performance. Resveratrol treatment in healthy older adults is associated with increased cerebral blood flow, verbal learning, and decreased risk of AD. Also, it seems that resveratrol is beneficial for memory performance in overweight people as well as AD patients. Additionally, in healthy young adults, regular peanut and peanut butter intake may amplify memory function and decrease anxiety and depression behavior (Parilli-Moser et al. 2021). Furthermore, based on studies, this agent may be applicable for menopausal women due to decreased incidence risk of menopausal related cognitive decline (Davinelli et al. 2017).

The other important potential cognitive nutraceutical belonging to the group of non-flavonoid polyphenols is curcuminoids. This compound is obtained from *Curcuma longa* and found in turmeric. Curcumin is used as a pigment and additive. In animal studies, its beneficial effect on neurogenesis has been reported repeatedly. Its stimulatory effect on BDNF expression and proliferation has been explored in stress-induced rats. Accordingly, it is able to improve hippocampal dependent spatial learning and memory (Poulose et al. 2017). In human trials, results are inconsistent, but there is evidence about the efficacy of curcumin administration on working memory and attention. Curcumin also has antidepressant potency by modulating the release of serotonin and dopamine. Accordingly, anxiety and depressive disorder in obese ones, as well as patients with major depression and diabetic polyneuropathy, can be prevented or even treated by this valuable agent (Asadi et al. 2020).

The flavonoids resveratrol and curcumin both possess powerful antioxidant and anti-inflammatory properties. Furthermore, they can inhibit the activity of β-secretase and prevent the formation of Aβ-oligomers. Moreover, they inhibit Aβ-induced tau hyperphosphorylation, stimulate the expression of BDNF, and interact with NMDA receptors (Poulose et al. 2017; Villaflores et al. 2012; Mallozzi et al. 2018; Hsieh et al. 2021).

Phenolic acids (phenol carboxylic acids) are aromatic acid agents that are found in dietary sources such as certain cereals (for example, grain and brown rice), tea,

olive oil, red wine, and fruits like cherries and plums (Caruso et al. 2022). There is a limited number of evidence about the possible effects of phenolic acids on cognitive outcomes. However, existing researches showed that consumption of phenolic acids (coffee, alcohol, and green tea as the most studied compounds) reduces the risk of cognitive impairment and dementia (Ran et al. 2021). Multiple mechanisms underlie the neuroprotective effects of phenolic acids, which vary among their members. Generally, phenolic acids have antioxidative, anti-inflammation, and anti-apoptotic potency; they also induce the release of neurotrophic factors (Caruso et al. 2022).

2.3.2 Vitamins and Minerals

The other vital nutrients for the proper function of the body are vitamins and minerals. They are found in animal and plant sources as well as food supplements. In the field of cognitive and mood, vitamins including vitamin B group, vitamin E, vitamin C, and vitamin D are explored and mostly discussed.

2.3.3 Vitamin B Family

The B vitamins play a key role in the synthesis of deoxyribonucleic acid (DNA) and monoamine oxidase. They are also essential for membrane maintenance and neuronal function. The B vitamins are found in liver, milk, eggs, beef, salmon, yogurt, legumes, nuts, grains, soy products, and fortified cereal. Vitamin B complex comprises B1, B2, B3, B5, B6, B9, B12, and biotin. Importantly, the vitamin B complex shows a beneficial effect on anxiety and depressive symptoms. So, their deficiency may result in neurocognitive disorders such as AD, dementia, stress and anxiety, and depression (Ekong and Iniodu 2021). Having a healthy nervous system is closely dependent on B vitamins. They balance mood and improve cognitive performance. They act as coenzymes in multiple enzymatic reactions. Therefore, they contribute to the metabolism of proteins, carbohydrates, lipids, minerals, drugs, as well as other vitamins (Mikkelsen and Apostolopoulos 2018).

Vitamin B1 (thiamine) is vital for brain function because it acts as a coenzyme in the metabolism of glucose and energy. Moreover, vitamin B1 contributes to the synapse formation, the growth of axons, and the genesis of myelin. In addition, it contributes to apoptosis by binding to its special binding sites on biological membranes (Tardy et al. 2020). Vitamin B1 also contributes to the synthesis of neurotransmitters such as glutamate and acetylcholine (Tardy et al. 2020). Cerebral beriberi is a degenerative disease caused by vitamin B1 deficiency, which may lead to cognitive impairment and memory disorders. This disease most often occurs in people with heavy alcohol consumption, but it has also been found in people with insufficient dietary intake of vitamin B1 (Tardy et al. 2020). It has been shown that a high dose of vitamin B1 can reverse the symptoms of Parkinson's disease in newly

diagnosed patients. Furthermore, vitamin B1 supplementation may improve cognitive symptoms in elderly ones (Mikkelsen and Apostolopoulos 2018).

Vitamin B2 (riboflavin) is a potent antioxidant that is involved in various reactions as a coenzyme. The antioxidative function of vitamin B2 is mediated by both inhibition of lipid peroxidation and attenuation of reperfusion oxidative injury. Vitamin B2 is vital for the metabolism of cells, production of energies, iron metabolism, and regulation of vitamins B1 and B3. Its deficiency may result in iron deficiency and disruption of the glycolysis pathway (Mikkelsen and Apostolopoulos 2018). Moreover, vitamin B2 is important for the conversion of B6 and B9 to their coenzymes (Huskisson et al. 2007). The cognitive symptoms of B2 deficiency are mostly accompanied by deficiency of other micronutrients such as B3, B6, and iron. Vitamin B2 is also important in the synthesis of neurotransmitters like noradrenaline and serotonin (Huskisson et al. 2007).

Vitamin B3 (niacin) is the precursor of the two coenzymes, nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADPH). So this vitamin is necessary for the catabolism of proteins, carbohydrates, and fats and synthesis of cholesterol and fatty acid as well as DNA repair (Mikkelsen and Apostolopoulos 2018). Also, it protects against oxidative stress and inflammation. Niacin receptors are distributed throughout the brain. Clinical studies showed that its receptor is affected in Parkinson's disease and schizophrenia. A low vitamin B3 level is associated with cognitive symptoms like anxiety, depression, tension, and schizophrenia (Kennedy 2016). Cognitive decline and AD are more common in people with B3 deficiency. B3 is also important in the B2 and B6 conversion into their active forms.

Choline (vitamin B4) is classified in the literature with B vitamins due to its chemical structure, but in fact, it is not a real vitamin. Choline plays multiple roles such as involving in cell signaling as well as membrane function and structure. During pregnancy, intake sufficient amounts of choline is important as choline contributes to fetus's brain development. Choline like folate acts as a methyl donor in DNA methylation, and it is vital for neural tube closure. Moreover, choline has a significant role in hippocampal development by inducing changes in the expression of genes involved in synaptic plasticity, learning, and memory (Irvine et al. 2022). Choline is also a precursor to the neurotransmitter acetylcholine (Mikkelsen and Apostolopoulos 2018). As known, acetylcholine is a neuronal messenger which is important for several functions, including attention, alertness, learning, and memory. Accordingly, a randomized controlled trial study has demonstrated that maternal consumption of choline during the last trimester of pregnancy produces cognitive benefits for infants, which were determined by comparing information-processing speed of infants (Caudill et al. 2018). Furthermore, maternal choline supplementation seems beneficial for improving neural function and cognition of infants with Down syndrome (Strupp et al. 2016). Another important finding about maternal choline administration is its efficacy against the adverse effects of heavy prenatal alcohol exposure on the cognitive performance of infants (Jacobson et al. 2018). Animal studies have reported that maternal choline deficiency would be accompanied by reduced progenitor cell proliferation and neurogenesis as well as

increased apoptosis in the fetal hippocampus (Irvine et al. 2022). Besides meat, egg yolk is the main source of choline and particularly phosphatidylcholine. There is a precious association between a high intake of eggs and better cognitive performance accompanied by a lower risk of dementia (Ylilauri et al. 2019). As known, acetylcholine deficits are present in AD. Based on published studies, CDP-choline, which is a natural supplement, seems safe and positive to help in neural repair in patients with AD (Arenth et al. 2011). Moreover, combined treatment of cholinesterase inhibitors (such as donepezil) plus choline alphoscerate has represented a prolonged beneficial effects on cognition in AD patients (Amenta et al. 2012).

Vitamin B5 (pantothenic acid) is a substrate for the biosynthesis of the ubiquitous coenzyme A (CoA). CoA contributes to oxidative metabolism as well as synthesis of fatty acids, cholesterol, phospholipids, and amino acids. Beyond that, vitamin B5 through CoA is involved in the production of the neurotransmitter acetylcholine and the steroid hormone melatonin (Kennedy 2016). B5 deficiency is rare, but it can account for symptoms such as depression, fatigue, irritability, and insomnia (Mikkelsen and Apostolopoulos 2018).

Vitamin B6 (pyridoxine) contributes to mental function and mood. This vitamin is involved in immune function with interleukin-2 (IL-2) production, hemoglobin formation, and neurotransmitter synthesis such as GABA. This vitamin is essential for the conversion of tryptophan to vitamin B3, so its deficiency may result in the pathological outcomes that we have after vitamin B3 deficiency (Huskisson et al. 2007). Additionally, vitamin B6 is an essential cofactor for homocysteine re-methylation, and its deficiency results in elevated levels of homocysteine in the blood.

Homocysteine is toxic for neurons and also increases the incidence of cerebrovascular disease. Vitamin B6 deficiency also leads to neuropsychiatric disorders like migraine, seizures, and depression. Moreover, hyperhomocysteinemia has been considered a mediating factor for AD development and other kinds of dementia (Malouf and Grimley 2003).

Vitamin B7 (biotin) acts as a cofactor for the carboxylases, which play a critical role in the energy production and storage in the cells. So, biotin is involved in the energetic metabolism of cells, and in this way, its importance for the normal function of the central nervous system (CNS) is not far from expected. Nutritional biotin deficiency is rare; however, it is noteworthy to notice that regular intake of raw eggs may cause biotin deficiency. There is a protein in raw egg called avidin that binds to biotin and makes it unreachable for intestinal absorption (Dasgupta 2019). Generally, biotin deficiency may result in the CNS abnormalities, depressed mood, and irritability (Huskisson et al. 2007). In more detail, it has been reported that biotin deficiency positively correlated with the emergence of depressive symptoms in children (Rubio-López et al. 2016). Moreover, in a study on old Korean people with mild cognitive impairment, a lower intake of biotin has been reported (Kim et al. 2018). There is limited evidence of the implication of this vitamin on cognition and mood, and further studies are needed.

The important point about this vitamin is that a high dose of biotin shows hopeful results in the treatment of progressive multiple sclerosis as well as the prevention and

management of AD. It has been reported that the protective effects of biotin are mediated by the regulation of cyclic guanosine monophosphate (cGMP) in the brain (McCarty and DiNicolantonio 2017).

vitamin B9 (folate or folic acid) contributes to the synthesis of monoamine neurotransmitters (such as serotonin) and catecholamines. Like B6 and B12, vitamin B9 is involved in homocysteine metabolism. In this process, it acts as a methyl donor (Singh et al. 2021). Thus, vitamin B9 deficiency, like other vitamin deficiencies, such as those in B6 and B12, can contribute to cognitive decline as a result of the accumulation of homocysteine (Singh et al. 2021). In this regard, the efficacy of vitamins B6, B9, and B12 in improving cognitive performance in patients with AD and dementia has been reported (Zhang et al. 2017). It has been reported that 3-year B9 supplementation in healthy aged adults resulted in increased global cognitive function, memory storage, and information-processing speed (Durga et al. 2007). B9 supplementation in the later teenage years and early 20s cannot significantly decline the incidence of mood disorders; however, it may delay the onset time of mood disorder in this population (Sharpley et al. 2014).

Vitamin B12 (cobalamin) is a general term for a group of compounds called corrinoids that are the biologically active form of vitamin B12. This vitamin is needed for the methylation of homocysteine to methionine. Also, as a cofactor, it plays a role in the synthesis as well as the function of neurotransmitters. Vitamin B6, B9, and B12 supplementation in patients with AD or other forms of dementia is helpful for improving cognitive performance (Zhang et al. 2017). Aside from AD, B6, folate, and B12 have been demonstrated to improve the cognitive performance of healthy women, although it is not clear whether they impact mood (Bryan et al. 2002).

Vitamin B12 and B9 are two essential micronutrients in erythrocyte production, which play pivotal roles in cognitive development, either directly or indirectly. Given that the process of neurogenesis requires enough blood supply in order to occur, and that vitamin B12 and folate deficiency leads to anemia, it is clear that enough vitamin B12 and folate indirectly facilitate neurogenesis. Furthermore, these micronutrients also participate in different aspects of brain development such as neurogenesis in a direct manner (Bryan et al. 2002). Vitamin B12, found in animal-source foods, plays critical roles in multiple aspects of cellular processes, which promote neurogenesis and cognitive development, particularly during crucial stages of infants' growth. For instance, vitamin B12 contributes to DNA synthesis, methylation reactions, and maintenance of genomic stability and regulates gene expression (Rush et al. 2014). At the cellular level, vitamin B12 participates in synaptogenesis, myelination, and neurotransmitter synthesis (e.g., serotonin, dopamine, norepinephrine, acetylcholine), processes that contribute to cognitive development at the brain level (Black 2008). Many studies in different populations have found a positive correlation between maternal and childhood vitamin B12 levels and better cognitive functions of children later in their life (Venkatramanan et al. 2016). In addition, studies have linked maternal intake of vitamin B12 during pregnancy with slightly higher offspring IQs, despite some controversy (Bonilla et al. 2012). Studies have also examined the possible association between cognitive functions and

level of blood vitamin B12 in children, and most of them showed a positive link between them (reviewed in (Venkatramanan et al. 2016)). On the other hand, observations in children receiving an inadequate supply of vitamin B12 during fetal and early childhood showed long-lasting negative effects on cognitive development, confirming the positive role of vitamin B12 in cognitive function. Additionally, studies in children supplemented with dietary vitamin B12 also showed boosting effects of vitamin B12 on cognitive function (reviewed in (Venkatramanan et al. 2016)).

2.3.4 Antioxidant Vitamins (Vitamins E and C)

Vitamins E and C (L-ascorbic acid) are potent natural antioxidants in the CNS. In CNS, vitamin E protects against lipid peroxidation via scavenging free radicals in the cell membrane (Lewis et al. 2021). A higher intake of vitamin E in children is associated with better cognitive development (Zyśk et al. 2020). Since vitamin E promotes neural survival and correlates positively with cognitive function, its deficiency has been reported among patients with mild cognitive impairment and AD (Joshi and Pratico 2012). However, the efficacy of vitamin E supplementation on cognitive function has not been confirmed, and the results are contradictory (Joshi and Pratico 2012).

The antioxidant potency of vitamin E is lost after neutralizing a free radical. Vitamin C can regenerate the antioxidant capacity of vitamin E inside oxidative-reductive reaction chains (Sies et al. 1992). Moreover, vitamin C is an essential redox homeostatic factor in the CNS. Inadequate intake of vitamin C may negatively impact cognitive performance (Hansen et al. 2014). Maternal as well as early-life vitamin C deficiency have been accompanied by perinatal mortality, cerebral hemorrhage, decreased hippocampal volume, and impaired spatial memory in animal models (Hansen et al. 2014). Moreover, a controlled trial study in adults showed that vitamin C supplementation in people with inadequate vitamin C status can increase attention, work motivation, and cognitive performance (Sim et al. 2022). There is some evidence to suggest that vitamin C can act as an antidepressant and improve mood (Moritz et al. 2020). There is evidence that maternal and cord blood vitamin E and C status may influence children's behavior and cognitive development (Chen et al. 2009).

2.3.5 Vitamin D

Vitamin D is a steroid hormone that has taken more attention in recent years. Among five isoforms of vitamin D, vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) are the two most used isoforms in supplements. The active form of vitamin D is called 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Dietary intake of vitamin D is critical for

maintaining the normal amount of vitamin D, particularly for people with low direct sun exposure. Vitamin D receptors are distributed in several brain regions, for instance, hippocampus, hypothalamus, substantia nigra, and prefrontal cortex. These regions are involved in cognition as well as emotional processing. Of note, this vitamin is vital for embryonic neuronal differentiation and other developmental processes, which are involved in neurocognition. Second-trimester maternal consumption of D supplementation accompanies higher IQ in 4–6-year-old children (Melough et al. 2021). However, some studies believe that there is no association between maternal vitamin D and its effect on offspring (Veena et al. 2017). Studies have clarified that in a range of neurological disorders such as neurodegenerative, neuroinflammatory, and neuropsychological diseases, the level of this vitamin is low. Moreover, the level of vitamin D receptors is changed in the mentioned disease; for example, depressed patients have a lower number of receptors compared to normal ones (Boulkrane et al. 2020). So, it sheds a light that vitamin D may play a role in the pathogenesis of these diseases. Several mechanisms are involved in the effect of vitamin D on neurocognition. Vitamin D contributes to the synthesis of several neurotransmitters such as acetylcholine, noradrenaline, serotonin, and dopamine. Moreover, it modulates the activity of GABA-A receptors through its steroidal structure. The other beneficial effect on mental function is due to its potency in the enhancement of neurotrophic factors. Importantly, it acts as an antioxidant and anti-inflammatory agent in the CNS. A stimulatory effect on the gene expression of c-glutamyl transpeptidase has been demonstrated. C-glutamyl transpeptidase modulates the generation of glutathione as the key antioxidant in the brain. Also, vitamin D via its effect on vascularity can indirectly impact neurocognition (Humble 2010; Bivona et al. 2019).

2.3.6 Minerals

Minerals are chemical compounds that are essential to body development and health. These vital elements such as iron, zinc, magnesium, sodium, selenium, iodine, copper, and calcium contribute to neuronal functions leading to effects on cognitive and psychological processes (Tardy et al. 2020).

Iron and zinc are involved in neuronal development (differentiation, proliferation, formation, and migration of neurons). Also, these minerals with magnesium have important roles in neurotransmission. Thus, many vital neuronal performances can be affected by the inappropriate intake of them. For instance, cognition is disrupted by low dietary intake of iron and magnesium. Noteworthy, iron, zinc, and magnesium overload can be considered threats to mental health, leading to dementia. Furthermore, insufficient dietary magnesium and zinc intake impact mood. As for zinc deficiency, low and high magnesium serums are linked to a higher risk of depression (Tardy et al. 2020; Wang et al. 2018).

Although sodium is one of the crucial minerals the body requires to survive, excessive sodium intake gets it in trouble. The role of sodium in hypertension and

cardiovascular diseases is clear. The importance of sodium intake in mental health has also been studied in numerous papers. Recent findings from a systematic review point to the association between impaired cognition and excessive salt consumption in middle-aged and aged individuals though the authors also represent that this association needs more clinical trials (Mohan et al. 2020).

Another element that is crucial for a wide range of physiological functions is selenium. Selenium has anti-inflammatory and antioxidant effects and contributes to thyroid hormone production through selenoproteins (Rayman 2012). Moreover, in the brain and nervous system, selenium is known as a neuromodulator factor (Gao et al. 2012; Mokhber et al. 2011). With these functions, several studies depicted that inadequate selenium intake correlates with depression signs. Dialysis, age, and alcohol are imperative confounders of this association, which in turn leads to selenium deficiency (Wang et al. 2018). Low plasma selenium also contributes to cognitive impairment. It increases the risk of cognitive decline in elderly people (reviewed in (Rayman 2008)).

Iodine is a trace element. The importance of this element is in thyroid hormone production. We know that thyroid hormones are essential during fetal and early postnatal life, resulting in brain development. Thus, iodine deficiency can precede cognitive impairment, permanent brain disorders, and mental retardation (Wang et al. 2018). In adults, hypothyroidisms made by severe iodine deficiency can associate with mood alteration (Livingston 2019; Mlyniec et al. 2015).

In the brain, copper (Cu) is known as an essential compound contributing to cortical and hippocampal neuronal transmission (Katarzyna et al. 2015; Zheng et al. 2010), and it is necessary for a normal LTP response (Opazo et al. 2014). Based on these studies and other investigations, dyshomeostasis of Cu levels in the brain can be significantly related to cognitive deficits (Mao et al. 2012; Rembach et al. 2013). Recently, the association between Cu serum concentration and cognition, depression, and anxiety was assessed in older adults. Although findings indicated that a higher level of Cu is linked to lower depressive signs, there is no relationship between cognitive function and Cu in greater serum levels (Mravunac et al. 2019). Consistently, more results indicated that Cu serum level in depressed patients is increased (Narang et al. 1991; Zieba et al. 2000) and treatment with antidepressant drugs diminishes Cu serum concentration (Maes 1995).

Calcium is a crucial molecule in learning and memory mechanisms, and it can affect cognitive function and mood. Noteworthy, despite the importance of calcium in memory, there is no association between calcium serum levels and cognitive performance in childhood and adolescents (Tolppanen et al. 2011), but it was suggested that supraphysiologic serum level of calcium promotes cognitive reduction in older adults (Schram et al. 2007). Moreover, recent studies revealed that low calcium intake is related to anxiety and depression in young people (Alkhatatbeh et al. 2021).

2.4 Bad Nutrition as an Underpinning Factor in Cognitive/Mood Disorders

In the present day, eating habits have changed around the world, and consumption of high-calorie foods is globalized, without considering that their consumption can negatively affect the performance of the brain, such as cognition and emotion. In accordance, increased risk of cognitive decline and mood disturbance is associated with poor diets. One definition of a poor diet is being rich in fat and/or sugar. Studies have suggested strategies that include changing lifestyles to reduce the incidence of cognitive and mood disorders, in which reliable results have been obtained about the effectiveness of diet modification in preventing cognitive impairment and mood disorders.

Having a healthy diet is important even early in life. Studies have reported that poor diet in early postnatal life would make long-lasting changes in cognition determined by a negative effect on selective attention ability (de Rooij et al. 2010). The other example of this significant impact is the disturbance of reward processing in offspring brains that they prefer high-fat food (Ong and Muhlhausler 2011).

Inflammation is one of the possible explanations for how diet induces cognitive impairment. A primary physiologic change in obesity is low-grade systemic inflammation. Regardless of obesity, consuming unhealthy food (for example high unsaturated fat diet) just for 1 week can also trigger neuroinflammation. However, it is noteworthy that these adverse effects of an unhealthy diet are not dependent on obesity phenotype and cognitive impairment can occur without obesity (de Rooij et al. 2010). As known, white adipose tissue constantly produces chemokines, cytokines, and hormones during life. In obesity, because of persistent energy surplus, as an adaptive mechanism, the size of adipocytes increase, and they secrete pro-inflammatory cytokines. Secretions of pro-inflammatory cytokines such as IL-6 and TNF-α attract migrating pro-inflammatory macrophages, which in turn leads to an elevated amount of circulating pro-inflammatory cytokines and corticosterone. It has been shown that this peripheral inflammation can trigger an inflammatory response in the CNS. In this regard, it has been shown that the production of microglial pro-inflammatory cytokines is elevated in response to leptin receptor signaling. In addition, elevated corticosterone primes the hippocampal microglia and surprisingly enhances inflammatory response in this region, an effect that is unlike its classical role as an anti-inflammatory hormone (Bazinet and Layé 2014). Hypothalamic inflammation, on the other hand, promotes a state of hyperphagia and weight gain by causing leptin and insulin resistance in the arcuate nucleus (Jais and Brüning 2017). Other brain structures, including the hippocampus, cortex, cerebellum, and amygdala, are also affected by diet-induced neuroinflammation, linking diet-induced metabolic diseases with cognitive deficits. In spite of the fact that effective learning is dependent on proper microglia activity, over-activated microglia could suppress LTP by releasing large amounts of pro-inflammatory cytokines, particularly in hippocampal cells. Furthermore, they interfere with the production

of synaptic plasticity-enhancing molecules, such as BDNF and insulin-like growth factor-1 (IGF-1) (de Rooij et al. 2010). Further, poor diets and/or obesity can alter the composition of the gut microbiome (dysbiosis), which also increases inflammation in the CNS. On the other hand, dysbiosis can be detected in the aging process and neurodegeneration diseases such as AD. Dysbiosis triggers low-grade inflammation by stimulating endotoxin excretion such as microbial amyloids and lipopolysaccharides (LPSs). These endotoxins increase the permeability of the gut wall and secrete pro-inflammatory cytokines. Also, endotoxins activate innate resistance receptors (TLR) to intensify chronic neuroinflammation. Thereafter, gut-derived bacteria and toxins impair the BBB integrity and contribute to neuroinflammation. The events contribute to neurodegeneration, which is evident in vulnerable areas of the brain in AD, such as hippocampal formation. Diet is attributed to making about 60% of changes in the gut microbiome. So, an effective approach to controlling the inflammatory process in aging and AD can be possibly via dietary means. Although the amount of research on which kinds of diets can change gut microbiota and reduce inflammation is limited, it seems that the Mediterranean diet has anti-inflammatory properties. The Mediterranean diet is briefly described as a high intake of whole grains, legumes, seeds, nuts, fruits, and vegetables. Fish, poultry, and dairy are eaten in moderation, and red and processed meat are eaten rarely. Studies have shown that key components of this kind of diets such as fish and polyphenols found in vegetables and fruits can decrease pro-inflammatory markers (Spencer et al. 2017), and adherence to a Mediterranean style in midlife is accompanied by less incidence of cerebral atrophy and cognitive impairment. In contrast, a high intake of inflammatory dietary elements such as red and processed meat, peas, and fried food with a low intake of whole grains is increasing the risk of cognitive decline (Modlinska and Pisula 2018). Noninvasive measuring inflammatory markers such as IL-6 and CRP in the blood can help to predict whether cognitive impairment is likely to happen in late life or not (Modlinska and Pisula 2018).

2.5 Summary and Conclusions

Both cognitive and emotional processes are higher order processes in the brain that differentiate animal and human brain functions. These processes are known to be affected by many factors, including nutritional factors, which are often shown to have a double-edged effect. Appropriate consumption of nutritional ingredients is essential for the development and maintenance of neuronal circuits that govern cognition and emotions. Nevertheless, excessive nutrition and/or consumption of an unhealthy diet can damage these functions and even cause diseases in children and adults. This chapter discussed the latest knowledge about the role of different macro- and micronutrients on the brain, concluding that a balanced intake of long-chain polyunsaturated fatty acids, proteins containing essential amino acids, carbohydrates, and different minerals and micronutrients like vitamins can promote different aspects of brain function such as cognition. Meanwhile, it was discussed

how a change in diet habits known as the "Western diet" and its resulting obesity could bring about disorders affecting cognitive function of the brain. Given that the maintenance of cognition and emotion is the underpinning factor in the improvement of quality of life and, on the other hand, disorders affecting these functions of the brain impose a huge burden on the family and society, this chapter further highlights the importance of taking nutritional precautions in order to develop a healthy and well-functioning brain and, as a consequence, improve the quality of life.

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Chapter 3
Ketogenic Diet: Implications for Treatment and Injury in Neuropsychiatry and Motor Functioning

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Contents

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Abstract The robust evidence of the ketogenic diet's (KD) success in the management of epilepsy has encouraged conducting studies on its effects in other neurological diseases. Despite disparities in characteristics, symptoms, and pathogenesis, these diseases share similar mechanisms that can be targeted by KD. The latter has been implicated in various neuroprotection processes, including neuronal energy replenishment, inflammation reduction, and gut microbiota modulation. Here, we review evidence from literature on the role of KD in the management and treatment of neuropsychiatric disorders and motor dysfunction. We provide an overview of preclinical and clinical assessments to identify the current gaps that need to be filled in future research studies. Finally, we summarize the various adverse events that may be associated with KD implementation.

Keywords Ketogenic diet · Neuropsychiatry · Motor dysfunction · Neuroprotection · Oxidative stress

Abbreviations

ACA	Acetoacetate
AD	Alzheimer's disease
AIS	Abbreviated Injury Score
ALS	Amyotrophic lateral sclerosis
AMPK	AMP-activated protein kinase
ASC	Apoptosis-associated speck-like protein containing a CARD
ASD	Autism spectrum disorder
ASIA	American Spinal Injury Association
BDH	β-Hydroxybutyrate dehydrogenase
BHB	Beta-hydroxybutyrate
BMC	Bone mineral contents
BMD	Bone mineral density
CARS	Childhood autism rating scale
CAU	Care as usual
CNS	Central nervous system
CPZ	Cuprizone
DA	Dopamine
DMD	Duchenne muscular dystrophy
EAE	Experimental autoimmune encephalomyelitis
EPM	Elevated plus maze
FST	Forced swim test
GERD	Gastroesophageal reflux disease
GI	Gastrointestinal
HDL	high-density lipoprotein
HFD	High-fat diet
IBM	Inclusion body myositis

KB	Ketone bodies
KD	Ketogenic diet
KDTs	Ketogenic Dietary Therapies
KME	Ketone monoester
LDL	Low-density lipoprotein
LGIT	Low glycemic index treatment
LPS	Lipopolysaccharide
MAD	Modified Atkins diet
MCT	Medium-chain triglyceride diet,
MDD	Major depressive disorder
MeS	Metabolic syndrome
MS	Multiple sclerosis
OFT	Open field test
PAS	Parkinson Anxiety Scale
PCS	Post-concussion syndrome
PD	Parkinson's disease
RES	Reactive electrophile species
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
R-SDS	Repeated social defeat stress
SCI	Spinal cord injury
SD	Standard diet
TBI	Traumatic brain injury
UPDRS	Unified Parkinson's Disease Rating Scale
VHF-KD	Very-high-fat ketogenic diet
WD	Western diet

3.1 Introduction

There are two high-fat diet (HFD) types: the ketogenic diet (KD) and the Western diet (WD). The former is a low-carbohydrate and high-fat diet that aims to decrease the glucose dietary intake, inducing ketosis state. For many decades, the KD has been used for weight loss, metabolic disorders, and seizure management in pediatric patients (Kinsman et al. 1992). Four forms of ketogenic dietary therapies (KDTs) are available: the classic KD, the medium-chain triglyceride diet (MCT), the modified Atkins diet (MAD), and the low glycemic index treatment (LGIT) (Kapoor et al. 2021). A 3:1 to 4:1 fat-to-carbohydrate ratio is used in a classic KD. The MAD restricts carbohydrates to 20 g/day while increasing the fats. Unlike classic KD, it is possible to commence the MAD treatment on an outpatient basis. Medium-chain triglycerides are used as the ketogenic source in the MCT, thus facilitating the relative liberalization of carbohydrates. Finally, the LGIT employs complex carbohydrates that have a high glycemic index. The WD, on the other hand, is a high-

carbohydrate and high-fat diet directly associated with conditions like obesity and metabolic syndrome (MeS) (Kopp 2019). MeS is defined by the occurrence of at least three of the following morbidities: hypertension, hyperglycemia, hypertriglyceridemia, visceral obesity, and low high-density lipoprotein (HDL) levels (Grundy et al. 2005). Many preclinical studies that investigated the KD effect on neurodegenerative disorders provided evidence that it improves various outcome measures and reduces pathology (Brady et al. 2022; Brownlow et al. 2013; Liu et al. 2020; Yang and Cheng 2010). Moreover, clinical studies also suggested that KD ameliorated the quality of life in patients suffering from various neurological diseases (Phillips et al. 2018, 2020, 2021). This granted the topic of KD in neuroprotection a heightened attention within the scientific community. The "neuroketotherapeutics" term is now utilized to indicate the utilization of ketosis for the amelioration of neurological disorders. The safe and effective ketone blood concentration target range was reported to be between >0.2 and 5–8 mM (Hashim and VanItallie 2014). Notably, KD is still not recommended for tackling symptoms and decreasing the degeneration pace in neurological conditions, except for epilepsy. This chapter illustrates the various KD and HFD effects on neuropsychiatric conditions. Moreover, it summarizes their impact on the motor dysfunction associated with many neuromuscular diseases. Furthermore, it describes the mechanisms that may be implicated in the KD neuroprotection effects. Finally, it highlights the key knowledge gaps and research needs related to KD as a potential treatment in neuropsychiatry and motor dysfunction.

3.2 Ketone Body Metabolism

Ketone bodies (KB) play a role as alternative fuels for metabolism in the brain. This sustains ATP production, mitochondrial function, and survival of neurons. Ketogenesis is a process by which ketone bodies are produced. Beta-hydroxybutyrate (BHB), acetoacetate (ACA), and acetone are the most well-known KB. They are used as surrogate sources of metabolic energy when glucose stores become depleted in the body. The glycolytic inhibition in KD triggers ketogenesis, which occurs mainly in liver hepatocytes (Puchalska and Crawford 2017), neuronal cells, and epithelium of the retinal pigment (Adijanto et al. 2014). β-Oxidation reactions transform fatty acids originating from the diet into acetyl-CoA. The latter is further processed into ACA and BHB through the action of various cofactors and enzymes (Gough et al. 2021). Monocarboxylate transporters transport the obtained ketone bodies out of the liver into the blood. The brain and other organs take up the ketone bodies and reconvert them into acetyl-CoA through ketolysis. The integration of acetyl-CoA into the Krebs cycle produces GTP and ATP in the mitochondria. Moreover, β-hydroxybutyrate dehydrogenase (BDH) can convert back BHB into acetoacetate. This generates NADH, which in turn assists the function of the electron transport chain. Acetone is mainly excreted outside the body through exhalation. However,

the metabolism of acetone may yield lactate, acetate, and pyruvate. These products can serve as additional energy sources for the cells.

3.3 KD Neuroprotection Mechanisms

3.3.1 Energy Supplementation

Neurological diseases are often associated with changes in glucose metabolism. The main benefit from KD is its ability to restore the energy supply to neuronal cells. In the MPTP neurotoxicity murine model, BHB was shown to act on complex II resulting in the prevention of mitochondrial respiration decline and ATP production restoration (Tieu et al. 2003).

3.3.2 Reduction of Inflammation and Oxidative Stress

Neuroinflammation represents an innate reaction to neuronal damage and disease. To repair neuronal injury, phagocytosis is enhanced by inflammatory cells. Moreover, the secretion of neuroprotective and anti-inflammatory molecules is induced (Yong et al. 2019). However, the release of neurotoxic and inflammatory molecules and the reactive oxygen species (ROS) accumulation during unregulated neuroinflammation can exacerbate neuronal loss. KD can protect against neuroinflammation by inducing anti-inflammatory pathways. AMP-activated protein kinase (AMPK) is a protein that can sense energy levels in the cells. When the levels of energy are below average, AMPK is activated to decrease the consumption of ATP. Moreover, AMPK plays a role in regulating inflammation by activating NF-κB. The latter promotes the transcription of TNFα, IL-1β, and IL-6 (Nunes et al. 2015), which serve as pro-inflammatory molecules. KD was found to reduce AMPK activation in a glaucoma mouse model, leading to reduced expression of pro-inflammatory molecules (Harun-Or-Rashid and Inman 2018). In the central nervous system (CNS), the NLRP3 inflammasome represents a key mediator of inflammatory signaling. BHB inhibits NRLP3 inflammasome activation by blocking the ATP-induced ASC oligomerization and the potassium efflux required for inflammasome assembly (Youm et al. 2015). The mitochondrial dysfunction secondary to neuronal injury leads to the generation of ROS, reactive electrophile species (RES), and reactive nitrogen species (RNS). These molecules are associated with neuronal death and neurotoxicity in neuronal diseases (Espinós et al. 2020). A study demonstrated the role of BHB in scavenging ROS and hydroxyl radicals (Haces et al. 2008). Moreover, BHB preserved mitochondrial functioning and increased cell survival by directly reducing cellular ROS levels. Another study showed that KD decreased the expression of the oxidative stress marker malondialdehyde in a murine model of multiple sclerosis (MS) (Liu et al. 2020).

Moreover, KD induced the activity of glutathione peroxidase, an enzyme that decomposes H2O2. The KD impact on oxidative stress markers was associated with ameliorated improved myelination in the hippocampus.

3.3.3 Gut Microbiome Interaction

Various metabolites are secreted by microbial species in the gut. These include short-chain fatty acids, immunomodulatory molecules, neurotransmitters, and tryptophan. Indeed, several neurological disorders are associated with microbial derived molecules from the gut microbiome. CNS homeostasis and possibly neuroprotection may be affected by KD-induced alterations in the microbiome (Zhu et al. 2020). Olson et al. utilized two murine epilepsy models to demonstrate that mice fed KD had increased levels of the *Akkermansia* and *Parabacteroides* gut bacteria species (Olson et al. 2018) and significantly fewer seizures. KD led to a decrease in gamma-glutamyl transpeptidase in the stomach leading to increased production of GABA in the brain.

3.3.4 Epigenetic Regulation

The histones in the promoters of active genes can be modified directly on lysine residues by BHB (Xie et al. 2016). This process is known as β-hydroxybutyrylation, a major epigenetic regulatory pathway, with more than 1300 proteins identified as targets for ketone-related modifications (Huang et al. 2021). Thus, KD may influence epigenetic regulation through the upregulation of ketone bodies.

3.4 KD Effects on Neuropsychiatric Disorders

3.4.1 Anxiety and Depression

HDL is lowered in several neuropsychiatric diseases such as major depressive disorder (MDD) (Péterfalvi et al. 2019), bipolar disorder, and schizophrenia. Moreover, the degree of reduction in HDL is associated with the severity and duration of symptoms in MDD (Aksay et al. 2016; Lehto et al. 2010). Clinical studies show that KD increases HDL levels (Sharman et al. 2002) while decreasing those of the low-density lipoprotein (LDL) cholesterol (Dashti et al. 2004). Moreover, KD is strongly linked to an elevated ratio of GABA/glutamate (Calderón et al. 2017). This suggests a favorable effect of KD on the prognosis of neuropsychiatric diseases in which reduced GABA and/or HDL levels are involved. To explore the antidepressant effects of KD, a study used the Porsolt test, which is an in vivo depression

model (Murphy et al. 2004). The rats on KD displayed behavior similar to those on antidepressants. They spent less time immobile and had a lower chance of exhibiting "behavioral despair." KD coupled with regular voluntary exercise was shown to reduce depression and anxiety in Balb/c mice (Gumus et al. 2022). Additionally, these mice had increased levels of BHB and lower insulin and glucose levels. Moreover, their LDL/HDL ratio was reduced. Lower anxiety and depression levels were reflected by a decrease in the time spent in periphery walls of open field test (OFT) and in the closed arms of elevated plus maze (EPM) and reduced immobility time in the forced swim test (FST). Further research is required to improve our knowledge of the mechanisms by which the nervous system and behavior are influenced by pairing KD with voluntary exercise. KD treatment was found to dramatically ameliorate depressive-like behaviors in the lipopolysaccharide (LPS) and repeated social defeat stress (R-SDS) murine models of depression (Guan et al. 2020). The study further shows that KD reverses the neuronal excitability induced by LPS or R-SDS in the lateral habenula of mice. KD additionally rescues these mice from the vigorous activation of microglial cells in the lateral habenula. Another study showed that sociability is increased in CD-1 mice fed KD (Arqoub et al. 2020). Female and male CD-1 mice were subjected gestationally to KD or standard diet (SD) and cross-fostered at birth with dams fed SD. From that point onward, they remained fed with SD. At 10 weeks of age, they were tested for depressive-like behaviors with the forced swim test and for sociability with the three-chambered test. Additionally, their brain tissue was processed by immunohistochemistry to assess the expression levels of oxytocin in the hypothalamic and limbic areas. Although oxytocin expression was not affected in the quantified areas, the KD offspring had reduced depressive-like symptoms and increased sociability. Thus, gestational exposure to KD has a lasting positive impact on developmental disorders associated with behavioral disturbances in mice. A study by Sussman et al. demonstrated that depression behaviors were less likely in the offspring of mice fed KD during pregnancy (Sussman et al. 2015). In addition to reduced proneness to depression and anxiety, this offspring showed an elevated physical activity level both in utero and postnatally. In conclusion, published evidence from preclinical studies has further strengthened the notion of induced ketosis in psychiatry as "food for thought."

Campbell et al. explored the role of KD in mood stabilization in 274 people with bipolar disorder (Campbell and Campbell 2019). The majority of participants (85.5%) reported a favorable effect from KD on mood stabilization. Moreover, KD was found to be superior over other diets and significantly associated with higher odds of mood stabilization or diminution of symptoms. KD was also linked to reduced depression episodes, increased energy, weight loss, and improved speech coherence. A clinical assessment of 16 adults with Parkinson's disease (PD) on KD reported anxiety symptom alleviation evaluated using the Parkinson Anxiety Scale (PAS) (Tidman et al. 2022). A case report revealed the safety and effectiveness of KD in ameliorating health biomarkers, anxiety, and depression in a 68-year-old female patient suffering from stage I PD (Tidman 2022). Epilepsy is a common neurological disorder associated with wide-ranging neuropsychiatric manifestations.

A retrospective study conducted at the Johns Hopkins Adult Epilepsy Diet Center examined the psychiatric impact of MAD on chronic epilepsy (Shegelman et al. 2021). An association was reported between fewer symptoms of depression and anxiety and a longer diet duration in adults with epilepsy. However, significant changes in anxiety or depressive symptoms were not experienced in prospective participants on MAD in the same study. Still, a significant correlation between responder rate ($\geq$50% seizure reduction) and higher ketone level was found in the prospective cohort. Ijff et al. evaluated the KD impact on the cognitive function and behavior of adult epilepsy patients (IJff et al. 2016). In this randomized clinical trial, a total of 50 patients were included. Compared to the group that received care as usual (CAU), the KD group was appraised as being more productive and exhibited reduced anxious behavior and mood disturbances.

3.4.2 Addiction

Somatic and mental health can be adversely affected by alcohol abuse (Probst et al. 2014). Indeed, alcohol dependence is associated with the development of psychiatric disorders such as depression (Kessler et al. 1997). A recent study by Blanco-Gandía et al. found that mice on KD had a net reduction in alcohol consumption compared to the SD group (Blanco-Gandía et al. 2021). However, their motivation to drinking remained the same. Moreover, KD was found to decrease the severity of alcohol withdrawal symptoms in a clinical cohort of 19 inpatients with alcohol-abuse disorder (Wiers et al. 2021). The KD treatment was administered for 3 weeks and resulted in reduced dependence on psychoactive drugs during detoxification.

Studies also showed that KD had effects on drug addiction. It was shown that OF1 male mice fed KD needed lower numbers of sessions to eliminate drug-related memories. In addition, KD inhibited the reinstatement of drug seeking triggered by cocaine priming. However, KD did not prevent the mice from acquiring drug-conditioned place preference (Ródenas-González et al. 2022). Another study suggested that KD acts on drug addiction by directly influencing dopamine-linked behaviors (Martinez et al. 2019). The authors demonstrated that mice fed KD followed by cocaine treatment showed a reduction in cocaine-induced behaviors in comparison to the control group. Hence, KD possesses a therapeutic potential for cocaine addiction and possibly other drugs.

KD was described recently as a potential treatment for eating disorders. A recent pilot clinical study reported weight loss and improvement of binge eating and food addiction symptoms in five women (Rostanzo et al. 2021). The authors concluded the feasibility and potential of KD in the treatment of high-calorie food addiction. A case series revealed that KD was feasible and well tolerated in three patients with excessive eating disorders (Carmen et al. 2020). Both cravings and control-lack symptoms of food addiction were significantly decreased by KD. Moreover, fewer episodes of binge eating were obtained with KD treatment.

3.4.3 *Other Psychiatric Diseases*

KD may serve as a tool for the management and treatment of several psychiatric diseases. A case series of two females suffering from type II bipolar disease revealed the safety of management by KD and the lack of adverse events (Phelps et al. 2013). Moreover, the diet exerted beneficial effects such as mood stabilization and symptom improvement as reported by the patients. A case report implemented KD in the treatment of an elderly woman who had been suffering from schizophrenia since teenage years (Kraft and Westman 2009). KD successfully eliminated the psychotic symptoms, which the patient had been suffering for a long time. She stopped experiencing hallucinations that prompted suicidal thoughts and lost weight. Recent preclinical and clinical studies demonstrated that KD improves behaviors linked with autism spectrum disorder (ASD) in mice (Ruskin et al. 2017) and children (Lee et al. 2018). The KD benefits extend to various psychiatric disorders and deserve additional investigations in large clinical cohorts to assess both KD safety and efficacy.

3.5 Evidence for KD Effects in Diseases Associated with Motor Dysfunction

3.5.1 *Findings from Preclinical Studies*

Several studies assessed the KD effects in diseases associated with motor dysfunction. In vivo models of Alzheimer's disease (AD) (Beckett et al. 2013; Brownlow et al. 2013) and Parkinson's diseases (Shaafi et al. 2016; Yang and Cheng 2010) showed that KD improves motor function. In a rat model, Kuter et al. showed that long-term hyperketonemia from KD did not protect against the dopaminergic neuronal damage instigated by 6-OHDA (Kuter et al. 2021). However, KD improved the movement and motion of rats and normalized their dopamine (DA) turnover in the striatum. KD may not necessarily act against the neurodegeneration feature of PD. However, it may aid in bolstering the late compensatory mechanisms. Long-term and durable metabolic studies using standardized diet parameters are needed to evaluate the extent of the KD impact on PD. Multiple sclerosis is an autoimmune chronic disease in which the CNS is affected. It is marked by inflammation associated with the impairment of nerve cell processes and myelin. KD was demonstrated to have a neuroprotective effect in the hippocampus of the cuprizone (CPZ)-induced demyelination murine model (Liu et al. 2020). KD additionally reduced the lesion size and improved motor ability in CPZ mice. KD-treated mice had better motor coordination and remained significantly longer on the rotarod device. Another study utilized a murine model of autoimmune encephalomyelitis (EAE) to assess the KD effect on CNS inflammation (Kim et al. 2012). Both motor disability and CA1 hippocampal synaptic plasticity were improved by KD. In addition, the Morris

water maze assessment revealed better spatial learning and enhanced memory in the KD group. The authors concluded that KD attenuates the oxidative stress and robust immune response seen in EAE animals.

Repetitive motor behaviors are repetitious and monotonous movements with no recognized function. They are associated with different psychiatric and neurological diseases such as ASD. KD was applied in a rodent model to assess its effect on abnormal repetitive circling behavior (Brady et al. 2022). After older (15+ months) male and female mice were fed KD, less rounds of repetitive behavior were detected. The positive KD impact on repetitive motor behavior was replicated in female mice between 4 and 6 months of age. Moreover, pharmacological assessment suggested an increased expression of the D2 receptor in the indirect basal ganglia pathway. Thus, it is relevant to directly examine the KD effects on the dopamine receptor function. Duchenne muscular dystrophy (DMD) is a disease of genetic origin that is characterized by muscle weakness and atrophy. A KD that was supplied with medium-chain triglycerides was shown to significantly inhibit the key features of DMD in a rat model (Fujikura et al. 2021). This diet prevented muscle necrosis, inflammation, and subsequent fibrosis. Moreover, it increased muscle strength and fiber diameter and promoted the proliferation of smooth muscle cells. KD supported with medium-chain triglycerides ameliorates muscular dystrophy by enhancing muscle regeneration and inhibiting myonecrosis.

Diet and metabolic health go hand in hand. Many neurodegenerative and neuromuscular diseases are linked to mitochondrial dysfunction. Ahola-Erkkilä et al. demonstrated that KD delayed mitochondrial myopathy progression in transgenic deletor mice (Ahola-Erkkilä et al. 2010). These mice exhibited reduced levels of cytochrome c oxidase-negative muscle fibers. Moreover, KD completely halted the development of mitochondrial ultrastructural malformations in muscle cells. Additionally, KD restored the metabolic and lipidomic changes associated with mitochondrial myopathy to wild-type levels. Amyotrophic lateral sclerosis (ALS) is a chronic progressive neurodegenerative disease that does not have a known treatment. The loss of muscle control is one of the main features of ALS. KD was shown to alter the clinical and biological manifestations of ALS in a mouse model (Zhao et al. 2006). Baseline motor performance loss was delayed in mice that were fed KD. Moreover, motor neurons were more abundant in the spinal cord sections of KD-fed animals. The authors also demonstrated that BDH—a principal ketone body—protects motor neurons from cell death. Zhao et al. treated ALS mice with caprylic triglyceride, which is a medium-chain triglyceride that is metabolically transformed into ketone bodies (Zhao et al. 2012). The treatment group had significantly improved motor performance and were protected from spinal cord motor neuron loss. The authors suggested that caprylic triglyceride alleviated motor impairment in ALS rats through the restoration of energy metabolism.

Streijger et al. assessed the KD efficacy in the treatment of spinal cord injury (SCI) in a rat model (Streijger et al. 2013). The authors observed a stable improvement in the forelimb function of KD-fed rats compared to rats on a standard diet based on carbohydrates. Moreover, rats fed KD had more grey matter sparing and smaller lesions in their spinal cords. The ad libitum administration of KD in rats

post-SCI was shown to rescue mitochondrial function (Seira et al. 2021). KD improved post-SCI metabolism by altering the regulation of mitochondrial related genes, activating the NRF2-dependent antioxidant pathway, and increasing parameters of mitochondrial biogenesis. Zeng et al. further explored the KD mechanism of action post-SCI in Sprague-Dawley rats (Zeng et al. 2021). The transcriptome level changes and myelin expression were assessed in rats fed KD or standard diet (SD). The authors found that KD had reprogrammed the steroid metabolism in SCI treatment. Moreover, these alterations in the metabolism of steroids were introduced at the transcriptional level. Myelin areas were observed to be significantly vaster in SCI rats that were fed KD. Additionally, these rats had a significant decrease in the expression of genes implicated in immunological pathways. Thus, the KD-induced reprogramming of steroid metabolism may improve the myelin growth and immune microenvironment in rats with SCI. Traumatic brain injury (TBI) is a dysfunction in the brain resulting from an external force's impact on it. Har-Even et al. examined the cognitive, cellular, and molecular effects of KD post-injury using a closed-head murine model of TBI (Har-Even et al. 2021). The authors showed that KD reduces reactive astrocytes, mitigates TBI-induced neuroinflammation, and prevents TBI-induced neuronal loss. KD may represent a useful tool to bolster the protective mechanisms from injury in the brain. It may also constitute a prospective novel treatment for TBI. Mayr et al. called for the careful exploration of dietary effects on neurotrauma in animal models (Mayr et al. 2020). The authors demonstrated that KD did not play a role in the sensorimotor recovery in a mouse model of SCI. The sensorimotor behavior of the mice was examined post-injury using the von Frey, open field, and ladder-rung crossing tests. The authors concluded the need to assess ketogenic diets according to the category and position of neurotrauma. Moreover, it is essential to gather knowledge on the secondary injury mechanisms and the metabolic deficits' extent post-TBI or SCI.

3.5.2 Evidence from Clinical Evaluations

Several clinical studies exist on the effects of KD on the motor function and quality of life in patients with various neurological diseases. We summarized in Table 3.1 the clinical trials and case reports that evaluated KDTs in disorders associated with motor dysfunction. The KD efficacy and safety in AD seem promising, but additional randomized trials are needed. In a randomized clinical trial including 26 AD patients on KD, high rates of safety, adherence, and retention were obtained (Phillips et al. 2021). Patients on KD experienced an improvement in quality of life compared to patients following a usual low-fat diet with healthy eating guideline. Moreover, patients on KD had an ameliorated daily function. Results from the Ketogenic Diet Retention and Feasibility Trial revealed an improvement in cognitive function in AD patients on MCT-KD (Taylor et al. 2018). Most of the adverse events experienced in this study were related to MCT. The pilot study concluded by justifying additional KD trials in mild AD. A case report of an AD patient revealed beneficial effects from

Table 3.1 The clinical trials and case reports that evaluated KDTs in disorders associated with motor dysfunction

Condition	Type	Year	Number of patients	Intervention	Main findings	Reference
Parkinson's disease	Pilot study	2005	5	Hyperketogenic diet	KD improved the UPDRS scores including motor function	Vanitallie et al. (2005)
Acute spinal cord injury	Pilot clinical trial	2014	10	KD	KD is a safe and feasible treatment for acute SCI KD increased the average motor American Spinal Injury Association score	Guo et al. (2014)
Alzheimer's disease	Case report	2015	One 63-year-old male	Ketone monoester (KME)	KME is safe and well tolerated KME improved cognitive and daily activity performances	Newport et al. (2015)
Mitochondrial myopathy	Pilot study	2016	5	Modified Atkins diet (MAD)	All patients experienced adverse events (muscle damage)	Ahola et al. (2016)
Acute spinal cord injury	Pilot feasibility and safety trial	2018	7	KD	KD is a safe and feasible treatment for acute SCI KD significantly increased the extremity motor scores	Yarar-Fisher et al. (2018)
Alzheimer's disease	Pilot clinical trial	2018	10	MCT-KD	KD improves cognitive function	Taylor et al. (2018)
Parkinson's disease	RCT	2018	38	KD	KD is a safe and feasible treatment for Parkinson's	Phillips et al. (2018)

(continued)

Table 3.1 (continued)

Condition	Type	Year	Number of patients	Intervention	Main findings	Reference
					disease KD significantly improved motor and nonmotor symptoms	
Parkinson's disease	Pilot clinical trial	2019	14	KD	KD did not affect motor function in PD KD improved cognitive function in PD	Krikorian et al. (2019)
Sporadic inclusion body myositis (IBM)	Case report	2020	One 52-year-old female	KD	KD reduced muscle inflammation KD decreased the muscle atrophy rate The patient regained independent walking	Phillips et al. (2020)
Post-concussion syndrome (PCS)	Pilot feasibility study	2020	14	Very-high-fat ketogenic diet	KD is safe and feasible in PCS KD improves cognitive function	Rippee et al. (2020)
Alzheimer's disease	RCT	2021	26	KD	KD is a safe and feasible treatment for AD KD ameliorates the daily function in AD	Phillips et al. (2021)
Traumatic brain injury	Open-label, single-arm clinical trial	2022	10	KD	KD is a safe and feasible treatment for TBI	Arora et al. (2022)

(continued)

Table 3.1 (continued)

Condition	Type	Year	Number of patients	Intervention	Main findings	Reference

Abbreviations: *AD* Alzheimer's disease; *IBM* inclusion body myositis; *KD* ketogenic diet; *KME* ketone monoester; *MAD* modified Atkins diet; *PCS* post-concussion syndrome; *PD* Parkinson's disease; *QoL* quality of life; *RCT* randomized controlled trial; *SCI* spinal cord injury; *TBI* traumatic brain injury; *UPDRS* Unified Parkinson's Disease Rating Scale

ketone monoester (KME)—a potent ketogenic agent—administration (Newport et al. 2015). Throughout the 20-month treatment period, the patient tolerated KME well. Moreover, he ameliorated in cognitive performance, self-care, and daily activity. Phillips et al. compared KD to a low-fat diet in a total of 38 patients with PD (Phillips et al. 2018). Significantly improved nonmotor and motor symptoms were observed in both diet groups. The KD group had greater improvements compared to the group following the low-fat diet, but in nonmotor symptoms only. A controlled pilot trial revealed that motor function was not affected by KD in PD patients (Krikorian et al. 2019). However, cognitive performance was improved due to nutritional ketosis.

A case series evaluated the impact of KD in five PD patients who followed the diet for a duration of 28 days (Vanitallie et al. 2005). The authors observed improved Unified Parkinson's Disease Rating Scale (UPDRS) scores in all participants. The improvement included motor function, but the authors could not rule out the placebo effect. Additionally, cholesterol increases were prevented in four out of five patients due to the substitution of unsaturated fats with saturated ones. HFD is associated with a lower risk of ALS development (Fitzgerald et al. 2014; Veldink et al. 2007). However, the KD effect on motor function in ALS patients requires further clinical investigation. Sporadic inclusion body myositis (IBM) is an inflammatory disorder characterized by muscular degeneration and currently lacks a known treatment. In a case report of a female with deteriorating IBM, KD was chosen as the primary approach for treatment (Phillips et al. 2020). The patient on KD had substantial clinical improvement, with stabilization of muscle inflammation and reduction in the rate of muscle atrophy. The patient regained independent walking 1 year posttreatment.

In a case series by Ahola et al., five mitochondrial myopathy patients were managed with MAD (Ahola et al. 2016). However, all patients experienced major adverse events between 1.5 and 2 weeks posttreatment. Serious symptoms such as progressive muscle pain and drainage of muscle enzymes prompted the early cessation of the diet in all patients. The authors warned about the muscle damage effect that can be induced by MAD in a certain subgroup of the population. They concluded that disease progression can be modified by nutrition in mitochondrial disorders. They recommended the incorporation of dietary counseling in mitochondrial myopathy care.

In a pilot feasibility and safety trial, KD was found to be safe as a treatment for acute SCI (Yarar-Fisher et al. 2018). The study included seven patients with acute

SCI assigned to KD and standard diet groups. An improvement in the levels of inflammatory markers was observed in the sera of patients on KD. Compared to the SD group, KD resulted in significantly higher extremity motor scores. The safety and feasibility of KD were also demonstrated in a clinical trial that included ten acute SCI patients (Guo et al. 2014). During KD, glycemia remained in the normal range. Moreover, the liver and kidney function remained unchanged after KD. An increase in the average motor American Spinal Injury Association (ASIA) score was observed after KD. Another study evaluated the efficacy and feasibility of the very-high-fat ketogenic diet (VHF-KD) in patients with post-concussion syndrome (PCS) symptoms (Rippee et al. 2020). A total of 11 out of 14 participants achieved ketosis by implementing the VHF-KD (79% compliance). This confirmed the ability of PCS patients to achieve adherence to VHF-KD. Moreover, an improvement in cognitive function was observed, but the results need to be interpreted with caution. The study had limitations in its design including a small sample size and a single-arm nature. Arora et al. demonstrated the feasibility of adopting KD for the treatment of TBI (Arora et al. 2022). The study included ten male patients with TBI and an Abbreviated Injury Score (AIS)-Head $\geq$3. None of the participants experienced clinical adverse effects from KD. The authors justified the need for additional randomized controlled trials to decipher the KD dose, duration, and effects on TBI outcomes.

3.6 Adverse Effects of the Ketogenic Diet

The metabolic changes induced by KD force every cell to rely primarily on beta-oxidation for energy production (Yudkoff et al. 2008). This can lead to alterations in genetic regulation, hormonal pathways, and neurotransmitter production. Unless properly supplemented, people on KD are expected to have deficiencies in several essential vitamins, electrolytes, and trace minerals (Zupec-Kania and Zupanc 2008). A major challenge for KD implementation is achieving a good adherence level to dietary recommendations. Insufficient adherence may result in poor tolerance and a range of frequently encountered short-term side effects. The latter are known as keto flu and include symptoms such as nausea, vomiting, headache, fatigue, dizziness, insomnia, difficulty in exercise tolerance, and constipation (Masood et al. 2022). Adequate fluid and electrolyte intake can ameliorate some of these symptoms. Long-term side effects that usually present 3 months post-KD include kidney stones, fatty liver disease, hypoproteinemia, hyperlipidemia, reduced bone mass density, and vitamin and mineral deficiencies.

3.6.1 Hyperlipidemia

The incidence of hyperlipidemia is elevated in patients treated with KD (Nizamuddin et al. 2008). However, genetics and heredity play a significant role in its development (García-Giustiniani and Stein 2016). The majority of food allowed in KD contains a high amount of saturated fat, which can lead to an undesirable lipid profile. This is characterized by elevated levels of VLDL and LDL and a low level of the anti-atherogenic HDL (Fenton et al. 2009). By introducing minor modifications such as using oil instead of butter and substituting egg whites for whole eggs, a normal lipid profile can be restored. KD was also found to increase the levels of polyunsaturated fatty acids in the serum (Fraser et al. 2003). Fortunately, omega-3 supplementation seems to reverse this side effect, thereby reducing the risk of cardiovascular problems (Dahlin et al. 2007).

3.6.2 Cardiac Disease

A systematic investigation of the long-term KD effects on cardiovascular health is still unavailable. One case series reported two mortalities related to cardiac complications in children treated with KD (Bank et al. 2008). Both cases suffered from selenium deficiency that was associated with QC interval prolongation and cardiac dysfunction. Xu et al. showed that the upregulation of BHB—an HDAC2 inhibitor—induced the expression of high Sirt7 levels (Xu et al. 2021). This resulted in the inhibition of mitochondrial biogenesis and the subsequent cardiomyocyte apoptosis and cardiac fibrosis.

3.6.3 Linear Growth Failure

The restrictive KD nature in terms of calories and protein intake is known to cause a growth reduction in children (Bergqvist et al. 2008; Neal et al. 2008). The growth rate during preadolescent years is mainly driven by insulin-like growth factor-1 (IGF-1) and growth hormone (Laron 2001). Spulber et al. reported a dramatic decrease of IGF-1 in children on KD compared to baseline measurements (Spulber et al. 2009). Another study found that KD did not induce significant changes in growth hormone levels. However, KD triggered hepatic growth hormone resistance via the downregulation of growth hormone receptor expression (Bielohuby et al. 2011).

3.6.4 Gastrointestinal Disorders

Gastrointestinal (GI) complications can occur in up to 75% of cases on KD due to the lack of the fibers needed for normal GI function (Bergqvist 2012). Ketosis promotes the downregulation of acyl ghrelin, which may lead to anorexia and refusal to eat (Vestergaard et al. 2021). Moreover, clinical studies reported acute pancreatitis (Stewart et al. 2001) and gallstone disease (Hassan et al. 1999) in patients on KD. Still, KD may improve the outcomes of certain GI disorders such as gastro-esophageal reflux disease (GERD). A comparative study by Austin et al. revealed that a diet very low in carbohydrates ameliorated the symptoms of GERD in eight patients (Austin et al. 2006). Jung et al. suggested that abnormal endoscopy results before KD initiation may explain the frequency of GI symptoms posttreatment (Jung et al. 2008). They concluded the importance of supplementation with GI medications in improving the tolerance to KD.

3.6.5 Kidney Stones

Due to the metabolic changes associated with the KD, patients may develop kidney stones (Kielb et al. 2000). Urolithiasis, elevated levels of uric acid, and a lower urine PH were observed in pediatric patients treated with KD (Furth et al. 2000). This may be attributed to the high amount of acidic ketone bodies, hypercalciuria, and low urine citrate. Routine monitoring and frequent hydration can minimize the risk of developing kidney stones.

3.6.6 Compromised Bone Density

In adults, the evidence of negative changes in bone mineral density (BMD) and bone mineral contents (BMC) is scarce (Andersen et al. 1997). The changes in BDM seem to be more dramatic during the preadolescent phase rather than adulthood (Bonjour et al. 1991). Bone mineralization peaks around the end adolescence. Consequently, the BMD level accrual during this phase will directly influence the risk of osteoporosis and fractures during adulthood. Indeed, high level of ketosis had a negative correlation with growth rate and bone mass accumulation (Merlotti et al. 2021). It is also worth mentioning that antiepileptic drugs can predispose to osteoporosis depending on the length of treatment. These drugs may interfere with the vitamin D function and calcium deposition and directly affect bone remodeling (Fitzpatrick 2004).

3.7 Future Research Directions

The preclinical research conducted so far provides evidence on the beneficial KD impact and its mechanism of action in neuropsychiatric diseases and motor dysfunction. However, more studies are needed to discern the specific pathways involved in these mechanisms. The existing clinical studies and case reports on the role of KDTs in neurological diseases share many limitations. As a starter, there are no unified KD parameters that allow the accurate comparison of these studies. Hence, assessing the different KDTs and their components (e.g., ratios, doses, duration) can be a starting point for standardizing randomized clinical trials (Habashy et al. 2022). Moreover, the design of many existing studies suffers from the lack of randomization, being single arm and/or having a small sample size. Therefore, the current focus for future studies should be to conduct adequately planned clinical trials with solid protocols that ensure the generation of reliable results.

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Chapter 4
Effects of Malnutrition on Brain Development

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Contents

Abstract One of the most significant variables that can hinder the development of the brain is malnutrition. Malnutrition can lead to aberrant growth and behavioral issues. Brain growth, synapse formation, and cell differentiation are all impacted by nutritional deficiencies. A diet deficient in protein during pregnancy is associated with alterations in the neurotransmitters as well as the oxidative state of the brain. As a result, psychosocial problems emerge in childhood that last throughout adulthood. Understanding the deleterious effects of a nutrition deficiency on brain function requires an understanding of the length and commencement of dietary requirements. Many concerns remain unanswered about the long-term implications of prenatal starvation, even after decades of research. Since children's neurological systems are still developing, they are more vulnerable to the consequences of nutritional inadequacies than adults' brains. Some of the impacts of caloric deficiency [including in some cases protein-calorie malnutrition (PCM), and a lesser degree of essential fatty acid (EFA) deficit] on some indices of brain damage, behavioral change, and intellect (IQ tests) have been studied in the context of the war years in Europe and the emergence of famine circumstances in other nations. Research on the impact of

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malnutrition on the developing brain can be broken down into two categories: studies that focus on physical and clinical brain growth and maturation, and studies that focus on the development of "brain function," which includes neurological, psychomotor, and intellectual development. This chapter explores the effects of a lack of nutrients on the neurodevelopment.

Keywords Malnutrition · Neurological development · Brain chemistry · Protein malnutrition · Cell division · Brain growth

4.1 Introduction

The growth and normal functioning of the central nervous system are both dependent on proper nourishment. The formation of the brain is an intricately orchestrated process in which the proliferation of cells, their division, migration, and interconnections are all dependent on different developmental stages that overlap in time. Any disruption to this mechanism could potentially have an effect on the functioning of the brain. When examining the effects of malnutrition, it is important to keep in mind that the time of commencement and timeframe of developing brain vary not just among species but also between various regions of the brain in the same species. In children who have been malnourished, epidemiological studies demonstrate profound behavioral alterations (Richardson et al. 1972; Galler et al. 1984). Maternal malnutrition disrupts embryonic brain growth, resulting in altered developmental patterns that affect cognition and social emotional control, as well as causing problems with memory and learning. Many such impairments persist even after birth and are likely to carry on into adolescence (Kar et al. 2008; Landon et al. 2007; Morgane et al. 2002), which increases the chance of psychological conditions such as schizophrenia, anxiety, depression, personality disorders, and emotional problems (St Clair et al. 2005; Shen et al. 2008). It has been demonstrated that malnutrition is associated with an increased risk of attention deficiencies, agitation, aggressiveness, and other antisocial behaviors (Duran et al. 2005; Liu and Raine 2011; Ogundele 2018). Specific vulnerability to malnutrition has been found in various parts of the brain, and this vulnerability seems to be linked to the particular set of biological activities taking place in that region at any one time (Dobbing 1990; Morgane et al. 2002). Malnutrition slows the process of cell proliferation during development and can lead to a permanent reduction in the total number of cells produced (Winick 1971; Kwong et al. 2000).

The proliferation of oligodendrocytes, which occurs before myelination, is dependent primarily on the expansion of cells in different parts of the brain (Fields 2015). Malnutrition may slow down myelin production but does not alter the quantity of metabolically functional myelin that currently exists (Dobbing 1964; Chase et al. 1967; Royland et al. 1992). Because of this, along with DNA and the overall number of cells, total myelin content will significantly decrease only if

someone is undernourished (Winick 1971, 1972). When a child is malnourished, their brain's myelin content is diminished (Winick 1969). Distinct regions of the central nervous system have different crucial times for cell differentiation in different species. Observations in humans corroborate animal studies, showing that the brain's development during early childhood (infant stage) is particularly vulnerable to the devastating impacts of starvation (malnutrition) (Winick 1975). So this chapter focuses on how the deficiency of different macro- or micronutrients of the diet hampers the brain development.

4.2 Various Macronutrients in the Brain Development

4.2.1 Role of Proteins and Brain Development

Behavioral repercussions might occur from aberrant development caused by protein deficiency. Brain growth, dendritic arborization, and cell maturation are all reduced by protein deficiency (Chertoff 2015). Furthermore, a low-protein prenatal diet alters the brain's neurotransmitter and oxidative state (Bonatto et al. 2005, 2006; Lieberman et al. 2005; Guest et al. 2012). Social and behavioral problems persist throughout adulthood as a result of the child's failure to grow normally. To understand the harmful effects of a low-protein diet on the brain, it is crucial to know the length and the point of commencement of dietary restriction. Many concerns remain unanswered about the long-term implications of prenatal starvation, even after decades of research. Brain and behavior development is influenced by both prenatal diet and postnatal environmental stimuli. When it comes to the CNS, these pre- and postnatal alterations can have a significant impact on the brain, especially hippocampus and hypothalamus. Study by Kehoe et al. (2001) revealed that in response to severe and persistent isolation stress, it was shown that starved 9-day-old pups weighed less, had reduced hypothalamus, and produced little corticosterone. Even so, their hypothalamic dopamine metabolism was elevated after 9 days of severe isolation. Additionally, study found that prenatal protein deficiency had a direct impact on the levels of serotonin, 5-hydroxyindoleaceticacid (5HIAA) in the hypothalamus, and dopamine in the hippocampus. 5HIAA levels in the brains of control pups were reduced after prolonged isolation. When these prenatal and postnatal stressors are combined, they may have an additive effect on the central nervous system's stress response and serotonergic activity in both the hypothalamus and hippocampus (Kehoe et al. 2001).

The research that was conducted by Tonkiss and Galler in 1990 demonstrated that prenatally starved adult animals do not always exhibit the classic symptoms of the "hippocampal syndrome" but showed enhanced resilience to the extinction of learned alternation responses.

Besides this, Feoli et al. (2006) investigated oxidative state, free radical content, indices of lipid damage, and protein damage in addition to overall oxidative stress

markers in various cerebral regions and revealed that protein deficiency markedly enhanced ROS production and thus increased oxidative damage.

Additionally, study conducted by Wang and Xu (2007) found a link between perinatal protein deficiency and reduced spatial navigation and BDNF levels in rats. Rats starved of protein may have less BDNF in their hippocampi, which could have an effect on their learning and memory.

Protein deficiency during the postnatal phase or during adulthood phase results in impaired learning, while hyperactivity, including greater emotional instability and greater responsiveness to stressful events (Rushmore et al. 2020). An altered dopaminergic system is most likely to blame for this hyperactive state (Alamy and Bengelloun 2012).

Thus, from the abovementioned studies, it is evident that protein deficiency can adversely affect brain development and can lead to various neurological complications (Morgane et al. 1993).

4.2.2 Role of Carbohydrates and Brain Development

Carbohydrates have recently become a hot topic in the field of brain development. Carbohydrates (carbs) are carbon-hydrogen-containing compounds found in the human body as well as many food items. Monosaccharide, disaccharides, and polysaccharides are all possible chemical forms (Berger et al. 2020).

Carbohydrates are the most abundant source of energy since they not only provide but also restore energy. They improve digestive health, heart health, and blood glucose levels when it comes to their involvement in physiology. Carbs are converted to glycogen, which serves as a source of energy for brain function. According to studies, our brain gets the greatest energy from the food. As per studies, our brain takes in most of the energy from carbohydrates itself (Murrey and Hsieh-Wilson 2008).

A requirement of healthy food is vital in the forefront of human brain development. Lactose, a carbohydrate found in milk, acts as a digestible carbohydrate during an infant's growth. Later on, extra sources of carbohydrates, such as starch and other dietary products, play an important role. Glucose is a kind of carbohydrate that exists in the body. Glucose serves as the apex of energy generation for maintaining basic brain function at any age. The studies that demonstrated a link between oligosaccharide concentrations and neurodevelopmental effects in the first 24 months are perhaps the most intriguing (Wahl et al. 2018).

Specific enzymes in the gut break down carbohydrate supplements before they are absorbed through sodium/glucose transporters. The mechanisms of glycolysis and the Krebs cycle are used in its glucose uptake. Pentose phosphate, as referred to by the HMP shunt pathway, is the first type of carbohydrate that initiates metabolism. The creation of ATP^{+}, NADH, and glycerophosphate is the outcome of these processes (Dienel 2019).

These by-products are the brain's primary source of energy. While it has been widely established that a paucity of carbohydrate is associated to neuromuscular fatigue and central fatigue syndrome, more research is needed. The relationship between sweets and cognition is somewhat complex, as optimal carbohydrate intake leads to improved memory, information processing, and attention. Overeating, on the other hand, contributes to obesity and can also boost blood glucose levels (Khong et al. 2017).

The effect of a single dosage of carbohydrate and its derivative on healthy people was investigated in a study by Wang et al. (2004). Glyconutrients were proven to improve alertness and attention at a dose of 0.5 g. Carbohydrates store 45–65% of total calories, according to dietary standards. According to the National Institute of Nutrition 2021 report, a good brain balance necessitates roughly 2000 calories each day. To that end, about 225–325 g of carbohydrate should be consumed on a regular basis.

The carbohydrate supplement dramatically increased power in three abnormal electrical frequencies (theta, alpha, and beta) known to be connected with attention and alertness when compared to placebo (Stephen et al. 2012).

Additional sugars in the glyconutritional supplement, according to a study, aid in the improvement of brain electrical activity. The interactions of sialic acid-containing glycosphingolipids known as gangliosides in myelin development and brain regeneration have been widely explored.

On the other hand, a well-known monosaccharide, fructose, plays a role in brain development. Studies also suggest that it regulates signaling by causing conformational changes. Fructose is abundant at neural synapses, and numerous studies on undertaking acquisition have suggested that fucosylation plays a role in memory and learning (Wang et al. 2004).

Glycocalyx contains gangliosides, which offer the variety of carbohydrate moieties required for cell development, cell–cell connections, and cell signaling. Increases in the proportions of GD1b, GM3, and GD3, as well as declines in the proportions of GM1 and GD1a, continue to affect the composition of brain gangliosides. The overall quantity of brain gangliosides declines dramatically with age (>70 years) (Schengrund 2015).

A spike in KD leads to a large number of ketone bodies in the brain, which causes oxidative stress and affects the prognosis of different neurodegenerative diseases. Maintaining calorie intake may have a neuroprotective effect on the brain, improving mitochondrial functioning, lowering ROS levels, and increasing energy output. However, the significance of carbohydrates in neuronal imbalances that contribute to seizures is yet unknown (Baquer et al. 1977).

According to a case report published in Clinical Application of Science Innovation in 2018, bipolar adolescents who were given an optimal low-carbohydrate high-lipid diet found mood stability. Glyco-nutritional supplements have been proven to be effective in a variety of clinical diseases, including those involving attention deficit hyperactivity disorder. The effects of nutrition and carbohydrates on restful cognitive function and nervous system in children and adults, however, are little understood.

Low attention, attentiveness, and mental activity are all symptoms of carbohydrate deficiency. Although there is little evidence of a link between depression and a low-sugar diet, its link with anxiety is striking. Low carbohydrate consumption in the diet causes behavior problems and hyperactivity in children, as well as uneasiness. The imbalance of hormones such as dopamine and serotonin can be seen as a result of low carbon-hydrogen chain levels. As a result, a variety of neurological problems develop (AD, PD, anxiety, autism). The malnutrition of carbs may alter the psychotic neuronal endings proceeding the chances of some psychic disorders like schizophrenia which is known for its altered cognition pattern. Repetitive and altering behavioral pattern is also linked with low-carbohydrate diet.

According to the Academy of Nutrition and Dieticians, consumption of at least 130 g of carbohydrate/day is valuable in optimum brain functioning. A rise or least than this may lead to CNS alteration. In the nutshell, the role of carbs is helpful in explaining various symptomatic neuropsychological disorders. An appropriate consumption of carbohydrate helps in maintaining as well as boosting the physiology of brain. On the contrary, malnutrition leads to inducing of brain-related disorders with remarkable symptoms.

4.2.3 Role of Fats and Brain Development

During prenatal and postnatal stages of life, fatty acids, especially n-3 long-chain polyunsaturated fatty acids, play a critical part in the development of central nervous system (Uauy and Dangour 2006). It is becoming more widely accepted that they can help prevent cognitive deterioration as we get older. n-3 and n-6 long-chain polyunsaturated fatty acids both play significant roles in neural development, formation of synapses between neural cells, and transcription of genes controlling cellular proliferation and development (Liu et al. 2010). It has been found out that newborns fed with docosahexaenoic acid exhibited considerable greater cognitive and sensorimotor performance compared to those given a diet low in essential fatty acids (Greiner et al. 1999; Janssen et al. 2015). Supplemental DHA appears to increase eyesight and psychological development by helping the retina and visual brain reach their full functional maturity potential (Grayson et al. 2014; Carlson et al. 2019). Fish eating has been linked to a reduced risk of dementia and Alzheimer's disease, as there has been evidence that daily utilization of fish-oil supplementation increased intellectual and emotional functional scores, although further confirmation is needed.

Long-chain polyunsaturated fatty acids (LCPUFAs) are generated from the linoleic and a-linolenic acids and are necessary for proper retinal and CNS development; however, it is unclear how much of these fatty acids can be generated from their parent fatty acids (Crawford 1993). In comparison to their parent fatty acids, LCPUFAs have a notable effect on the composition of the tissue lipids (Sanders 1999). Because of this, it is being suggested that LCPUFAs should be included in the diet. Because plant diets typically lack long-chain polyunsaturated fatty acids

(LCPUFAs), understanding how vegans meet their essential fatty acid (EFA) needs is critical. It is possible for a growing fetus to acquire LCPUFAs from the plasma of its mother through a process known as preferential absorption, and LCPUFAs can be found in the breast milk of vegan and vegetarian (Sanders 1999; Haggarty 2004; Lauritzen and Carlson 2011). Vegetarians' ability to manufacture LCPUFAs appears unrestricted. On the other hand, in comparison to omnivores, vegetarians have higher amounts of n-26 LCPUFAs and lower proportions of n-23 LCPUFAs in their bodies (Phillips 2005; Gould et al. 2013). It can be due to vegetarians' preference for foods high in linoleic acid (Phillips 2005). Docosahexaenoic acid concentrations in the blood and arterial phospholipids of vegan newborns have been found to be lower than those of omnivorous newborns, but it is not known whether this is also true of the brain phospholipids (Nettleton 1993; Hornstra 2000). When a-linolenic acid (18:3n23) was substantially depleted in the diets of mice and prosimians, the animals displayed abnormal ocular acuity and behavioral difficulties; this knowledge was critical for scientists preparing therapeutic studies (Crawford et al. 2022). Docosahexaenoic acid (22:6n23) and arachidonic acid (20:4n26) supplementation, on the other hand, has garnered a significant amount of interest in clinical research, in contrast to animal studies, which have primarily concentrated on 18:3n23 deficit.

It has been shown in animal experiments that 22:6n23 concentrations in the brain and retina reach a steady state when 18:3n23 intakes are less than 0.7% of total caloric intake; however, this need is affected by dietary 18:2n26 consumption (Arterburn et al. 2006; Calder 2014). When 22:6n23 consumption rises, so do blood and tissue levels, and this can have detrimental effects on growth and function at high doses.

The majority of human brain growth occurs within the first 2 years of life (Knickmeyer et al. 2008; Hedman et al. 2012). Maximum of the brain's cells divide throughout the first year of life (Johnson 2003; Courchesne et al. 2003). During fetal development and cell division, the long-chain derivatives of essential fatty acids are most active. After birth, the human brain's focus shifts fast to myelination (Clandinin 1999). When it comes to myelin fatty acids, the long-chain saturated and monounsaturated fatty acids like lignoceric and nervonic acids are more prevalent than in the cellular lipids (Dhopeshwarkar and Mead 1973; Jamieson 1998). For the development of the brain, cell membrane lipids are essential. During the last phase of the pregnancy and also in the first few weeks of postnatal life, brain tissue is rapidly synthesized. Among the complex lipids involved in the production of brain structure are chain-elongated desaturated homologs of important fatty acids.

All these studies and findings indicate that fatty acids are a very important component of the diet whose deficiency can have a devastating effect on the brain development and thus can lead to a variety of neurological complications (Igarashi et al. 2015).

4.3 Various Micronutrients in the Brain Development

4.3.1 Role of Vitamins and Brain Development

4.3.1.1 Vitamin B12

Vitamin B12 is enriched in the fetus throughout pregnancy and stored in the liver (Ball 1998; Ozougwu 2017). Deficiency in vitamin B12 is extremely uncommon in infants younger than roughly 4 months (Green et al. 2017). Between the ages of 6 and 12 months, infants who have moms who are deficient in vitamin B12 and who breastfeed, as well as newborns who consume insufficient amounts of foods derived from animals, are at risk of developing vitamin B12 insufficiency (Halicioglu et al. 2011; Bousselamti et al. 2018). The majority of the original findings addressing vitamin B12 deficiency in infancy come from case reports of babies who were exclusively breastfed by women who were fruitarian or consumed a diet of dairy products, eggs, vegetables, fruits, grains, and nuts (Melina et al. 2016). A number of publications have reported instances of development and cognitive impairment as well as the "infant tremor syndrome" in infants born to vegan women in India who were between 4 and 11 months old (Garewal et al. 1988; Black 2008). The treatment had a mixed effect on the recovery of cognitive skills, which has reported two patients with persistent delays in development and one patient with developmental restoration (Sklar 1986).

Within the first 2 years of a person's existence, brain development is extraordinarily rapid, especially in the cortex region, which is connected with cognitive thoughts and complex reasoning. Vitamin B12 deficiency may affect brain myelination, which is most active during the second year of life but continues into adolescence (Bourre 2006; Prado and Dewey 2014). Many studies have linked a lack of vitamin B12 in children to demyelination and brain shrinkage (Benton 2008; Glaser et al. 2015).

Brain development starts prenatally and develops till school age. It starts with brain cell formation, cell differentiation and migration, and development of synapses, which is important for cell communications. Myelin provides a supportive network to the nerve cell. Nutrient deficiency can cause problem for early development of brain. Previous study found that vitamin B12 concentration in plasma among school children affects the growth and development. It was clinically reported that deficiency of vitamin B12 in infants causes them to present with megaloblastic anemia having the symptoms of a neurological disorder (Stollhoff and Schulte 1987). Vitamin B12 plays a key role in cognitive functioning, neurotransmitter synthesis, and neuronal myelination (Venkatramanan et al. 2016).

4.3.1.2 Vitamin D

Vitamin D modulates many neurotrophic agents like nerve growth factor, which is important for growth and survival of cells in brain. Vitamin D regulates NGF. Hippocampus development is modulated by vitamin D, which increases NGF level (Neveu et al. 1994; Wion et al. 1991). Vitamin D enhances neurite outgrowth in the embryonic hippocampal cultures (Brown et al. 2003). Vitamin D affects cellular development in brain. Vitamin D provides protection against glutamate, which is an excitatory neurotransmitter (Ibi et al. 2001). Vitamin D increases antioxidant level like glutathione in non-neuronal cells (Garcion et al. 1998). Cytokine production is regulated by vitamin D in noninfected brain. Prenatal deficiency of vitamin D can cause schizophrenia (Davies et al. 2003). DVD deficiency shows alteration of function and structure of brain in rodents (Becker and Grecksch 2006).

4.3.2 Role of Minerals and Brain Development

There are 17 basic minerals that are required for the human body and must be supplied through diet or supplements. Deficiencies are common, especially in low- and middle-income nations, with small children and pregnant women bearing the brunt of the disease. Among various minerals, the most serious mineral deficits, in terms of public health, are due to iron, zinc, and iodine (Shankar 2020). Deficiency of Zn shows a depressant effect. Researchers discovered that patients with lower levels of zinc in their serum exhibit depressive behavior as compared to healthy people (Nowak and Schlegel-Zawadzka 1999). Maes reported that depression and impaired cognition function are the hallmarks of Zn deficiency.

Lower level of dopamine D2 receptor and impaired dopaminergic functions are seen in the iron deficiency lab animals (Weiser et al. 1994). In 18% of children and pregnant women, iron deficiency leads to anemia and decreased work capacity and causes cognition, whereas in 28% of people globally, iodine deficiency leads to four million DALYs for mortality in infant and brain damage. The most beneficial intervention is salt iodization. It was reported in the study that lower level of magnesium in patients has been reported with schizophrenia and depression as compared to the health controls (Kirov and Tsachev 1990). Some study examined that the adjuvant therapy of magnesium was effective in bipolar disorder. Heiden et al. (1999) reported administration of magnesium sulfate i.v. to mania patients. Rapid cycling bipolar disorder was treated with either magnesium compound or lithium for 32 weeks, and magnesium showed the equivalent effect as that of lithium in more than half of the patients (Chouinard et al. 1990). Iodine is one of the important components of thyroxine (T4) and triiodo-thyronine (T3), which is produced by the thyroid gland. It is also essential for the myelination and normal neuronal migration during the postnatal life (Rohner et al. 2014). Worldwide, one-third of children living in Southeast Asia, Africa, and the Western Pacific are

iodine deficient. Brain damage in children is the main result of iron deficiency. After birth, during brain development after 3 weeks of pregnancy, iodine deficiency can lead to thyroid failure and irreversible brain damage (Andersson et al. 2012). Deficiency of copper can be due to lower dietary intake and genetic abnormalities that can modify metabolism of copper. As that of zinc deficiency, copper deficiency is likely to be seen in embryonic stage. The feeding of a copper-deficient diet beginning in midgestation through lactation results in a diminished auditory startle response, which indicates persistent neurobehavioral abnormalities despite copper repletion (Prohaska and Hoffman 1996). From all the above studies, it is evident that various minerals play an essential role in the brain development and their deficiencies can lead to abnormal brain development, hampering normal functioning of the brain.

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Chapter 5
Nutrition, Neurotransmitters, and Behavior

Sumit Kumar, Tejesvi Mishra, Aradhana Prajapati, and Pranshul Sethi

Contents

Abstract We consume food not simply for energy, but also to produce neurotransmitters. Foods include naturally occurring chemicals that can have a substantial influence on the human neurological system. Learning about the significance of nutrition in brain development: The brain increases dramatically during the first 1000 days of life, increasing in size and specialization while losing its ability to adapt. The neurotransmitters acetylcholine (ACh), glutamate, and gamma-aminobutyric acid (GABA) are among them, as are the biogenic amines dopamine, serotonin (5-HT), and histamine. The increased use of dietary approaches into neuropsychiatric clinical practice necessitates a better knowledge of some of these

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dietary neurotransmitters (NTs). NTs have been discovered in animal food, fruits, edible plants, roots, and botanicals. These molecules can be found naturally as by-products of essential metabolic processes and ecological interactions, or they can be synthesized through regulated or uncontrolled food technology processes. These natural food products can benefit brain health, and adding them into daily life intake may result in a reduction in different neuropsychiatric and neurological dysfunctions such as Alzheimer's disease, Parkinson's disease, and depression.

Keywords Nutrition · Food products · Neurotransmitters · Brain health

5.1 Introduction

The formation of the human brain is a tremendously complicated process. The differentiation of neural progenitor cells starts in the third gestational week and lasts until late adolescence, if not the remainder of one's life (Joan and Terry 2010). By the conclusion of the embryonic phase, the major compartments of the central and peripheral nervous systems will have formed (eighth week postconception) (Joan and Terry 2010). Complex processes occur as soon as the external shape is formed. Important proliferative processes occur 2–4 months after conception: neurons and glia begin to develop and proliferate during this time. Glial proliferation occurs throughout the fifth month of pregnancy and the early postnatal period (Harris et al. 2012). Different brain areas must be linked together by progenitor cells that migrate from their initial places. This is most likely to occur during the third and fifth months of pregnancy (Harris et al. 2012). As soon as the cells arrive to their target region of the brain, they need to produce neural processes (dendritic and axonal ramifications) that allow them to interact via synaptic connections. These organizing actions are crucial for the development of the extraordinary circuitry that differentiates the human brain, beginning in the fifth month of pregnancy and lasting for many years after birth. Myelin, which encases the axons, significantly improves information transmission throughout the pathways. Human myelination is a time-consuming process that begins during the second trimester of pregnancy and continues throughout maturity (Joan and Terry 2010).

This is the most rapid period of growth in a person's life. When an organ's growth rate is faster than usual, it is more vulnerable to being injured by a lack of nutrients. Because of this, there is a substantial danger of harm to the developing brain. The brain is a multifaceted organ. Neurotransmitters, myelination, and other processes (such as those in the hippocampus, cortex, and striatum) all have discrete developmental trajectories and specific dietary needs (Sobel and Corriveau 2010). Many of these regions or systems begin and accelerate their development trajectories during fetal life or shortly after birth. A crucial phase and a sensitive period are two critical phases in any activity or place. The distinctions between the two periods are becoming increasingly blurred. As a general rule, they may be described as follows:

If an injury happens during this phase, it has long-term consequences that cannot be reversed; if it occurs later in life, it is more sensitive to environmental effects, such as vitamin and mineral insufficiency (Bornstein 1989; Colombo 1982). Because there are multiple critical times during development, the effects of dietary shortages on brain sensitivity are determined by two factors: the timing of a nutrient shortfall and the specific region's demand for certain nutrients at that time (Cusick and Georgieff 2016). If a brain area is not built at its key time, it might result in long-term effects such as structural deformities (Jorgenson et al. 2003), neurochemical and electrophysiological abnormalities, and altered gene expression (Tyagi et al. 2015; Zeisel 2017; Ly et al. 2016; Barks et al. 2018). Adequate dietary intake is essential for promoting timely cerebral growth and formation of a functionally integrated brain structure. The first link between inadequate nutrition and disease was established in a cohort study that examined the health of children born during a severe famine or whose mothers were pregnant during a severe famine, such as the Dutch Hunger Winter. Prenatal exposure to severe famine has been linked to an increased risk of coronary heart disease, atherogenic lipid profiles, blood coagulation issues, higher stress response, obesity, and glucose intolerance in adulthood (Roseboom et al. 2006). Neuropsychiatric conditions, such as schizophrenia and affective disorders, were found to have an increased risk (Susser and Lin 1992; Susser et al. 1996; Wang et al. 2016). In recent years, there has been a surge of interest in epigenetics. According to a novel concept, epigenetic changes generated by early-life environmental risk factors such as insufficient or improper nutrition may explain some of these unfavorable health outcomes. Evidence suggests that early hunger alters the DNA and has long-term health consequences. Over the course of a person's life, a number of epigenetic processes, such as DNA methylation, histone modifications, and noncoding microRNAs, alter gene expression levels and timing (Canani et al. 2011). Prenatal stress (including starvation) has been shown to cause long-lasting epigenetic changes in the brain, which have been connected to alterations in brain gene expression, stress reactivity, and behavior (Kundakovic and Jaric 2017), according to several animal studies.

During pregnancy, extra macronutrients and micronutrients are required. A well-balanced nutritional diet is critical for preventing harmful health consequences for the growing fetus. According to the 2014 Italian RDA, pregnancy-related calorie needs rise by 69 kcal/day during the first trimester, 266 kcal/day during the second trimester, and 496 kcal/day during the third trimester (for a grand total of an additional 76,530 kcal). According to the European Food Safety Authority, very similar amounts (70 kcal/day in the first trimester to 260 and 500 kcal/day in the second and third trimesters, respectively) have been established, with an increase of approximately 500 kcal/day during the first 6 months of exclusive breastfeeding (Marangoni et al. 2016). The scope of this chapter does not allow for a comprehensive explanation of macronutrient needs in humans. Those who are deficient in micronutrients will find the following sections particularly interesting.

5.2 Role of Some Basic Nutrients

5.2.1 Vitamins

Vitamins are fat-or water-soluble organic molecules that are necessary for normal physiological function. As coenzymes, vitamins participate in a variety of catabolic and anabolic enzymatic actions. Energy generation, DNA/RNA synthesis/repair, and neurochemical synthesis are all affected by vitamin deficiencies. B vitamins are involved in the synthesis of numerous neurotransmitters such as GABA, glutamate, acetylcholine, and catecholamines as cofactors, according to research (Kennedy et al. 2006). In the citric acid cycle, vitamins B1, B3, and B6 are used as coenzymes by NAD+ and CoA to convert pyruvate to A-CoA. The parasympathetic neurotransmitter acetylcholine requires A-CoA for its production (Mikkelsen et al. 2016). A-CoA also produces citrate with the help of coenzyme B2, which is then catabolized into alpha-ketoglutarate in several intermediary steps (Ragsdale and Pierce 2008). GABA and glutamate, two more key CNS neurotransmitters, are synthesized from alpha-ketoglutarate as a precursor (Peng et al. 1993). Another enzyme that uses vitamin B6 as a coenzyme in the production of catecholamines including dopamine, noradrenaline, and adrenaline is dopamine decarboxylase (Lovell 1963). Another neurotransmitter derived from the amino acid tryptophan is serotonin. In the manufacture of serotonin, the tryptophan hydroxylase used vitamin C and B6 as coenzymes. As a result, we can conclude that vitamins are important biological chemicals that regulate a variety of physiological functions (Parra et al. 2018; Varderand Fekkes 2008). The correct functioning of the central nervous system requires vitamin D. Vitamin D may act as a neurosteroid hormone in neurotransmission, neuroprotection, and neuroimmunomodulation throughout brain development (Annweiler et al. 2010). Vitamin B12 is essential for DNA synthesis, brain development, neural myelination, and cognitive function (Venkatramanan et al. 2016) (Table 5.1).

5.2.2 Minerals

Minerals (selenium, magnesium, sodium, copper, and manganese) are inorganic macronutrients that occur naturally. The appropriate physiological function of the central nervous system requires enough of these macronutrients (Soetan et al. 2010). Iron is a macronutrient that is necessary to produce neurotransmitters like dopamine, noradrenaline, adrenaline, and serotonin. For the manufacture of neurotransmitters, iron-dependent enzymes such as tyrosine hydroxylase, tryptophan hydroxylase, and phenylalanine hydroxylase are required (Gottschall et al. 1982; Ramsey et al. 1996; Kuhn et al. 1980). Another important element involved in neurotransmitter release is calcium. During exocytosis of neurotransmitter-bound vesicles, calcium is necessary to generate an action potential, which causes neurotransmitter to be released into the

Table 5.1 Involvement of nutrients in various neurological dysfunctions

Vitamin	Disorder	Dose/duration/patient populations	Key findings	Reference
Vitamin A	Multiple sclerosis	25,000 IU/day for 6 months, 10,000 IU/day for another 6 months; 101 patients (77 women, 24 men)	Enhances TH2 cytokine production ↓TH1 cytokine production ↑IL-4 production in antigen-primed CD4T cells	Mohammadzadeh Honarvar et al. (2013)
Folic acid Vitamin B12 Vitamin B6	Alzheimer's disease	800 μg FA, 500 μg vitamin B12, 20 mg vitamin B6 2 years; 156 patients	B vitamin treatment reduced grey matter atrophy in regions associated with AD	Douaud et al. (2013)
Folic acid Vitamin B12 Vitamin E	Alzheimer's disease	400 μg folic acid 6 μg Vitamin B12 30 IU Vitamin E 40 mg S-adenosyl methionine 600 mg N-acetyl cysteine 500 mg acetyl-L-carnitine For 3 months; 106 patients	Improves cognitive function	Remington et al. (2015)
Vitamin B12	Autism	75 μg/kg Methyl B12, s.c. once every 3 days; 8 weeks 50 patients	Led to improvements in clinician-rated symptoms of autism Improvements in transmethylation metabolism	Hendren et al. (2016)
Folic acid Vitamin B12	Cognition impairment	100 μg vitamin B12 + 400 μg folic acid, p.o.; 24 months; 900 patients	Improvement in cognitive functioning after 24 months, particularly in immediate and delayed memory performance	Walker et al. (2012)

synaptic cleft (Südhof 2012). Furthermore, a low intracellular Mg/Ca ratio increases catecholamine release under stress. Mg also inhibits excitatory neurotransmitters and calcium entry via voltage-gated channels, affecting many neurotransmitter systems (Cuciureanu and Vink 2011). Furthermore, several neurotransmitters including GABA, glycine, and acetylcholine require sodium and chloride ions to activate channels (Aprison et al. 1996; Breitinger and Becker 2002). The enzyme tyrosine hydroxylase requires manganese as a cofactor in the production of catecholamines (Berresheim and Kuhn 1994) (Table 5.2).

Table 5.2 Involvement of macro- and micronutrients that play an important role in the brain development

Nutrients	Normal intake (mean value)	Role in brain development	References	Deficiency complications	References
Iron (mg/day)	**Infant:** 11 **Toddler-adolescent:** Male: 13 Female: 18 **Adults:** Male: 10 Females: 18	Normal anatomic brain development, myelination, neurotransmission	Greminger et al. (2014); Carlson et al. (2009); Lozoff et al. (2006); Tran et al. (2015); Christian et al. (2010)	Neurocognitive and behavioral disorders Altered hippocampal DNA methylation and gene regulation Adult hippocampal transcriptome	Georgieff (2011); Schachtschneider et al. (2016); Barks et al. (2018)
Zinc (mg/day)	**Infant:** 3 **Toddler-adolescent:** Male: 12 Female: 9 **Adults:** Male: 12 Females: 9	Neurogenesis, neuronal migration, synaptic genesis, myelination, modulation of intra- and intercellular signaling (GABAergic neurons)	Sandstead (1991); Sandstead (1985)	Sensorimotor and cognitive impairment; compromised memory functioning; autism spectrum disorder Attention deficit hyperactivity disorder	Black (1998); Fuglestad et al. (2016); Pfaender and Grabrucker (2014); Yasuda and Tsutsui (2013); Elbaz et al. (2017)
Iodine (μg/day)	**Infant:** 70–130 **Toddler-adolescent:** Male: 130 Female: 130 **Adults:** Male: 150 Females: 150	Neurodevelopment, dendritic and axonal growth, synaptic function, histogenesis, and cerebral cortex cytoarchitecture	Moog et al. (2017); Mohan et al. (2012)	Neurological damage; hypothyroxinemia; disrupted neocortical layering; cognitive deficits and poor psychomotor development	Pharoah et al. (2012); Thilly et al. (1978); Furnica et al. (2015); Min et al. (2016); Lavado-Autric et al. (2003)

5.2.3 *Trace Elements*

Inorganic chemicals present naturally in humans that are necessary in trace amounts are known as trace elements. Cobalt (Co) is an important component of cobalamin, a trace element that is necessary for human health (the scientific name of vitamin B12). It is also involved in amino acid and neurotransmitter production. Glutathione peroxidase and thioredoxin reductase are antioxidant enzymes that include selenium (Se) (Al-Fartusie and Mohssan 2017). Copper (Cu) appears to be involved in several important physiological functions in the body, including immune function, bone health, and hemostasis. Etiology of several degenerative illnesses may be linked to long-term marginal Cu deficiency. Copper can act as an antioxidant as well as a prooxidant. Cu scavenges or neutralizes free radicals as an antioxidant, potentially lowering or eliminating part of the damage they cause (Bonham et al. 2002). Zinc (Zn) is a mineral that is extremely vital for human nutrition. Zinc is essential for the structure and function of over 300 enzymatic activities, as well as for the structure and function of a wide spectrum of macromolecules (Tapiero and Tew 2003). The word "chromium" comes from the Greek word "chrome," which means "color." The full name of chromium is chromium acetylacetonate, which was first recognized as PbCro4 (Atkin's and Shriver 1999). The deficiency impairs glucose tolerance, whereas intoxication causes renal failure, dermatitis, and pulmonary carcinoma (Cefalu and Hu 2004). Iron is a nutrient that is required for the brain's ATP production. As a component of hemoglobin, it keeps the brain's oxygen levels stable. Iron is necessary to produce neurotransmitters like dopamine and serotonin. It is also engaged in a few metabolic pathways (Anderson and Erikson 2011).

5.3 Link Between Nutrition, Neurotransmitters, and Brain Functions

5.3.1 *GABA*

Gamma-aminobutyric acid (GABA) is a primary inhibitory NT found widely in plants, where it is predominantly produced from glutamic acid using the glutamate decarboxylase enzyme. Drought, presence of salt, wounds, hypoxia, infection, soaking, and germination have all been shown to raise GABA levels in response to biotic and abiotic stressors (Gan et al. 2017). Its prominent actions are restricted to not only induction of sleep but also reducing mental stress and anxiety (Jembrek and Vlainic 2015). GABAergic neurotransmitters are found in the hippocampus, thalamus, hypothalamus, basal ganglia, and brain stem, but they are most plentiful in the nigrostriatal area (Frangaj and Fan 2018). A higher level of GABA in the brain is linked to better sleep and reduced anxiety-related agitation. Complications such as schizophrenia and depression are associated with a decrease in GABA levels (Wisden et al. 2019). Many biological activities in the brain, such as cognition,

learning, emotions, movement, circadian rhythms, and sleep, have been researched using this inhibitory neurotransmitter (Ebert et al. 1997). GABA also plays a part in cellular processes such as differentiation, proliferation, migration, axonal growth, synapse formation, and neuron death. In particular, sprouts of *Lupinus angustifolius* L. (lupin) (Villaluenga et al. 2006; Briguglio et al. 2018), *Vigna angularis* W. (adzuki bean) (Li et al. 2011), and other germinating edible beans, such as *Glycine max* L. (soya bean) (Xu and Hu 2014), common bean, and pea (Kuo et al. 2004), were reported to increase GABA content when compared to their raw beans. Furthermore, grains of the Gramineae family, such as *Avena nuda* L. (oat) (Xu et al. 2010), *Triticum aestivum* L. (wheat) (Hung et al. 2015), and *Hordeum vulgare* L. (barley) (Oh et al. 2003), and many species of the Oryza genus (for example, white, black, brown, and red rice) (Gan et al. 2017) can also significantly accumulate GABA. Sprouts of *Fagopyrum esculentum* M. (buckwheat) (Lin et al. 2008) and fruits of tomato also contain a substantial amount of this amino acid during the mature green stage (Akihiro et al. 2008).

GABA is an antianxiety, anti-analgesic, and antihypertensive neurotransmitter. Microbial fermentation, enzymatic or whole-cell biocatalysis (for example, GABA soya yoghurt) (Park and Oh 2007), black raspberry juice (Kim et al. 2009), and chemical synthesis are all used to make GABA (Steenbergen et al. 2015). According to some studies, raw spinach has the greatest GABA level, at 414 nmol/g dry weight, followed by *Solanum tuberosum* L. (potato), *Ipomoea batatas* L. (sweet potato), and *Brassica oleracea* L. (cruciferous such as kale and broccoli). GABA was also discovered in mushrooms like *Lentinula edodes* B. (shiitake) and Castanea species nuts (chestnut) (Oh et al. 2003). White tea had the greatest level of caffeine among the many types of Chinese teas (Zhao et al. 2011). GABA is found in mistletoe, *Phytolacca americana* L. (pokeroot) (Funayama and Hikino 1979), *Valeriana officinalis* L. (valerian), *Angelica archangelica* L. (wild celery), *Hypericum perforatum* L. (St. John's wort), and *Hieracium pilosella* L. (mouse-ear hawkweed) (cruciferous such as kale and broccoli). GABA was also discovered in *Lentinula edodes* B. (shiitake) mushrooms and Castanea species (chestnut) nuts (Oh et al. 2003). Mistletoe contains GABA (Sainte 1981), as well as *Phytolacca americana* L. (pokeroot) (Funayama and Hikino 1979), *Valeriana officinalis* L. (valerian), *Angelica archangelica* L. (wild celery), *Hypericum perforatum* L. (S.t John's wort), and *Hieracium pilosella* L. (mouse-ear hawkweed), used in the treatment of mental stress and as a sleep aid.

5.3.2 Serotonin: 5HT

Serotonin is a neurotransmitter that has a wide range of presence throughout the body, earning it the moniker "larger abundant family of neurotransmitters." Serotonergic neurons are primarily found near the brain stem's midline raphe nuclei and project to the cortex, cerebellum, and spinal cord. It can also be found in enterochromaffin (90%), platelets, and brain tissue (10%) (David and Gardier 2016). In the

central nervous system, serotonin 5-HT pathways impact behavior, appetite, and sleep, and in the stomach, they govern gastrointestinal motility. Various food items, such as potato, kiwi, coffee, green onion, and wild rice, ingest it in the form of tryptophan in the body (Briguglio et al. 2018). It has seven categories 5-HT1, 5-HT2, HT3, 5-HT4, 5-HT5, 5-HT6, and 5-HT7, in which 6-HT6 and 5-HT7 are not yet defined for clinical use. It helps with schizophrenia, nausea stimulation, temperature regulation, and eating disorders. In the pineal gland, it is a precursor of melatonin (Prasad et al. 2019). A high level of serotonin induces muscle rigidity, fever, and convulsions, whereas a low level causes depression symptoms (Barnes et al. 2021). According to research, this hormone may also play a role in the hypothalamus control of pituitary hormone secretion.

Melatonin, which promotes late vegetative growth in many tissue sections, has substantially aided a number of studies on the quantity of 5-HT in plants in recent years (Huang and Mazza 2011). Green Musa genus fruits (such as the prata banana and other species) contained high levels of 5-HT, ranging from 7100 to 21,000 ng/g of fresh weight, with a significant drop during ripening (Adão and Glória 2005). Banana peels contained more potassium than banana pulp (Udenfriend et al. 1959). *Capsicum annuum* L. (pepper) and paprika both showed 5-HT buildup (Kang and Back 2006) (Ly et al. 2008). 5-HT has been discovered in hazelnut *Corylus avellana* L., tomato fruits, and cherry tomatoes (Ly et al. 2008) (Foy and Parratt 1961). It has also been seen in the fruits of the Actinidia genus (kiwi), *Prunus domestica* L. (plum) (Udenfriend et al. 1959), *Passiflora edulis* S. (passion fruit), *Carica papaya* L. (pawpaw) (Council 1973), and *Prunus domestica* L. (plum) (Udenfriend et al. 1959). (Feldman and Lee 1985). Like dopamine, 5-HT was identified in the velvet bean (Bowden et al. 1954). The researchers discovered 34,400 ng/g dry weight in spinach (Ly et al. 2008). 5-HT was also discovered in *Brassica rapa* L. (Chinese cabbage), potato leaves (Engstrom et al. 1992), rice plant, and *Oryza sativa* L. (wild rice) seeds (Ly et al. 2008) (Kang et al. 2007). This NT was detected in green coffee beans, as well as coffee granules, due to its high roasting resistance (Ramakrishna et al. 2012). It is also found in fruits of *Punica granatum* L., Fragaria genus (strawberry), *Cichorium intybus* L. (chicory), *Allium ascalonicum* L. (green onion), and *Lactuca sativa* L. (lettuce) (Badria 2002) (Udenfriend et al. 1959). Plants like nettle (Collier and Chesher 1956) and *Griffonia simplicifolia* DC have been found to contain 5-HT. Griffonia was advertised as having anxiolytic qualities, which were later connected to the existence of 5-hydroxy-L-tryptophan, a direct precursor to the formation of serotonin (Carnevale et al. 2011).

5.3.3 Dopamine

Dopamine is produced by removing a carboxyl group from a molecule of the precursor chemical L-DOPA, which is produced in the brain and kidneys (Patrick et al. 2015). Parkinson's disease is a neurodegenerative ailment characterized by a significant decline in dopamine concentration in the basal ganglia (Volkow et al.

2009). On the other side, schizophrenia is caused by overactivity in the mesolimbic-mesocortical-mesofrontal circuit. Dopamine receptors D1, D2, D3, D4, and D5 have been found (Miller 2020). D1 and D5 activation stimulates adenylyl cyclase and increases cAMP release, whereas D2, D3, and D4 activation inhibits adenylyl cyclase and decreases cAMP release. According to studies, a high level of dopamine causes attention deficit hyperactivity disorder (ADHD), binge eating, and addiction-like symptoms in people (Wolfram et al. 2007). Dopamine levels in Musa genus fruits such as bananas and plantains, as well as *Persea americana* M. species (avocado), have been discovered to be high (Feldman et al. 1987). The banana peel (700 g/g), banana pulp (8 g/g), and avocado (4–5 g/g), to name a few, all contain dopamine. In plants, dopamine is involved in reproductive organogenesis, ion permeability (Odjakova and Hadjiivanova 1997; Briguglio et al. 2018), antioxidant activity (Kanazawa and Sakakibara 2000), and synthesis of alkaloids (Kanazawa and Sakakibara 2000) (Kanazawa and Sakakibara 2000) (Udenfriend et al. 1959). The leaves of *Mucuna pruriens* L. (velvet bean) have been found to contain dopamine (Wichers et al. 1993), implying that they may be involved in the seeds' well-known anti-parkinsonian qualities (Cassani et al. 2016). Tomato, aubergine, *Citrus sinensis* L. (orange), *Malus sylvestris* L. (forest apple), spinach, pea, and the common bean all had low levels (Feldman et al. 1987).

5.3.4 Glutamate

In the central nervous system, glutamate is the most important excitatory amino acid neurotransmitter. In synaptic terminals, glutamine is the most prevalent glutamate precursor. It is also known as glutamic acid, and it is one of the body's most prevalent amino acids (Meldrum 2000). Glial cells release glutamine, which is metabolized to glutamate at presynaptic terminals by the mitochondrial enzyme glutaminase (Magistretti 2009). Glutamate is a nonessential amino acid that is the most important excitatory neurotransmitter in the brain. Almost all foods include glutamate and glutamic acid. It is also involved in the creation of cell energy and protein synthesis. Excessive levels, on the other hand, cause neurological and mental illness (Pinheiro and Mulle 2008). Glutamate is beneficial to cognitive function, memory, learning, and other aspects of the brain. Excess glutamate in the brain, on the other hand, could be a risk factor for brain disease and cognitive decline (Brosnan and Brosnan 2013). Excess levels of the glutamate receptor mGluR5 have been linked to epilepsy in studies. Changes in glutamate energy production, on the other hand, have been linked to depression (Onaolapo and Onaolapo 2020). Glutamic acid builds up in nerve cells, causing amyotrophic lateral sclerosis, a degenerative and devastating disease.

In Alzheimer's disease patients, disruptions in glutamate transmission in the brain have been related to memory and learning loss (Tzingounis and Wadiche 2007). Glutamate is found in a wide range of foods. Glutamic acid in the food is converted to glutamate, an anionic form, at pH 7. Glutamic acid is naturally found in

high-protein foods such as stews, soups, meats, shellfish, and sauces (Rangan and Barceloux 2009). Free glutamic acid was found in substantial amounts in seaweeds, soy sauces, fermented beans, cheeses, fish sauces, and *Solanum lycopersicum* L. (tomato) (Jinap and Hajeb 2010; Briguglio et al. 2018). This amino acid can be found in dried fish, cracklings, salami, caviar, and instant coffee powder. Potassium, calcium, sodium, and magnesium are all glutamic acid salts that can be employed to enhance the flavor of foods or sauces (Zhang et al. 2017). In the stomach, monosodium glutamate and other glutamate salts break down, producing free glutamate. Monosodium glutamate and glutamic acid can be found in a variety of foods, including fish sauces, oyster sauce, Parmesan cheese, tomato sauce, gravies, miso, noodle dishes, savory snacks, chips, and ready-to-eat meals, as well as mushrooms and spinach (Skypala et al. 2015).

5.3.5 Acetylcholine

Acetylcholine is one of the most widely used neurotransmitters. It can be found in abundance in the central nervous system and on the end plates of neuromuscular muscles, where it aids the visceral motor system (Tsetlin 2020). Choline is a precursor to acetylcholine. Choline was recognized as an essential vitamin by the Institute of Medicine in 1998 (Food and Nutrition Board, Institute of Medicine 1998). Acetylcholine production, phospholipid signaling, lipid transport (lipoproteins), and methyl group metabolism are all dependent on it (homocysteine reduction). Choline intake should be 425 mg/day for women, 450 mg/day for pregnant women, 550 mg/day for breastfeeding mothers, and 550 mg/day for men (Food and Nutrition Board, Institute of Medicine 1998). Bitter orange, steak, spinach, and squash are all high in this useful neurotransmitter (Briguglio et al. 2018). More than 40 plant species are found, representing all major taxonomic groupings and the three most commercially important plant families: Gramineae, Leguminosae, and Solanaceae (Odjakova and Hadjiivanova 1997). *Cucurbita pepo* L. (squash), *Solanum melongena* L. (aubergine), and *Spinacia oleracea* L. (spinach) extracts all had a significant level of ACh (Hartmann and Kilbinger 1974). ACh was discovered in the seeds of *Pisum sativum* L. (pea), *Phaseolus radiatus* L. (mung beans), and *Phaseolus vulgaris* L. (common bean), implying that it is involved in seed germination (Odjakova and Hadjiivanova 1997). *Fragaria vesca* L. (a wild strawberry) (Fryer et al. 2012), bitter orange (*Citrus aurantium* L.), and radish (*Raphanus raphanistrum* subspecies sativus L.) (Wessler et al. 2001) were discovered to contain Ach. *Urtica dioica* L. (0.5 mol/g dry weight of roots) (Fryer et al. 2012) and *Urtica urens* L. (Wessler et al. 1998), whose folium and mistletoe (*Viscum album* L.) and foxglove (*Digitalis purpurea* L.) are two other plants that contain a lot of ACh (Odjakova and Hadjiivanova 1997). Acetylcholine primarily exerts its effects through binding to muscarinic and nicotinic receptors. Acetylcholine is known to boost motivation, arousal, attention, learning, and memory in the central nervous system (Marina et al. 2012). Increased salivation, lacrimation, muscle weakness,

paralysis, and other symptoms are associated with a high acetylcholine level. On the contrary, low levels have been associated to a variety of brain illnesses, including dementia and Alzheimer's disease (Jillian Kubala 2020).

5.3.6 Glycine

The inhibitory neurotransmitter is glycine. It binds to multiple kinds of ionotropic and metabotropic receptors as a neurotransmitter, but its primary inhibitory effect appears to be the result of regulating chloride channels in a similar way to GABA (Hernandes and Troncone 2009). The spinal cord is the primary site of these effects. The glycine neurotransmitter is abundant in red meat, seeds such as sesame, pumpkin, poultry, and peanuts (Briguglio et al. 2018). Glycine's effects in the brain are less predictable. Glycine function enhancement may have consequences similar to GABAergic neurotransmission enhancement (fatigue, drowsiness, etc.) (López-Corcuera et al. 2001). Supplementing with glycine, however, may result in excitatory effects since glycine appears to have various effects in different areas of the brain. Overdosing on glycine, for example, can result in death due to the brain's hyperexcitability (Aubrey 2016). Many structural analyses have revealed that its receptors (and subunit) are related to the $GABA_A$ receptor and are linked to the Cl-ion channel (Nikandrov and Balashevich 2014) (Table 5.3).

5.4 Conclusion

Nutrition has an impact on the synthesis, production, and release of neurotransmitters that govern brain health. Any vitamin shortage might cause central nervous system physiological problems. Trace elements are required for normal brain health and growth. Deficiency in trace elements can lead to a few neurological and neurodegenerative diseases. Minerals like sodium and chloride are needed to open the channels of certain neurotransmitters including glycine, GABA, Ach, and others. GABA levels have been observed to rise in foods such as lupin, adzuki bean, soya bean, oat, wheat, rice, and pea, suggesting that it may be favorable for brain health by functioning as an antianxiety and anti-analgesic agent. Vitamins have been discovered to play a crucial function in the synthesis of several neurotransmitters in diverse studies. Plums, pineapples, coffee powders, pomegranates, strawberries, and green onions are high in 5-HT, a neurotransmitter that has anxiolytic characteristics and aids in behavior, eating, and sleep control. Avocado, banana peel, banana pulp, and velvet bean, among other natural sources, contain dopamine, a neurotransmitter. Its anti-parkinsonian benefits may be linked to its antioxidant qualities. Glutamate is found naturally in high-protein foods such as stews, soups, meats, shellfish, and sauces. Glutamate is found in a variety of foods, including seaweed, soy sauces,

Table 5.3 Involvement of nutrition, in maintaining balance of neurotransmitters with their physiological role

Name of neurotransmitters	Location	Food source	Normal levels	Physiological roles	Reference
GABA	Hippocampus, thalamus, basal ganglia, hypothalamus, and brain stem	• Shellfish • Beans, lentils • Sprouted grains • Potatoes • Tomatoes • Seaweed • Berries	100–130 pM/mL	Reduces neuronal excitability by inhibiting nerve transmission	Jembrek and Vlainic (2015)
Serotonin	Digestive system Blood platelets CNS	Potato Kiwi Coffee Velvet bean Strawberry Wild rice Green onion	0.28–1.14 μM/L	Regulates mood, emotions, appetite, and digestion	James Mclntosh (2020)
Dopamine	Substantia nigra, ventral tegmental area, and hypothalamus	Aubergine, avocado, banana, common bean, apple, orange, pea, plantain, spinach, tomato, velvet bean	~195.8 pM/L	Regulation of motor functions, non-motor functions such as motivation, cognition, emotion, and neuroendocrine secretion	Miller (2020)
Glutamate	Brain and spinal cord in neurons and glial cells	Meats, seafood, stews, soups, and sauces Seaweeds, cheeses, fish sauces, soy sauces, fermented beans	40–60 μM/L	Fundamental brain functioning including learning and memory Formation of neuronal networks during development of brain	Peter Jenner and Carla Caccia (2019); Bai et al. (2017)
Acetylcholine	Vesicles at the ends of cholinergic neurons Surface of muscle	Pea Beans Bitter orange Radish Spinach Squash	~0.5 μM/L	Pain perception, locomotion, salivation, thermoregulation, and regulation of circadian cycle	Tsetlin (2020)

(continued)

Table 5.3 (continued)

Name of neurotransmitters	Location	Food source	Normal levels	Physiological roles	Reference
Glycine	Brain stem and spinal cord	Red meat, sesame, pumpkin seeds, peanuts, and granola	0.9–4.16 μM/L	Contributes for motor and sensory information in brain (movement, vision, and audition)	Corcuera et al. (2001); Aubrey (2016)

fermented beans, cheeses, fish sauces, and tomatoes. Glutamate is required for learning and creation of neural networks.

Squash, aubergine, spinach, pea, mung beans, bitter orange, and radish have all been shown to have Ach. Pain perception, movement, salivation, thermoregulation, and circadian cycle are all coordinated by Ach. Glycine is present in red meat, sesame seeds, pumpkin seeds, peanuts, and granola, and it helps the brain interpret motor and sensory information, especially vision and audition. Lack of sufficient nutrition can result in neurotransmitter depletion, which can lead to neurological disorders such as Alzheimer's, depression, multiple sclerosis, and Parkinson's disease, all of which can be eliminated by incorporating these natural food components in our dietary.

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Chapter 6
OMICS in Schizophrenia and Alzheimer's Disease

Aradhana Prajapati, Tejesvi Mishra, Sumit Kumar, and Pranshul Sethi

Contents

Abstract Proteomics and metabolomics are two distinct fields that have the potential to shed insight on the molecular pathways that lead to neurodegenerative disorders. Specific metabolites and proteins that can be targeted by therapeutic interventions aimed at slowing or reversing neurological processes that may be discovered and quantified as a result of this research. The goal of this study is to give a broad overview of the present state of proteome and metabolomic profiling in neurodegenerative and neuropsychiatric illnesses. The most common neuropsychiatric and neurodegenerative illnesses, such as schizophrenia and Alzheimer's disease, are the focus of our research. The importance of cutting-edge metabolomics and proteomics methods, as well as their potential for biomarker development, is discussed. A good biomarker should be present in the bloodstream before the diagnosis is made, have high sensitivity and specificity, and be repeatable. Finally, we examine the progress gained thus far, emphasizing how metabolomics and proteomics may play a key role in future therapeutic and biomarker development.

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6.1 Introduction

Since its introduction in the late 1990s, proteomics has been considered a high-throughput research technique that may be used to generate hypotheses (Wilkins et al. 1996). Proteomics is similar to transcriptomics in that it evaluates global mRNA. To better understand the biology of brain disease, the area of clinical neuroproteomics is a branch of proteomics that focuses on the identification of biomarkers for disorders of the central nervous system (CNS) or therapeutic responses. Protein-protein interactions, organization, and networks are some of the other focuses of the neuroproteomics field, while others focus on the characterization and description of whole proteomes in the central nervous system. In addition to the role of autoantibodies in illness (Robinson et al. 2002) and serum proteomic work concentrating on prediagnostic lung and early-stage ovarian cancer indications, other clinical proteomic research has given therapeutically useful discoveries (Qiu et al. 2008; Jackson et al. 2007; Zhang et al. 2004). Clinical neuroproteomics research has mostly focused on neurodegenerative illnesses like Alzheimer's and Parkinson's (Song et al. 2009). One study explores the use of high-throughput approaches in the development of biomarkers for schizophrenia (Kurian et al. 2009). Protein accumulation, mislocalization, posttranslational alteration like phosphorylation, ubiquitination, oxidation, nitrosylation, or multimerization, which can cause neurodegeneration via processes that are currently unclear, are now well recognized as causes of protein toxicity (Ruz et al. 2020; Chung et al. 2018). Inflammation and cell death are just a few of the unfortunate side effects of these alterations. For designing disease-modifying medicines and reliable diagnostic techniques, we need to understand the structure and function of each protein in our proteome, as well as the complexity of protein-protein interactions. Our proteome may currently be screened using spectroscopy and protein microarrays, two modern technologies. Proteomic studies in the context of neurodegenerative diseases are on the rise.

Analyzing biological specimens for their metabolic signatures can provide valuable information about their health state in the context of precision medicine. In the past, metabolites have been used to diagnose both complicated metabolic illnesses and inborn metabolic anomalies (Clish 2015). Clinical chemistry lab findings typically establish metabolite concentrations as "proximal reporters of illness" by correlating them with pathogenic processes (Gerszten and Wang 2008). In contrast to genomics and proteomics, metabolomics has an analytical challenge since it attempts to measure molecules with various physical characteristics (e.g., ranging from water-soluble organic acids to very nonpolar lipids) (Kuehnbaum and Britz-McKibbin 2013). If you divide down the metabolome into smaller subsets, such as those with comparable functional groups and structural similarities, you may also

construct suitable sample preparation and analytical techniques for each subset. The metabolome reflects the relationship between the genome and the environment. A metabolomic connection between genetics and environment can impact clinical outcomes and pharmaceutical responses (Walker et al. 2019). Neurodegenerative Diseases Across the Spectrum: Metabolites and Proteins. Research investigations utilizing green, red, and blue circles have linked amyotrophic lateral sclerosis, Parkinson's, and Alzheimer's disease etiology. There are a variety of xenobiotics and medicines that are not ordinarily produced by an organism, including toxins in the environment, food additives, poisons, and a variety of additional xenobiotics (Wishart 2007). Fast metabolite screening is now possible using high-resolution methods such as nuclear magnetic resonance spectroscopy and mass spectrometry (Emwas 2015). HMDB, urine metabolome (https://urinemetabolome.ca/), cerebrospinal fluid metabolome (https://csfmetabolome.ca/), and serum methylome (https://csfmetabolome.ca/) are just a few examples of the many metabolome databases that have been made possible by these new technologies.

Modern living is characterized by high levels of stress and bad dietary habits. Both stress and inadequate nutrition can affect the brain's function, but the connection between the two is not fully known (Simopoulos 2009; Hammen 2005; Li et al. 2017). This study raises the question of how stress sensitivity in the brain is affected by a poor dietary regimen. The study's major focus is on the susceptibility to stress, which can lead to neuropsychiatric and neurological illnesses when consumed regularly in a Western diet (WD). Environmental risks are governed by an animal's ability to handle stress (Selye 1936, 1956). Depending on how well animals can cope with external dangers or stresses, stress may be either beneficial (eustress) or harmful (distress) (Tafet and Bernardini 2003; Herman et al. 2003). Both eustress and distress can be acute and persistent at the same time. Depression and other mental health issues are not caused by stress, although it is a significant risk factor. Cereal and cereal products, fruits and vegetables as well as meat and nonmeat alternatives, and dairy and nondairy substitutes may all be part of a healthy diet (Schulze et al. 2018). There has been a dramatic increase in the consumption of unhealthy foods globally between 1990 and 2010 (Imamura et al. 2015). For this chapter, a "whole" dietary pattern is defined as the amounts, proportions, variety, and combination of various foods about the five food groups of the Eatwell Guide, UK (Choices 2015), and the MyPlate, USA (MyPlate 2011) (fruits and vegetables, macronutrient, protein, fats, and oils) (Panagiotakos et al. 2007). An overview of the current state of proteomic and metabolomic studies for Alzheimer's disease (AD) and neuropsychiatric diseases such as schizophrenia is provided in this chapter.

6.2 OMICS and Schizophrenia

Research on depression-related drugs has progressed significantly since 2001 (Emmett et al. 2014). There is still a need for new biomarkers and therapeutic targets for schizophrenia, though. Integrating biological approaches such as proteomics,

transcriptomics, metabolomics, and glycomics yields new treatment targets and biomarkers for personalized medicine (Emmett et al. 2014). Risperidone-treated first-episode schizophrenics had a significantly greater apolipoprotein A-1 level than those who had not (Li et al. 2012). Schizophrenics treated with risperidone had lower amounts of haptoglobin protein as a side effect (Li et al. 2012). The LC-MS (E)-based proteome analysis of the maternal protein deprivation rat model of schizophrenia revealed translational changes in frontal cortex glutamate neurotransmission and hormone signaling networks (Guest et al. 2012). Anomalies in cytoskeletal proteins, which control hormone release and synaptic reconfiguration, were seen in the hypothalamus as well (Guest et al. 2012). Proteins that regulate energy metabolism, calcium homeostasis, myelination, and cytoskeleton are more prevalent in the brains of schizophrenia patients than those of healthy controls (Martins-de-Souza 2011). Protein phosphorylation patterns in serum from schizophrenia patients and healthy controls have recently been used in LC-MS(E) and IMAC combined approaches to find altered expression of 35 proteins in schizophrenia (Martins-de-Souza et al. 2012). Sixty-one biomarkers discovered through proteomics quantitative proteomic analysis have been employed extensively in schizophrenia susceptibility pathways (Gokhale et al. 2012). It was shown that 24 proteins were linked to the development of BLOC-1 (lysosome-related organelle complex 1) in the genomes of dysbindin-null mice (*Mus musculus*) and schizophrenia patients (Gokhale et al. 2012). In the study of schizophrenia's pathogenesis, reverse genetics from mice to humans has been used. In this study, researchers looked at the link between schizophrenia and interferon-gamma (IFNG). We found five proteins that were elevated and five that were downregulated in the brains of interferon-gamma knockout (Ifng-KO) mice using MALDI-TOF/TOFMS (Kim et al. 2012). According to a SELDI-TOF MS research, the CSF Ab peptide profiles of people with Alzheimer's disease and those with schizophrenia vary (Albertini et al. 2012). Dysmetabolism of the amyloid precursor protein (APP) is seen in the brains of elderly people with schizophrenia (Albertini et al. 2012). A variety of aging-related pathophysiological processes can be detected with Ab1–42 in AD and elderly SCZ patients. Proteome investigation of the cerebral cortex from MK-801-treated rats uncovered stathmin, adenosine triphosphate synthase, pyruvate dehydrogenase, beta-actin, and alpha-enolase as potential contributors to schizophrenia pathogenesis (Paulson et al. 2003). Clathrin light chain B, syntaxin-binding protein 1b, and visinin similar protein 1 were found to be involved in a neurodevelopmental model of schizophrenia using an organelle proteomic approach (Vercauteren et al. 2007). Free liquid chromatography-mass spectrometry (LC-MS) and proton nuclear magnetic resonance (NMR) metabolomic profiling approaches were used to analyze postmortem brain tissue from schizophrenia patients (Chan et al. 2011). Low-cumulative-medication patients showed altered synaptogenesis, presynaptic vesicle cycling, amino acid and glutamate metabolism, and energy-buffering systems (Chan et al. 2011).

6.3 OMICS and Alzheimer's Disease (AD)

Alzheimer's disease is the most common form of neurodegeneration. Worldwide, it is a major problem that is expected to worsen by the year 2050. In 2012, (Patterson 2018) since its original description in the early twentieth century, the diagnosis of Alzheimer's disease (AD) has evolved and now involves both molecular and clinical features (Scheltens et al. 2021). This disease's preclinical phases include the accumulation of amyloid-beta (Aβ), hyperphosphorylation of tau (p-tau) aggregation, and cell death, which are all preceded by several abnormalities in the nervous system and blood vessels (Scheltens et al. 2021). AD impacts a wide range of metabolic processes, including lipogenesis, mitochondrial function, inflammation, and neurotransmitter metabolism. Following these methods, fluid biomarkers that may be used in diagnostic criteria and novel therapeutic targets were created (Jack Jr et al. 2018). Biomarkers such as a lumbar puncture or pricey PET scans may be accurate, but the methods involved in obtaining them may be simplified. In light of the increasing recognition that A is not sufficient to cause neurodegeneration on its own, there is a constant hunt for new ways to explain the development of the illness and new diagnostic and prognostic biomarkers. Proteomics and metabolomics hold immense promise for improving our knowledge of Alzheimer's disease (AD) and identifying novel biomarkers as well as tracking the effectiveness of current treatments.

The pathophysiology of A and tau and the subsequent discovery of CSF and imaging biomarkers have allowed us to reclassify Alzheimer's disease as a distinct biological entity. There are novel diagnostic, prognostic, and therapeutic avenues to explore because of the drop in CSF A and the increase in p-tau (Dubois et al. 2014; Simonsen et al. 2017; McKhann et al. 2011). As part of a new systematic review and meta-analysis, researchers looked at how reliable these molecules in blood can be as a diagnostic tool, which requires fewer and less costly procedures (Cianflone et al. 2021). There was a strong association between the plasma Aβ1–42/Aβ1–40 ratio and the accumulation of p-tau and A1–42/A1–40 and the advancement of Alzheimer's disease. A mass spectrometry test revealed the A1–42/A1–40 ratio to be highly diagnostic (West et al. 2021). Phosphorylation patterns of certain tau isoforms have been proven to increase accuracy in the early stages of the illness, according to other researches. Even though NFL's specificity for Alzheimer's disease (AD) is limited, it has been widely studied as a marker of neurodegeneration. Recent research suggests that a network meta-analysis may be useful for treating Alzheimer's disease and other neurodegenerative diseases (Zhao et al. 2019). Astrocytic responses have been associated with Alzheimer's disease (AD) pathology, and GFAP has emerged as a biomarker (Garwood et al. 2017). Dementia and disease development can be predicted with greater accuracy when GFAP levels are higher. We still need to conduct a further study before we can use it as a biomarker for Alzheimer's disease in clinical practice (Bellaver et al. 2021). Numerous studies on proteomics and Alzheimer's disease have been conducted; however, the findings cannot be generalized due to methodological differences and varying inclusion criteria. Before

reaching any conclusions on the link between the two, more research into the mechanisms involved is required. To better detect Alzheimer's disease, Pedrero-Prieto et al. (2020) reviewed 47 studies involving 2022 AD patients and 2562 healthy controls and created a library of all the CSF proteins that evolved during that period. They found a panel of 27 proteins and 21 peptides to be a useful tool (Pedrero-Prieto et al. 2020). An ultradeep proteome coverage platform was used to acquire seven datasets from three different groups, and a meta-analysis was performed by Bai et al. (2021). Proteins linked to specific cell types including neurons and glial cells were discovered to have varying levels of expression when compared to epithelial cells. AD pathogenesis is incomplete without the addition of proteomic markers, despite our understanding of amyloid and tau pathology. As a result of enhanced sample processing and high-throughput mass spectrometry in combination with large cohorts of well-characterized individuals, these goals may be achieved (Bai et al. 2021). Tijms et al. (2020), for example, applied data-driven clustering to proteomic data from two separate cohorts. Three unique protein profiles—hyperplasticity, innate immunological activation, and disruption of the blood-brain barrier—point to separate Alzheimer's disease pathophysiologic subtypes, according to the scientists' findings. Studies have demonstrated that blood biomarkers can be utilized to diagnose illness sooner than CSF proteomics. Researchers were able to discover new therapeutic targets for A accumulation and tau hyperphosphorylation, in addition to immune-inflammatory reactions, oxidative stress and synaptic plasticity, energy and mitochondrial metabolic activity, vesicle-mediated transport, and lipid metabolism that had already formed (Hampel et al. 2021). A model based on machine learning and plasma protein profiling was developed to predict A in cognitively unimpaired people, with a focus on novel AD disease candidates among the 12 variables included in the model. For the first time, researchers have shown that Alzheimer's disease is linked to the complement coagulation cascade, which is linked to the interleukin-6 signaling molecules. They believe that synchronized immune responses between tissues in a systemic inflammation reaction might be responsible. In addition to CSF and blood, other fluids have been examined. People with Alzheimer's disease (AD) may also have a more protective oral cavity, according to a recent research by Contini et al. (2021), who found that saliva from AD patients had higher expression levels of proteins involved in homeostasis, ROS removal, neuroprotection, and antimicrobial activity. There was a significant difference between the urine and tear fluid samples in terms of proteins related to lipid metabolism, complement activation, and gluconeogenesis (Watanabe et al. 2019). In the year 2019, Kenny et al. This factor has already been related to Alzheimer's disease patients who have high levels of tau hyperphosphorylation (Li et al. 2004; Kenny et al. 2019) Tiwari et al. (2016).

Other groups of chemicals that may play a role in the etiology of Alzheimer's disease (AD) may be discovered through metabolome-driven research, although protein alteration studies have been the primary emphasis yet. After analyzing 600 members of the same cohort for their levels of lipid and protein and gene expression, researchers from the University of California-Davis used an unsupervised learning approach to find out whether AD is linked to networks of

lipids and proteins that are particularly involved in lipid metabolism and innate immunity, among other things. Clark et al. performed a multi-omics investigation on the cerebrospinal fluid (CSF) of 120 elderly people with average cognitive function, moderate cognitive impairment (MCI), and mild dementia (Clark et al. 2021). According to the findings of this study, AD is linked to hemostasis, immune response, and signaling in the extracellular matrix. Neuronal damage, amyloid and tau pathology, and a mix of chemicals that indicate cognitive loss and dementia are detailed by the scientists in their study (Xu et al. 2020). In research published earlier this month, scientists from 2020 used a targeted multi-omics method to examine blood and brain samples from two separate longitudinal cohorts. According to the study's authors, higher levels of serum acylcarnitine are associated with a reduced risk of Alzheimer's disease and cognitive impairment. Thirteen indicators in the bloodstream may suggest cognitive deterioration, and 28 may be connected to brain pathology evaluation, as outlined in the study. These findings indicate metabolic dysfunction in both the blood and brain. Due to the deterioration of the blood-brain barrier and the increased transfer of metabolites between these tissues in Alzheimer's disease, blood-based biomarkers have become an interesting method (Montagne et al. 2015; Zetterberg and Burnham 2019). In a transcriptomic, metabolomic, and lipidomic analysis, Xicota et al. (2019) analyzed the plasma samples of 48 persons with and without amyloid buildup on PET scans. Peripheral blood collection might provide a molecular marker for amyloid deposition at a far lower cost and with less intrusion than PET scans or CSF analysis, indicating that these two groups are different from one another (Scheltens et al. 2021). There are three distinct blood chemicals linked to CSF AD biomarkers that Niedzwiecki et al. (2020) found in blood and CSF from two cohorts in their high-resolution screening. Further evidence was provided by the finding of a previously undiscovered halogenated component in a substance investigated by this method. There are several fascinating compounds revealed through lipidomic research that may be linked to Alzheimer's disease, including sphingolipid, phospholipid, and ceramide (Panchal et al. 2014).

6.4 Conclusion

Biomarkers for neurological and behavioral illnesses might help physicians better address their patients' conditions. Finding people who suffer from a certain illness and providing them with the necessary care are doable. Most neuropsychiatric diseases resemble or overlap, which makes it difficult to separate the characteristic or symptomatic elements of particular brain disorders. This is one of the key hurdles in the diagnosis. Peptide and metabolomic studies in neuropsychiatric disorders show the value of this approach not only in understanding the disorder's complexity but also in the prospect of discovering disease-specific biomarkers and generating new treatment options. Overall, despite their potential, metabolomics and proteomics are still in their infancy and face many challenges. While it is not impossible to create continuity between studies, it is extremely difficult to do so when dealing with

very small compounds. Metabolites and proteins are not or only partially reproducible, with minimal overlap between tests, according to current research. Measures should be standardized and inter-study heterogeneity reduced by using a standard operational procedure (SOP). The best course of action would be to combine these many studies by prioritizing multi-omics. For example, a multi-omic study incorporating transcriptome, metabolome, and proteome data might be utilized to investigate mechanisms of selected vulnerability. Single-cell metabolomics and proteomics are also becoming increasingly popular, and this will undoubtedly help researchers better comprehend the complexity of neurodegenerative diseases.

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Part II
Psychiatric Disorders Related to Nutrition: Deficiency or Overload

Chapter 7
Effects of Depression and Antidepressant Therapy on Serum Zinc Levels

Ahmad Hassan, Rafia Ali, and Samer El Hayek

Contents

Abstract Recent studies have investigated the association between zinc deficiency and depression, as well as the effectiveness of zinc supplementation in patients with depression. There are several mechanisms with which zinc exerts its antidepressant properties; some have been extensively researched in preclinical and clinical studies, while others still lack supporting evidence. This chapter describes the various antidepressant mechanisms of zinc. It also reviews landmark preclinical and clinical studies that helped to better characterize the association between zinc deficiency and depression, and the importance of zinc supplementation in this condition.

Keywords Zinc · Depression · Antidepressants · Diet

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7.1 Introduction

The World Health Organization currently ranks depression as the leading cause of disability in the world, with over 300 million individuals living with this condition as outlined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) (World Health Organization 2021). It is estimated that around one in five individuals will experience a depressive episode during their lifetime, making depression one of the most diagnosed medical conditions and a significant contributor to the global burden of disease (Ferrari et al. 2013). Therefore, it becomes crucial to identify effective preventive measures and treatments for this condition. Current research suggests that the pathophysiology of depression is multifactorial in nature, with etiologies related to genetics and epigenetics (Howard et al. 2019), age (Almeida 2014), gender (Salk et al. 2017), and stress (Park et al. 2019), amongst other factors. Some moderators and mediators of depression also include physical activity (Schuch and Stubbs 2019) and diet (Molendijk et al. 2018).

Research suggests that depression is associated with not only the overall quality of one's diet (Molendijk et al. 2018), but also the consumption of certain types of food and drinks such as fish (Li et al. 2016), coffee (Wang et al. 2016), fruits, and vegetables (Liu et al. 2016). Several prospective studies showed that unhealthy Western diets high in sweetened beverages, processed meat, fried food, and refined grain are associated with a higher incidence of depression (Lang et al. 2015). Along the same lines, inadequate intake of certain nutritional compounds, including vitamin D (Geng et al. 2019), vitamin B (Mikkelsen et al. 2016), magnesium (Tarleton and Littenberg 2015), and zinc has also been linked to depression (Li et al. 2017).

Depression is associated with an increase in the level of inflammatory processes and oxidative stress parameters in the human body (Kohler et al. 2016). Research shows that many nutritional compounds modulate inflammatory biomarkers by decreasing inflammatory processes, possibly contributing to "antidepressant" properties (Kiecolt-Glaser et al. 2015). In recent years, zinc has emerged as an element of interest in the treatment of depression. Preclinical and clinical studies have demonstrated an antidepressant therapeutic effect of zinc, particularly in the context of zinc deficiency (Doboszewska et al. 2017). This chapter reviews the possible mechanisms of zinc contributing to its antidepressant effects, as well as relevant preclinical and clinical studies investigating the role of zinc in depression.

7.2 Potential Antidepressant Mechanisms of Zinc

The association between zinc deficiency and depression was first proposed in the late 1980s and early 1990s after multiple studies indicated decreased serum zinc level in patients with mood disorders, as well as a negative association between serum zinc level and severity of depression (Little et al. 1989; McLoughlin and Hodge 1990; Maes et al. 1994; Nowak et al. 1999). It is estimated that around half of the world's

Table 7.1 Representative list of zinc metalloenzymes, their enzyme classification, and physiological function

Zinc metalloenzyme	Enzyme classification	Physiological function
Alcohol dehydrogenase	Oxidoreductase	Conversion of alcohol into aldehydes or ketones while reducing NAD^+ to NADH
Carbonic anhydrase	Lyase	Catalysis of the conversion of carbon dioxide and water into carbonic acid, pH regulation, and maintenance of acid-base homeostasis
DNA ligase III	Ligase	DNA ligation and repair
Carboxypeptidase A	Protease	Hydrolysis of peptide bonds at the carboxy-terminal end of a peptide with aromatic or aliphatic side chains
Insulin-degrading enzyme	Protease	Insulin degradation, degradation of the beta-amyloid peptide, atrial natriuretic peptide, and glucagon
Phosphomannose isomerase	Isomerase	Interconversion of fructose-6-phosphate to mannose-6-phosphate

population is at risk for zinc deficiency and, with the increasing prevalence of depression globally, it becomes critical to understand the intricate relationship between zinc and depression (Takeda 2011).

Zinc deficiency typically occurs in the setting of a low dietary intake (Wang et al. 2018). For instance, adults who consume a vegetarian diet have lower serum zinc level as compared to nonvegetarian control groups (Foster and Samman 2015). This is thought to be due to decreased dietary zinc intake, as well as increased consumption of foods containing high levels of phytic acid—a substance which can bind to zinc and decrease its absorption in the body. Zinc deficiency can also be caused by insufficient absorption (Wang et al. 2018). One pertinent example is alcohol use, as ethanol is a modulator of zinc transport proteins and can lower zinc level throughout body tissues (Skalny et al. 2018). Zinc deficiency is also described in the context of medical conditions such as inflammatory bowel disease (Hwang et al. 2012), chronic kidney disease (Nakatani et al. 2021), and chronic liver disease (Ozeki et al. 2020).

Zinc plays a crucial role in the development and growth of the human central nervous system (CNS). It is essential for neurodevelopmental processes such as neurogenesis, neuronal differentiation, and white matter growth (Brion et al. 2021). It is also one of the most prevalent trace elements in the human body and is vital for cellular metabolism and many other systemic physiological functions (Jurowski et al. 2014). In fact, hundreds of enzymes involved in various cellular processes such as cell division and differentiation, DNA synthesis, and signaling pathways require zinc as a cofactor (Szewczyk et al. 2011). A representative list of important zinc metalloenzymes and their physiological function is detailed in Table 7.1 (McCall et al. 2000; Solomons 2013; Jurowski et al. 2014; Auld and Bergman 2008; Winum et al. 2008; Taylor et al. 2000; Han and Kim 2001; Leissring et al. 2021; Bangera et al. 2019).

Normal zinc plasma concentration in adults ranges between 0.66 and 1.10 mcg/mL, and intracellular and extracellular zinc concentrations must be carefully

balanced to maintain zinc homeostasis in different areas in the CNS (Test ID: ZNS 2022; Takeda 2011). The concentration of zinc in the CNS increases with development: the adult brain has a concentration of around 200 μM while the adult extracellular concentration is <1 μM (Markesbery et al. 1984; Weiss et al. 2000). Zinc concentration in the cerebrospinal fluid (CSF) is approximately 0.15 μM. The blood-CSF barrier and blood-brain barrier both play a role in maintaining zinc homeostasis in the CNS (Takeda 2000). Specific zinc transporters belonging to two gene families, the Zip and the ZnT proteins, regulate much of the zinc homeostasis centrally and in the CSF (Liuzzi and Cousins 2004). The Zip proteins serve to increase intracellular zinc cytoplasmic levels, by allowing extracellular and vesicular zinc transport into glial cells and neurons. Alternatively, the ZnT proteins serve the opposite function but decreasing intracellular levels of zinc via zinc efflux and vesicular uptake (Szewczyk et al. 2011). In depression, zinc homeostasis is spatiotemporally altered; this is postulated to play a role in the pathophysiology of the disease (Frazzini et al. 2006).

On the other hand, brain areas implicated in the pathophysiology of depression, and thus the ones mostly studied in the context of zinc deficiency, are the cerebral cortex, amygdala, and hippocampus (Bitanihirwe and Cunningham 2009). Interestingly, the concentration of zinc is relatively higher in the amygdala, hippocampus, and neocortex as compared to other areas of the CNS (Frederickson et al. 2000; Takeda 2011). Research showed that the hippocampus is the single-most brain region that is sensitive to zinc deficiency, which suggests that zinc plays a role in functions carried out by the hippocampus such as memory, learning, and neurogenesis (Suh et al. 2009). Zinc ions in these regions modulate ligand and voltage-gated ion channels and serve to regulate synaptic transmission (Wang et al. 2018). Neurological diseases arise upon the disruption of zinc homeostasis in these brain areas, which contributes to decreased neurogenesis and synaptic plasticity (Pfaender et al. 2016).

Synaptic zinc modulates glutamate receptors such as N-methyl-d-aspartate (NMDA) receptors, α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) glutamate metabotropic receptors (mGluR), and γ-aminobutyric acid (GABA) receptors (Szewczyk et al. 2011). The most studied and best characterized mechanism of zinc on glutamatergic receptors is via the NMDA receptor complex. Zinc functions as an antagonist of the NMDA receptor, affecting glutamate homeostasis (Nowak 2001). In depression, several preclinical and clinical studies have demonstrated a disruption in glutamate homeostasis (Pittenger et al. 2007), suggesting a possible pathway through which zinc modulates the treatment of depression. Zinc is also involved in the L-arginine-nitric oxide pathway where it functions as an inhibitor of nitric oxide synthase, and preclinical studies showed this function to be important and relevant in the antidepressant functions of zinc (Wang et al. 2018).

Another proposed mechanism for the antidepressant effects of zinc is through its antioxidant and anti-inflammatory properties, typically observed in response to dietary zinc supplementation. Clinical studies have shown that dietary zinc supplementation decreases the level of C-reactive protein (CRP), a plasma protein whose

serum concentration increases in response to inflammation (Mousavi et al. 2018). Clinical research has also established an association between elevated CRP level and depression (Köhler-Forsberg et al. 2017). Along the same lines, preclinical studies showed zinc to have protective properties against oxidative stress and lipid peroxidation (Mansour and Mossa 2009). Both processes of oxidative stress and lipid peroxidation have been linked with depression (Yager et al. 2010), suggesting that the antidepressant properties of zinc may partially stem from its antioxidative effects.

7.3 Experimental Animal Studies

Although the association between zinc and depression was first observed in clinical research, preclinical animal studies have provided much of the foundation for understanding the specific antidepressant mechanisms of zinc. Numerous studies in rodents have established the association between zinc deficiency and depressive symptoms (Młyniec and Nowak 2012; Tamano et al. 2009; Tassabehji et al. 2008; Whittle et al. 2009). Likewise, intervention studies in animal models have shown the antidepressant effects and mood-enhancing properties of dietary zinc supplementation in rodents with symptoms of depression (Lai et al. 2012).

For example, one preclinical study by Tassabehji et al. showed that adult rats given a zinc-deficient diet displayed significantly more anhedonia, anorexia, and anxiety-like behaviors than those fed a zinc-adequate or zinc-supplemented diet (Tassabehji et al. 2008). Anhedonia was characterized by reduced saccharin:water intake. Anxiety-like behaviors were observed in the light-dark box test, where anxious mice less frequently explored the light side of the box (Tassabehji et al. 2008). In another study performed by Joshi et al. using the forced swim test, zinc supplementation in rats was found to reduce immobility time, suggesting improvement in symptoms of depression (Joshi et al. 2012). The forced swim test is a behavioral test commonly used in preclinical studies assessing antidepressant medications, wherein rodents are placed in an inescapable tank filled with water, and their escape-related mobility behavior is monitored (Can et al. 2012). In the same study, zinc was found to reduce extrapyramidal symptoms associated with typical antipsychotics and had a potentiating effect when used with anxiolytic and antidepressant medications (Joshi et al. 2012). Along the same lines, the selective serotonin reuptake inhibitor fluoxetine was shown to decrease signs of behavioral despair in the forced swim test in rats fed zinc-adequate and zinc-supplemented diets but did not affect those fed a zinc-deficient diet (Tassabehji et al. 2008). These findings suggest that zinc deficiency can contribute to depressive symptoms that do not respond to standard antidepressant medications.

In another study performed by Ding et al., researchers induced depressive symptoms in adult mice using chronic restraint stress (CRS). As a result, mice were found to have decreased serum and elevated hippocampal zinc levels (Ding et al. 2016). Zinc and imipramine supplementation alleviated the depressive symptoms caused by CRS and were found to have a synergetic effect (Ding et al. 2016).

Cieslik et al. performed a similar experiment and showed that zinc has antidepressant properties when supplemented alone in rats and can also improve the antidepressant effects of imipramine (Cieślik et al. 2007). Similarly, Othman et al. found zinc to enhance the antidepressant effects of clomipramine (Othman et al. 2019). Both exerted antidepressant effects when administered separately; these effects were heightened when zinc and clomipramine were given concurrently. Clomipramine was also found to increase peroxide concentration in the liver. Zinc exerted antioxidant effects and enhanced catalase activity, which counteracted clomipramine-induced peroxide overproduction (Othman et al. 2019).

Zinc was also found to modulate immune pathways implicated in depression. A preclinical study showed that rats given lipopolysaccharide (LPS) to induce depressive symptoms had elevated levels of interferon-gamma and glial fibrillary acidic protein. However, administering zinc prevented the development of depressive symptoms or associated biochemical changes (Kirsten et al. 2020). Zinc and paracetamol showed to be slightly more beneficial than zinc alone in preventing depressive symptoms and biological changes induced by LPS (Kirsten et al. 2020). These results provide evidence that zinc can alleviate symptoms of depression via immunomodulatory functions, without the need of concomitant antidepressant medications, and that immune pathways should be more closely looked at in the context of depression.

Additionally, brain-derived neurotrophic factor (BDNF) has been linked to several important functions in the mammalian brain, most important of which is synaptic plasticity (Park and Poo 2013). BDNF is postulated to play a role in the pathophysiology of depression by its mediation of synaptic plasticity. Several clinical studies have supported this hypothesis, with serum BDNF levels found to be decreased in patients with depression but normalized following the provision of antidepressant medication (Aydemir et al. 2006). To understand the role of zinc in this process, a preclinical study by Cieslik et al. showed that chronic unpredictable stress decreased BDNF mRNA levels in the rat hippocampus and reduced serum zinc levels. Alternatively, chronic treatment with zinc counteracted this decrease in BDNF mRNA levels (Cieślik et al. 2011).

Zinc is also hypothesized to play a role in the endocrine pathway of depression. Alterations in endocrine function are associated with depression, and several studies have shown that the hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axes are often affected in this condition (Musselman and Nemeroff 1996). Increase in glucocorticoid levels and medical diagnoses, such as hypothyroidism, have also been linked with depression (Musselman and Nemeroff 1996). In preclinical models, Takeda et al. showed significantly increased serum glucocorticoid levels in zinc-deficient rats (Takeda et al. 2012). As such, increased plasma cortisol level can be another potential mediator between zinc deficiency and symptoms of depression.

On the other hand, several preclinical studies highlighted the role of zinc transporters and zinc-sensing GPR39 receptors in depression. A study performed by Suh et al. sought to further characterize the role of zinc in hippocampal neurogenesis (Suh et al. 2009). High levels of vesicular zinc are localized in the presynaptic

terminals of the dentate gyrus, an area where neurogenesis occurs in the adult CNS. The researchers experimentally manipulated the levels of vesicular zinc by either feeding adult rats a zinc-deficient diet or treating them with clioquinol, a zinc chelator. After 6 weeks of dietary zinc deprivation, the numbers of immature neurons and progenitor cells in the dentate gyrus significantly decreased. This effect was reversible following the supplementation with a 2-week normal zinc-containing diet. Along the same lines, zinc transporter 3 knockout mice had significantly fewer progenitor cells and immature neurons following hypoglycemia—a state which typically induces hippocampal neurogenesis in normal mice (Suh et al. 2009). This experiment served to establish the role of zinc in modulating neurogenesis in the hippocampus. Building on this, Mylniec et al. studied the effect of antidepressants in GPR39 knockout mice. The authors found that while monoamine-based antidepressants such as imipramine, escitalopram, and reboxetine reduced immobility time of the control mice in the forced swim test, they had no effect on the GPR39 knockout mice. Only MK-801, an NMDA receptor antagonist, and ketamine demonstrated antidepressant effects in GPR39 knockout mice. This study was the first to provide evidence that GPR39 is necessary for monoamine-based antidepressants to have an effect (Młyniec et al. 2015), further highlighting the role of zinc in depression.

7.4 Clinical Studies

The relationship between low serum zinc level and depression was first described in patients in the late 1980s and early 1990s, and subsequent studies showed that lower serum zinc levels corresponded with more severe depressive symptoms (Little et al. 1989; McLoughlin and Hodge 1990; Maes et al. 1994; Nowak et al. 1999). The DSM-5-TR criteria for major depressive disorder are provided in Table 7.2 (American Psychiatric Association 2013).

As previously mentioned, normal zinc concentration in the serum of adults ranges from 0.66 to 1.10 μg/mL (Wang et al. 2018). A meta-analysis of 17 studies measuring peripheral blood concentration of zinc in 1643 patients with depression and 804 control individuals showed that blood zinc concentration in those with depression was on average 0.12 μg/mL lower than that in control individuals (Swardfager et al. 2013). Another meta-analysis conducted by Yosaee et al. confirmed that dietary zinc intake and serum zinc concentration are both lowered in patients with depression (Yosaee et al. 2020). This association between zinc deficiency and depression has also been noted in cross-sectional studies of various populations, such as female adolescents (Kim et al. 2015), patients receiving hemodialysis (Roozbeh et al. 2011), postmenopausal women (Stanisławska et al. 2014), and older adults (Vashum et al. 2014; Jung et al. 2017). In a cross-sectional study performed by Maserejian et al., zinc deficiency was associated with depression only in females as opposed to males (Maserejian et al. 2012). Similarly, a 20-year prospective cohort performed by Lehto et al. found no association between dietary zinc intake and depressive symptoms in

Table 7.2 DSM-5-TR criteria and specifiers for major depressive disorder

Criteria	Specifiers
The individual must experience five or more of the following symptoms nearly every day within the same 2-week period, and at least one of the symptoms must be either (1) depressed mood or (2) loss of interest or pleasure: 1. Depressed mood (can be subjectively reported or observed by others) 2. Loss of interest or pleasure in almost all activities (can be subjectively reported or observed by others) 3. Significant unintentional weight loss or gain (5% change in 1 month) or a change in appetite 4. Sleep disturbances (insomnia or hypersomnia) 5. Psychomotor retardation or agitation (observed by others) 6. Fatigue or loss of energy 7. Feelings of worthlessness or guilt 8. Impaired ability to think, concentrate, or make decisions (can be subjectively reported or observed by others) 9. Recurrent thoughts of death, suicidal ideation, or suicide attempt	**Severity/course specifier** • Single episode vs. recurrent episode • Mild vs. moderate vs. severe • With psychotic features • In partial remission vs. in full remission • Unspecified **Other specifiers** • With anxious distress • With mixed features • With melancholic features • With atypical features • With mood-congruent psychotic features • With mood-incongruent psychotic features • With catatonia • With peripartum onset • With seasonal pattern
The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning	
The episode is not attributable to the physiological effects of a substance or to another medical condition	
The occurrence of the major depressive episode is not better explained by a psychotic disorder	
There has never been a manic or a hypomanic episode	

middle-aged males (Lehto et al. 2013). More follow-up studies are needed to expand upon these findings and to better characterize the role of gender in the association between zinc intake and depression. Possible explanations for the increased prevalence of zinc deficiency in certain demographic populations include gender-based hormonal variations, different eating patterns, or exposure to certain medications more commonly prescribed in one gender than the other.

Multiple randomized controlled trials showed that zinc supplementation, when combined with antidepressant medication, significantly reduces depressive symptom scores in antidepressant-resistant subjects, when compared to placebo and antidepressant (Ranjbar et al. 2013; Siwek et al. 2009, 2010; Nowak et al. 2003). These studies suggest that zinc may be beneficial to use as an adjunct to antidepressant medication, especially in patients who are resistant to antidepressant therapy. In agreement with this hypothesis, a recent meta-analysis by da Silva et al. analyzed five randomized controlled trials and found that zinc supplementation reduces depressive symptoms in patients diagnosed with clinical depression and already receiving antidepressant medication (da Silva et al. 2021).

Additionally, zinc monotherapy was found to reduce depression score in the absence of concomitant antidepressant medication. A systematic review conducted

by Lai et al. demonstrated that zinc is beneficial in patients with depression and can show benefits when used both as a stand-alone treatment and concomitantly with an antidepressant (Lai et al. 2012). Alternatively, some studies have investigated the antidepressant effects of zinc in healthy subjects, with mixed findings. A pilot study performed by Sawada and Yokoi recruited healthy women and measured their baseline depression scores. Those who received dietary zinc supplementation showed a decrease in their baseline depression score (Sawada and Yokoi 2010). However, studies by Nguyen et al. did not demonstrate any significant results in the reduction of baseline depression score with zinc supplementation in healthy individuals (Nguyen et al. 2008, 2009). Therefore, evidence on the effectiveness of zinc supplementation in healthy patients as a prophylactic treatment of depression is limited.

It is well established that depression is more common in lower income populations (Rojas-García et al. 2015; Han et al. 2018; Klawetter et al. 2020). Poor nutritional intake and a lower dietary intake of zinc may serve as potential mediators between low socioeconomic status and increased prevalence of depression. Vaghri et al. examined this association in preschool children and found that lower parental education was significantly associated with elevated hair cortisol and lower hair zinc levels—a biological marker for long-term zinc intake (Vaghri et al. 2008, 2013). More studies analyzing the relationship between socioeconomic status and zinc intake are needed to better characterize this relationship.

7.5 Conclusions

Zinc has long been established to play an important role in depression. There are several potential mechanisms through which zinc exerts its antidepressant effects, many of which have been extensively studied in preclinical models. There is also a growing body of evidence that zinc exerts antidepressant effects in human subjects, especially when combined with conventional antidepressant therapy. More studies are needed to assess the role of zinc-sensing GPR39 receptors in the treatment of depression. Studies should further look into the association between socioeconomic status and dietary zinc intake, and its impact on the prevalence of depression in low-income populations.

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Chapter 8
Nutrition and Depression

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Abstract Nutrition plays a variety of physiological roles in the maintenance of mental health, with some potential pathological participations as well. Indeed, suboptimal and anormal nutrition may be implicated in the underlying pathology of mental health disorders and may interfere with treatment response and recovery. Nutrient deficiency is widespread throughout the world, affecting in particular, but not only, low- and middle-income countries and individuals disproportionately. Therefore, the socially and economically disadvantaged population is at a higher risk of major mental health disorders, including depression. Robust recent data relates the poor nutrition or nutritional deficiency (e.g., dietary antioxidants, trace elements) to major depressive disorders. On the contrary, nutrients (e.g., essential fatty acids and folic acid) may be used effectively to treat depression or to augment the existing treatments. The purpose of this chapter is to discuss the current evidence regarding the role of nutrition in depression.

Keywords Behavioral health disorders · Diet · Depression · Gut-brain axis · Major depressive disorder · Nutrition · Serotonin · Treatment management · Tryptophan · Vitamin

8.1 Introduction

Depressive disorders are common and have been identified as the leading cause of global disease burden. They mainly include major depressive disorder (MDD), dysthymia, and bipolar disorder. The symptoms of MDD comprise disturbed sleep or appetite, loss of interest or pleasure, low mood, feelings of guilt or low self-worth, fatigue, poor concentration, and suicidal thoughts. In addition, patients affected by MDD are at increased risk of suicide.

The neuroendocrine, immunological, metabolic, and neurotransmitter systems (e.g., serotonin, gamma-aminobutyric acid) are impaired in patients with MDD. Gender, socioeconomic level, social support, stress, alcohol and drug use, genetic and epigenetic variables, inflammation, physical conditions, and food are the main risk factors that increase the chance of developing depressive disorders. Recently, there has been a growing body of evidence pointing to a link between food and depression, and nutritional deficiencies are linked to the underlying pathophysiology of depression. The neurotransmitters like serotonin, dopamine, and norepinephrine regulate mood, appetite, and cognition (Sarris et al. 2015). The tryptophan, vitamin B6, vitamin B12, folic acid, phenylalanine, tyrosine, histidine, choline, and glutamic acid are required for the synthesis of these neurotransmitters.

Furthermore, some nutrients, such as marine-derived omega-3 fatty acids, influence serotonergic and dopaminergic neurotransmission and can help to alleviate depressive symptoms (Lin et al. 2010). As a result, poor diet quality and insufficient nutritional consumption represent risk factors for depression of new rising interest for clinical as well as for scientific research. Indeed, healthy eating habits can lower

the incidence of depression, according to a meta-analysis of 21 observational studies (Li et al. 2017). Further, nutritional status contributes to the proper function of the innate immune system and hypothalamic–pituitary–adrenal (HPA) axis. The importance that the diet plays in the pathophysiology of depression also lies in the possibility of intervening in a clear and rapid manner on it. In this regard, diet, physical activity, and social interaction are modifiable lifestyle factors that have been shown to reduce the prevalence of depression (Worrall et al. 2020). Accordingly, correction of nutrient deficiencies may help in the prevention and management of depression. In this chapter, we discuss the role of nutrition or diet under the following headings: epidemiology, dietary patterns, foods/food groups, and nutrients.

8.2 Epidemiology

According to recent data, depression affects up to 13.3% of youths aged 12–17 years and 7.1% of adults aged older than 18 years, thus explaining why it is considered a high global public health priority (Substance Abuse and Mental Health Services Administration 2018). Indeed, its elevated high prevalence and the resulting severe disease burden with economic, personal, and healthcare consequences contribute to make MDD the second greatest contributor to global disease burden quantified as years of life lived in less-than-ideal health (Vos et al. 2012). The exact causes of depression are still far from being fully understood, but today we consider an interaction between genetic and epigenetic factors, gender, childhood adversities, socioeconomic status, job availability, social support, concomitant treatments, stress, alcohol and drug use, inflammation, microbiome, medical comorbidities, endothelial dysfunction, and diet (Bodnar and Wisner 2005; Kris-Etherton et al. 2021; Payne 2010). However, the epidemiology, as well as the causative link, becomes even more vague and evasive when considering the relationship between depression and nutrition.

8.2.1 Dietary Patterns

8.2.1.1 Dietary Inflammatory Index (DII)

The etiological model of depression explains the strong association between inflammation and depression (C.-H. Lee and Giuliani 2019; Zunszain et al. 2013). Dietary inflammatory index (DII) is a measure that indicates the pro-inflammatory potential of certain diets. It is known that certain diets increase the level of inflammatory cytokines in blood (Kanauchi et al. 2019; Liu et al. 2021; Saghafi-Asl et al. 2021; Shivappa et al. 2014). Higher adherence to the Mediterranean diet and a lower DII have been associated with a lower risk of depressive outcomes (Lassale et al. 2019).

Hence, diets with high DII are more likely leading to depression. Interestingly, the increase in depressive disorders over the past few decades parallels a decline in healthy lifestyle behaviors, including poorer diet quality (Benjamin et al. 2019). Depression is known to affect appetite; therefore, cross-sectional evidence of an association between diet and depression may reflect reverse causation.

Higher intake of both vegetables and fruits was associated with a lower risk of depression, whereas higher inflammatory diets and a dietary pattern rich in Western foods were associated with an increased risk of depression. A 2020 meta-analysis of 18 studies examining the relationship between diet and depression in elderly population reported that a healthy dietary pattern was associated with a reduced risk of depression (Wu et al. 2021). The relationship between nutrition and depression changes with age (Chang et al. 2016; Vermeulen et al. 2016). Further, a meta-analysis found no link between a Mediterranean diet, a "healthy" diet, or fish consumption and depression in old adults (Matison et al. 2021).

8.2.2 Epidemiological Evidence Relating Dietary Patterns to Depression

8.2.2.1 Mediterranean Diet

Mediterranean diet was firstly defined as that by Ancel Keys as observed in Southern Italy and Greece during the 1960s (Davis et al. 2015). This term is used to refer to a dietary pattern that uses olive oil as a major source of monounsaturated fats and is typically high on fresh fruits, vegetables, legumes, nuts, and whole grains. Fish, dairy, and poultry in small-to-moderate amounts are tolerated, but red meat consumption is discouraged.

According to Seven Countries Study, Mediterranean diet is associated with reduced risk of coronary heart disease (CHD) and cardiovascular diseases (CVD) compared to northern European countries and the United States after 25-year follow-up (Kromhout et al. 1995; Menotti et al. 1999). Moreover, there is data also supporting the idea that a Mediterranean-style dietary pattern lowers the risk of depression. A Mediterranean-style dietary intervention that included cooking classes, food hampers, and fish oil supplementation (900 mg/day docosahexaenoic acid [DHA] and 200 mg/day eicosapentaenoic acids [EPA]) improved adherence to the Mediterranean diet, reduced depression, and improved mental health-related quality of life (Parletta et al. 2019).

However, according to a recent meta-analysis, there was no difference in incident depression between participants in the highest and lowest categories of Mediterranean diet adherence (Li et al. 2017; Rienks et al. 2013). These differences may be attributed to methodological or clinical heterogeneity between studies. In addition, it should be taken into account that Mediterranean diet is more common in countries more exposed to the sun, with a mild climate and with more hours of light in the day, conditions that have always been associated with an improvement in depression,

thus acting as a confounding factor (Abraham et al. 2021; Murphy and Parletta 2018). Therefore, the debate is still open.

8.2.2.2 Dietary Inflammatory Index/Alternative Dietary Inflammatory Index

Either the original DII (Sánchez-Villegas et al. 2015; Shivappa et al. 2014) or the alternate DII (Adjibade et al. 2019) is used to assess the relationship between the level of inflammation in the diet and the risk of depression. The highest category of inflammatory diet is associated with a higher risk of depression. Also, the switch from the lowest to the highest category of inflammatory diet is associated with increase in depression incidence (Matison et al. 2021). Lucas et al. (2014) identified that the highest category of inflammatory diet is associated with increased levels of biomarkers of inflammation (Lucas et al. 2014). Overall, there is a detrimental association between the DII and incident depression.

8.2.2.3 "Healthy" Diet

Adherence to dietary guidelines is defined as a healthy dietary pattern (Das et al. 2021; Lai et al. 2017; Voortman et al. 2017). However, some studies used an a posteriori method to identify dietary patterns, which they labeled "prudent" (Chocano-Bedoya et al. 2013; Jacka et al. 2014), "whole food"(Akbaraly et al. 2009), or "vegetables-fruits" (Chan et al. 2014). Results showed that healthy dietary patterns are associated with less depressive symptoms. Lower odds of depression were linked to greater adherence to healthy/prudent, Mediterranean, pro-vegetarian (i.e., higher in plant foods than animal foods), and Tuscan dietary patterns. Increased nutrition quality was also linked to a lower incidence of depression (Molendijk et al. 2018). High intakes of fruits, vegetables, seafood, and whole grains characterized these healthy dietary patterns. Dietary patterns that included fish, olive oil, vegetables, fruits, and nuts were linked to a lower risk of depression (Martínez-González and Sánchez-Villegas 2016). In particular, the Tuscan diet takes its name from the homonymous northern Italian region famous for its healthy and local cuisine. In details, it is characterized by fish, olive oil, several vegetables, fruits, potatoes, cereals, eggs, wine, red and processed meat, and other sauces (particularly tomato sauce). This dietary pattern reflects a typical Tuscan diet and was therefore labeled as "typical Tuscan dietary pattern (Vermeulen et al. 2016)."

8.2.2.4 High-Fat/Sugar Diet

This dietary pattern is labeled as "convenience" (Gougeon et al. 2015), "Western" (Rienks et al. 2013), or "processed food" (Akbaraly et al. 2009). Overall, participants in the highest category of consumption of this diet or ultra-processed food had a

higher risk of depression. Further, the switch from the lowest to the highest category is associated with increase in the incidence of depression (Matison et al. 2021). Indeed, this diet category, which mainly includes fast and "junk food," presents an important impact on immunological system with many implications on mental and physical health, also through the Western diet-microbiome-host interaction (Myles 2014).

8.2.2.5 Other Dietary Patterns

There are a multitude of diets and dietary patterns that can be examined to study their association with physical and mental disorders, and depression in particular. Among them, we highlight the consumption of a traditional Taiwanese diet, which reported a higher incidence of depression among older adults, whereas higher consumption of a traditional Canadian diet was not associated with incident depression among those aged 67–84 years (Gougeon et al. 2015). Consumption of carbohydrates with a higher glycemic index was associated with higher depressive outcomes (Gangwisch et al. 2015). On the other hand, higher consumption of a "varied," "snacks-drinks-milk," "dairy," "meat-fish," "meat-processed/meat," "cooked vegetable," and "fruit" dietary pattern was not associated with longitudinal risk of incident depression (Matison et al. 2021). Other healthy dietary patterns, such as the Dietary Approaches to Stop Hypertension (DASH) diet (high in fruits, vegetables, and low-fat dairy, and low in saturated fat), have improved depressive symptoms. Overall, these studies imply that eating a nutritious diet that includes vegetables and fruits, fish, olive oil, nuts, and grains, in accordance with current dietary recommendations, may help to alleviate depressed symptoms. The risk of depression has been linked to vegetarian dietary patterns in a mixed bag of ways. Similarly, some studies have found a correlation between decreased meat consumption and an increased risk of depression, while others have found no such link.

8.2.2.6 Specific Food Components

Vegetables, fruits, and fish servings can be classified, and they are linked with depression (Matison et al. 2021) (Table 8.1).

8.2.2.7 Red Meat and Processed Meat

A pooled estimate of the association between red and processed meat consumption and depression observed a small but significant increase in the risk of depression in a meta-analysis. However, the analysis was limited by high heterogeneity (Nucci et al. 2020).

Table 8.1 Specific food components and risk of depression

Food servings	Categories	Risk of depression
Vegetable servings	• Five categories (0–1/day, 2/day, 3/day, 4/day, and ≥5/day) (Shang et al. 2020) • Three categories (0–1/day, 2–4/day, and ≥5/day) (Mihrshahi et al. 2015) • Two categories (≤5/week and ≥6/week) (Chi et al. 2016)	• The shifting from the lowest to the highest category of vegetable intake is associated with a lower risk of depression (Matison et al. 2021)
Fruit servings	• Two categories (≤5/week and ≥6/week) (Chi et al. 2016) or <2/day and ≥2/day (Mihrshahi et al. 2015) • Four categories (none, 1/day, 2/day, and ≥3/day) (Shang et al. 2020)	• Highest intake of fruit is associated with lower risk of depression • The shifting from the lowest to the highest category of fruit intake is associated with a lower risk of depression • Further, the higher consumption of citrus fruit and juices is associated with lower risk of depression
Fish	• Two categories (≥3/week and <3/week) (Almeida et al. 2013; Tsai et al. 2012) • Five categories (<1/month, 1–3/month, 1/week, 2–4/week and ≥5/week) (Lucas et al. 2011)	• There was no association between fish intake and incident depression • Furthermore, in a Taiwanese study of older adults, higher seafood consumption was not associated with an increased risk of depression (Tsai et al. 2012)

8.2.2.8 Other Food Types

Tea

The difficulty in studying the association between tea and depression also lies in the different types of existing tea, and the different methods of preparation and frequency of consumption, which can influence its effectiveness (Mancini et al. 2017). A Taiwanese study reported that higher tea consumption (mainly oolong tea) is associated with reduced incidence of depression (Chi et al. 2016), whereas the studies conducted in the United States found that hot or iced tea is not associated with depression (Chang et al. 2016; Guo et al. 2014); however, a detrimental association was noted with intake of decaffeinated iced tea (Guo et al. 2014).

Coffee and Caffeine

Similarly to what is considered for tea, the methods of cultivation and consumption of coffee are also varied and diversified all over the world (Ding et al. 2014). A higher caffeinated coffee intake was found to be related with lower incidence of depression (Guo et al. 2014; Lucas 2011); however, no such association was noted

with decaffeinated coffee. Combined intake of caffeinated coffee and tea was not associated with the risk of depression (Ritchie et al. 2014).

Analysis of the dose–response for caffeine intake and risk depression showed that caffeine was associated with nonsignificant decreased risk of depression only up to 300 mg/day (about 3–4 cups/day of coffee) (Grosso et al. 2016).

Grain

Higher whole-grain intake was associated with lower incidence of depression (Gangwisch et al. 2015). However, the non-whole grain-to-whole grain ratio was not associated with the risk of depression (Gangwisch et al. 2015).

Others

Increased risk of depression has been reported with higher intake of added sugar, but not total sugar (Gangwisch et al. 2015). Similarly, increased consumption of regular soft drinks, as well as increased consumption of diet soft drinks/fruit drinks/sweetened iced tea, is associated with an increased risk of depression (Guo et al. 2014). Results were mixed for studies that investigated associations with meat intake. Higher chicken consumption was associated with increased risk for depression (Shang et al. 2020), whereas meat (all types) (Almeida et al. 2013) as well as combined meat and poultry (Tsai et al. 2012) were not associated with depressive risk. Intake of dairy (Almeida et al. 2013; Tsai et al. 2012), legumes (Tsai et al. 2012), eggs (Tsai et al. 2012), nuts and seeds (Gangwisch et al. 2015), onions (Chang et al. 2016), cereal (Tsai et al. 2012), and alcohol (Tsai et al. 2012) was not associated with the risk of depression.

8.2.2.9 Nutrients

Dietary nutrients are classified into two types: macronutrients and micronutrients (Fig. 8.1). Micronutrients are further classified into four types: vitamins, macrominerals, trace minerals, and organic acids.

8.2.2.10 Macronutrients (Fig. 8.1)

A change in one macronutrient's intake causes a proportional shift in another macronutrient's intake. Hence, changing one macronutrient's intake cannot be done in isolation(s). Studies have reported that macronutrient consumption (total) is associated with depression and depressive symptoms. Furthermore, diets with varying macronutrient compositions have no effect on depressive symptoms, but weight-loss diets generally improve depressive symptoms (regardless of the

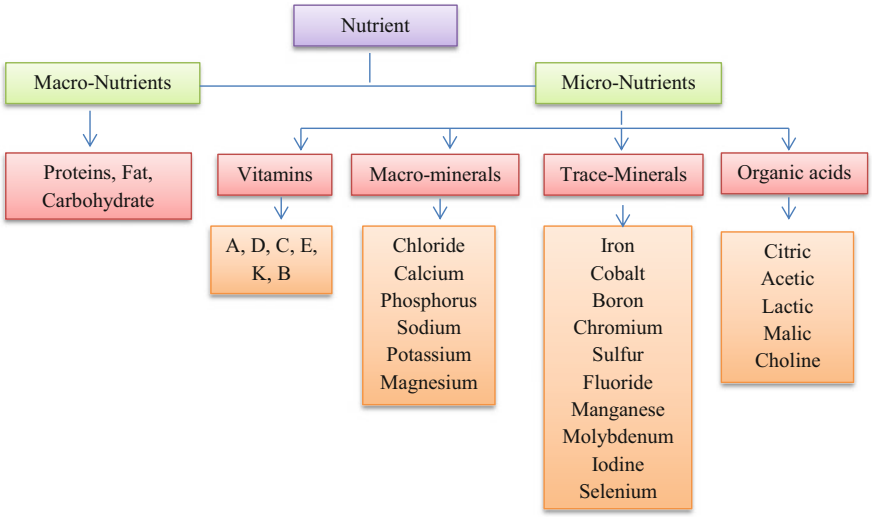

Fig. 8.1 Classifications of dietary nutrients

macronutrient composition) (El Ghoch et al. 2016). The epidemiologic studies show a consistent relation among depression and dietary sources of macronutrients.

Proteins

The National Health and Nutrition Examination Follow-Up Study showed that higher protein intake at baseline was associated with lower risk of severe depression. In contrast, among women, protein intake was not associated with depressed mood, but a higher percentage of energy from protein was associated with severity of depression. In a cross-sectional study of male Japanese workers at a manufacturing company, no association was observed between intake of protein, fat, and carbohydrate and depressive symptoms; however, plant protein intake was associated with lower odds of depression. In an Italian study, higher intake of fish/shellfish was associated with a decrease in depressive symptom. Notably, depressive symptoms were associated with a reduction in red or processed meat and an increase in dairy intake. However, this could be due to the reverse causality.

Fat

Literature on fatty acids and their role in mood disorders has been growing in recent years. Several studies have shown positive benefits for omega-3 polyunsaturated fatty acid supplementation on symptoms of depression. These benefits were noted for eicosapentaenoic (EPA)-pure or EPA-major formulations but not

docosahexaenoic (DHA) acid-pure or DHA-major preparations. For optimum benefits, an EPA-major preparation at dosages $\leq$1gm/day is suggested for unipolar depression. It is important to note that the physiological effect of fatty acids differs by type (Sacks et al. 2017).

Polyunsaturated Fatty Acid (PUFA)

Human body cannot synthesize the two families of essential long-chain PUFA: n-3 and n-6 fatty acids (Koletzko et al. 2008). Therefore, diets must contain either the n-3 or the n-6 PUFA or their precursor molecules (Table 8.2). Each parent fatty acid can be desaturated and elongated to a series of longer chain PUFAs. It is important to note that the synthesis of n-3 PUFA from α-linolenic acid in humans is inefficient, so humans are more dependent on seafood to meet their n-3 PUFA requirements.

Higher intake of the omega-6 PUFA, linoleic acid, was associated with increased risk of depression (Lucas et al. 2011). Furthermore, serum and dietary n-3 PUFA levels are low in patients with depression. Countries with lower levels of n-3 PUFA intake have higher rates of depression (Liperoti et al. 2009; Sontrop and Campbell 2006).

The n-3 PUFAs eicosapentaenoic acid and docosahexaenoic acid are the most biologically important for mental health and are most abundant in the brain. PUFAs are essential structural components of phospholipid membranes in all bodily tissues. They are particularly abundant in the brain, where they regulate the biophysical properties of neuronal membranes. Receptor activity, neurotransmitter absorption, and signal transmission are all affected by fatty acids. DHA is the most abundant n-3 PUFA in the brain. High DHA concentrations improve serotonin receptor sensitivity by increasing membrane fluidity. The n-3 PUFAs are also precursors to specific prostaglandins and leukotrienes, which are potent vasodilators and inhibitors of platelet aggregation. They reduce the inflammation.

In the United States, the ratio of n-6 PUFAs to n-3 PUFAs has been remarkably altered from about 1:1 before 1890 to between 10:1 and 25:1 in recent years. This shift in intake patterns, caused by a two- to threefold increase in intakes of vegetable oils at the expense of n-3 PUFAs from fish and plants, is thought to be responsible for the increased incidence of depressive disorders in the United States in the past century. Further, the concentrations of n-3 PUFAs in the blood have repeatedly been

Table 8.2 PUFA and dietary source

PUFA and its precursor	Dietary source
n-3 PUFA	Fatty fish and certain algae
Precursor of n-3 PUFA (-α-linolenic acid)	Flaxseed and walnuts
n-6 PUFA	In animals fed a high-cultivated cereal diet
Precursor of n-6 PUFA (linoleic acid)	Vegetable oil sources (e.g., maize, cottonseed, soya, and sunflower seed)

shown to be lower and the ratio of n-6 to n-3 PUFAs has been shown to be higher in depressed individuals compared with healthy control subjects, with blood concentrations strongly correlated with the severity of the disorder.

The higher intake of fish, EPA plus DHA, and total n-3 PUFA is associated with lower risk of depression. Higher intake of added sugars and refined carbohydrates is positively associated with depression; in contrast, higher consumption of fiber, fish, and n-3 fats may be protective.

Carbohydrate

Total carbohydrate consumption is not associated with depression. More specifically, the higher intake of lactose and fiber is linked to a lower risk of depression, whereas no links were found between glucose, sucrose, fructose, or starch consumption and incident depression (Gangwisch et al. 2015). Also, in context with hypocaloric diet, macronutrient composition has limited deleterious effects on depressive symptoms in nondepressed individuals.

Compared to low-glycemic diet, a high-glycemic-load diet causes major mood alterations, increased fatigue, and depression symptoms. Prospective cohort studies have found that a higher intake of added sugars from sugar-sweetened beverages, refined carbohydrates, and sweet foods is associated with a higher risk of depression. Data from the Women's Health Initiative cohort showed that a higher intake of added sugars, but not total sugars or total carbohydrate intake, was associated with higher odds of incident depression. Further, higher intake of fiber was associated with a lower risk of incident depression in this cohort.

The quality of carbohydrates is more strongly related to depression risk than total carbohydrates.

The published studies have measured carbohydrate in diet using the Carbohydrate Quality Index (a measure of intake of higher quality carbohydrates) and the glycemic index. However, the glycemic index is not a reliable proxy for the glycemic response to carbohydrate intake.

According to current dietary recommendations, whole-grain carbohydrate sources should be preferred over refined carbohydrate sources. In some published studies, exercise has been linked to a reduction in depressive symptoms, and thus exercise may have blunted any potential diet-induced effects.

8.2.2.11 Micronutrients

Micronutrients are essential for the optimal functioning of the central and peripheral nervous system. Inadequate intake of various micronutrients is linked to an increased risk of depression. Micronutrient-associated depressive disorders include vitamins (e.g., vitamin B6, vitamin B12, folic acid, and vitamin D) and minerals (e.g., zinc and magnesium). Identifying and managing deficiencies of micronutrients are critical in patients with depression.

8.2.2.12 B Vitamins

B vitamins are a group of eight water-soluble molecules that function as enzymes in metabolic processes.

B vitamins can be found in a wide variety of unprocessed foods. B vitamin deficiency can cause a variety of chronic illnesses, including anemia (vitamin B6: microcytic, vitamins B9 and B12: macrocytic), impairment in peripheral nervous system (vitamins B1 and B12), and severe mental disturbances (vitamins B1, B3, B6, and B12).

Depressive symptoms are a well-known feature of B vitamin deficiency (e.g., B12, B6, and folic acid). Higher intake of vitamin B12 and folate is linked with lower risk of depression; however, it is unclear whether adequate intake of vitamin B12 and folate prevents the onset of depression. Vitamin B12 and folate deficiencies disrupt one-carbon metabolism, resulting in higher homocysteine levels and lower S-adenosyl methionine levels. S-adenosyl methionine is a methyl donor for the rate-limiting step in the synthesis of neurotransmitters (e.g., serotonin, dopamine, and norepinephrine). Lower S-adenosyl methionine levels were frequently reported in patients with depression. Excess homocysteine, on the other hand, causes the production of neurotoxic agents, which overactivate the glutamatergic receptor (N-methyl-D-aspartate). Depression is linked with low levels of B vitamins and/or high levels of homocysteine in general populations. Vitamin B12 has strong correlation with depression in elder populations (Robinson et al. 2011), whereas vitamin B9 is correlated with depression in adult and adolescent populations (Beydoun et al. 2010; Murakami et al. 2010).

Further, either folate or vitamin B12 deficiency contributes to the pathogenesis of MDD by increasing the homocysteine level and causing a vascular response. It is often evident that patients with MDD have lower concentrations of serum or red cell folate. Also, the poor folate status and lower dietary folate are associated with the severity of depression and prolonged episodes of MDD.

8.2.2.13 Antioxidants

The brain requires oxygen for metabolism of various substrates. Due to high PUFA content, the neuronal membranes are vulnerable to lipid peroxidation. In addition to neuronal damage, reactive oxygen species can cause vascular changes through oxidative stress leading to depressive symptoms. Although antioxidants protect the brain from oxidative stress, the antioxidant content of the brain is unusually low. Antioxidant supplementation at high doses prevents the progression of neuronal damage, and thus it could be useful in preventing or treating MDD.

Vitamin C (Ascorbic Acid)

Vitamin C is a potent antioxidant that can help to prevent oxidative stress. High-dose ascorbic acid supplements (3 g/day) may reduce the severity of MDD and depressive scores. Some studies found no link between vitamin A, C, or E intake and the occurrence of depression (Das et al. 2021). Some preliminary data on animal models shows the potential use of ascorbic acid even on depressive symptoms, paving the way not only for its preventive but also therapeutic use (Moretti et al. 2012; Shivavedi et al. 2019).

Vitamin E

Vitamin E is the most important lipid-soluble antioxidant that protects neuronal membranes from peroxidation. Patients with MDD frequently have lower serum vitamin E concentrations than healthy control subjects, and this is also related to the duration of the disease. Some studies, however, found no link between vitamin E and depressive symptoms. The beneficial effects of vitamin E supplementation in MDD may be mediated through neuro-inflammation and oxidative stress modulation.

Selenium (Se)

Selenium is an important modulator of mood. The mechanism by which selenium influences mood is unknown. Selenium is required for the synthesis and metabolism of thyroid hormones. A selenium deficiency affects thyroid hormone metabolism and may be the underlying cause of depressive symptoms. Similarly, selenium deficiency reduces immune function, which is common in MDD patients. Additionally, selenium is needed for the antioxidant enzyme glutathione peroxidase, which protects nerves from lipoperoxidation and tissue damage. The supplementation of 100–150 g selenium/day for 5–6 weeks has significantly improved mood scores.

8.2.2.14 Vitamin D

Vitamin D is a steroid hormone required for calcium absorption and utilization, and bone and mental health. It is synthesized in response to UVB light and is also present in the food chain. To become biologically active, the molecule first undergoes hydroxylation in the liver, followed by a second hydroxylation reaction in the kidneys, brain, and immune system (Borges et al. 2011; Kesby et al. 2011). Vitamin D deficiency is mainly caused by lack of exposure to the sunlight and low vitamin D intake. In vitamin D deficiency, the brain receptors are understimulated, and this may lead to depressive symptoms. A low serum vitamin D level has been linked to depressive symptoms in the majority of cross-sectional studies (Lee et al. 2011).

Further, vitamin D supplementation may affect the inflammatory/oxidative processes among clinical responder subgroup of MDD. At present, there is insufficient evidence for vitamin D supplementation as a monotherapy or adjunct therapy to improve depressive symptoms. Interestingly, a meta-analysis showed positive benefits for adjunctive vitamin D supplementation among patients with major depression (Vellekkatt and Menon 2019) and among people with concurrent major depression and vitamin D deficiency (Vellekkatt et al. 2020).

8.2.2.15 Magnesium

Magnesium is involved in the body's inflammatory defense systems as well as over 300 cellular processes. Magnesium deficiency causes N-methyl-D-aspartate (NMDA) overactivity, which causes depressive symptoms and neuroendocrine changes (Zarate et al. 2013). Serum levels of magnesium are lower in adults with depression. However, the role of magnesium in the prevention of depression is unclear. Furthermore, a healthy dietary pattern is recommended to ensure adequate magnesium intake.

8.2.2.16 Oxidant and Antioxidant

Oxidative stress markers are elevated in patients with depression, while antioxidant markers are low (Liu et al. 2015). Antioxidants found in abundance in fruits and vegetables help in the prevention of depression (Smaga et al. 2015).

8.2.2.17 Gut Microbiota

The gut microbiota may have protective role against inflammation (Ghosh et al. 2020). Whole grains, resistant starch, and vegetables appear to improve the composition of the gut microbiome (Graf et al. 2015; Cebrino and Portero de la Cruz 2020).

8.2.2.18 Trace Minerals

Dietary minerals are elements found in the human body that are necessary for the proper functioning of human body. Macro-minerals are dietary minerals that are abundant in the human body and function as structural (Ca) and electrolyte (Na, K, Cl) minerals. Other dietary minerals exist in trace amounts and serve as enzymic cofactors and cell-signaling molecules. Food sources for dietary minerals vary widely and include animal products (Fe, Ca, P) or vegetarian sources (K, Mg). Mineral toxicity and deficiency can occur in humans. Compared to toxicity, mineral deficiency is common and caused by insufficient intake, excretion, medical

conditions, pregnancy, and lactation. The symptoms differ depending on the mineral and the degree of deficiency.

Iron

Iron deficiency affects the myelination, cellular and oxidative processes, neurotransmitter metabolism and function, and thyroid hormone metabolism. Reduced brain iron stores have an effect on iron-dependent enzymes that are required for neurotransmitter synthesis, function, and degradation (dopamine, serotonin, and noradrenaline). Iron deficiency in women of childbearing age causes cognitive function deficits such as memory, learning, and concentration. Fatigue, irritability, apathy, and an inability to concentrate are common symptoms of iron deficiency. Also, iron deficiency without anemia is associated with higher depressive scores.

Zinc (Zn)

Zinc has the highest concentration in the brain after iron. Zinc is necessary for optimal activity of hundreds of intracellular processes (e.g., enzyme cofactors and structure of amino acids). It is localized within synaptic vesicles of specific neurons and modulates synaptic transmission and also acts as a neurotransmitter. It is required in the synthesis of DNA and various regulatory, structural, and enzymatic proteins. Severe deficiency causes immunosuppression and behavioral disturbances such as depression and dysphoria (Maret and Sandstead 2006). Proposed antidepressant mechanisms for zinc include dampening NMDA and glutamatergic hyperactivity, multiple intracellular targets, and complex interactions with the serotonergic system (Nowak et al. 2003). Low levels of Zn are linked with depression among different subgroups of populations (infant, young children, young adult, adultery, elderly, pregnant). In patients with MDD, the blood zinc concentration is lower and correlated with the severity of depression (Swardfager et al. 2013). Supplementation with 25 mg of zinc for 6–12 weeks is used as an adjunct to antidepressant therapy in patients with MDD (Schefft et al. 2017).

Selenium (Se)

We discussed this under the antioxidant heading.

8.3 Potential Mechanism

The mechanisms underlying a possible link between nutrition and depression are unknown; however, it is widely assumed that inflammation plays a role in the pathogenesis of depression (Liu et al. 2016). In addition, the causal mechanisms for various nutrients have been proposed without sufficient evidence (Table 8.3). The B vitamins have no direct effect on the HPA axis or the immune system. B vitamins have an effect on cardiovascular inflammation through the pro-inflammatory amino acid homocysteine (Smulders and Blom 2011). Vitamins B9 and B12 are required for methionine-homocysteine metabolism; methionine is an amino acid required for the translation of protein synthesis. Also, vitamin B6 helps in the condensation of homocysteine into a precursor of the amino acid cysteine (Beydoun et al. 2010; Malouf and Grimley Evans 2003).

8.4 Preventive, Protective, and Therapeutic Role of Diet in Depression

Depression may be prevented and treated with nutrition. Therefore, the International Society for Nutritional Psychiatry Research has recommended that nutritional medicine should be considered mainstream in psychiatric practice. "Healthy" dietary patterns are associated with a lower risk of depression (Lassale et al. 2019; Molendijk et al. 2018). However, the observed associations are most likely the result of a number of biological mechanisms. Therefore, research is needed to explore the evidence for underlying mechanism.

8.4.1 Dietary Pattern

Only a limited number of intervention studies have examined the effect of dietary pattern on depression. Also, there is a lack of intervention studies examining the effect of nutrition on depression in different subgroups of population such as middle-aged to older adults. However, the literature suggests that a healthy diet has a beneficial effect on depressive symptoms (Thomas-Brown et al. 2018). The whole-of-diet (or dietary pattern-based) interventions reduced depressive symptoms in a single delivery mode (e.g., red meat intake, selecting lean meat, or following a low-cholesterol diet).

The Supporting the Modification of Lifestyle in the Lowered Emotional States (SMILES) study was the first RCT to evaluate whether improving diet quality improved symptoms of depression in individuals with MDD (Jacka et al. 2017). In this study, participants assigned to dietetic counseling to follow a modified Mediterranean diet had a greater reduction in their depressive symptoms over the

Table 8.3 Nutrients, dietary sources, and potential mechanism in depression

Nutrient	Sources	Mechanism of action	Effects of deficiency	Potential mechanism in depression
Vitamin B1 (thiamine)	Soymilk, ham, watermelon, acorn squash	Glucose decarboxylation, oxidation, and reduction reactions	Irritability, confusion, apathy	Low levels of vitamin B1 affect the carbohydrate metabolism
Vitamin B6	Fish, meat, poultry, legumes, soy products, bananas	Chemical mediator synthesis; alters NMDA receptors in the brain	Asthenia, irritability, depression	Low levels of vitamin B6 may affect the synthesis of the neurotransmitters (e.g., serotonin, noradrenaline, and dopamine) (Fava and Mischoulon 2009; Miyake et al. 2006)
Vitamin B12	Fish, poultry, meat, milk, fortified soymilk, cereals, and cheese	Works in conjunction with folate in the methionine-synthase-mediated conversion of homocysteine to methionine	Neurological disorders, psychosis, hematological alterations, abnormal peripheral sensation, memory loss, and pain	B vitamin deficiency promotes hyperhomocysteinemia that leads to vascular damage and chronic inflammation. Vascular damage to the carotid and intracerebral arteries can result in low oxygen delivery to the prefrontal cortex, leading to depression (Robinson et al. 2011; Smulders and Blom 2011)
Folic acid	Orange, fortified grains, spinach, cereals, broccoli, asparagus, legumes (black-eyed peas and chickpeas)	Methionine-homocysteine metabolism	Megaloblastic anemia, neural tube defects, and mood disturbances	The tetrahydrobiopterin is a cofactor in the synthesis of catecholamines and serotonin. Folate maintains its concentration in brain
Vitamin D	Ultraviolet B sunlight, fortified dairy, fatty fish, cereals, eggs, and beef liver	Protection of hippocampal neurons, modulates transport of glucose to the brain	Neuropsychiatric issues, depression	Vitamin D affects both cellular and humoral immune responses (Borges et al. 2011). In addition, vitamin D interacts with HPA axis and affects the hypothalamus function, HPA axis, and production of neurotransmitter

(continued)

Table 8.3 (continued)

Nutrient	Sources	Mechanism of action	Effects of deficiency	Potential mechanism in depression
Iodine	Iodized salt, seafood	Major constituent of thyroid hormones, affects gene expression of other hormones and growth factors	Low intelligence, cretinism, hypothyroid-associated depression	It affects thyroid hormone synthesis and gene expression of other hormones and growth factors
Selenium	Nuts, meat, and fish	Component of selenoprotein glutathione peroxidase. A selenoprotein glutathione peroxidase is an important antioxidant that is required for thyroid hormone synthesis and metabolism	Low selenium intake associated with poorer mood	The primary function of Se is anti-inflammatory action mediated through the selenoprotein glutathione peroxidase (Duntas 2009). The glutathione peroxidase reduces the COX pathway-mediated production of pro-inflammatory cytokines. Also, it is involved in processing thyroid H2O2, and thus, Se deficiency can cause depressive symptoms by impairing thyroid function (Sher 2001). The Se concentration influences dopamine metabolism (Castaño et al. 1997)
Zinc	Red meat, whole grains, and beans	DNA and protein synthesis	Impaired learning, reduced attention; impaired accumulation of PUFA in the body	Two mechanisms: 1. Zn affects the balance of pro- and anti-inflammatory cytokines (Prasad et al. 2008) 2. Zn changes the productivity of B and T cells and affects the HPA axis (Fraker and King 2004) The neuronal hypotheses suggest that the normal levels of Zn regulate the glutamate release from hippocampal neurons, thus protecting from depression (Szewczyk et al. 2008)

(continued)

Table 8.3 (continued)

Nutrient	Sources	Mechanism of action	Effects of deficiency	Potential mechanism in depression
n-3 fatty acids	Fish and other seafood (especially cold-water fatty fish), nuts, seeds, and plant oils	Constituent of cell membranes, substrate for cell-to-cell signal transduction and communication	Impaired sensation, accelerated aging; associated with mood disturbances, dementia, depression	1. PUFA limits the production of pro-inflammatory eicosanoids and cytokines. Thus, it prevents the inflammatory state leading to clinical depression 2. n-3 PUFA helps regulate the production, function, and metabolism of serotonin

12 weeks. The effects were unrelated to changes in physical activity or body weight but were closely related to the extent of dietary change. The modified Mediterranean diet was based on the Australian Dietary Guidelines and the Dietary Guidelines for Adults in Greece and included recommended servings for 12 food groups: whole grains; vegetables; fruits; legumes; low-fat and unsweetened dairy; raw and unsalted nuts; fish; lean red meats; eggs; chicken; olive oil; and limited intakes of sweets, refined cereals, fried food, fast food, processed meats, and sugary drinks. The type of micronutrient consumed (dietary, supplement, pharmaceutical grade, etc.).

Overall, consumption of more vegetables and fruits and less Western and pro-inflammatory foods lowers the risk of depression. Also, Mediterranean diets, "healthy" diets, and fish consumption may help prevent depression. The International Society for Nutritional Psychiatry Research and the 2015 Dietary Guidelines Advisory Committee report both recommend healthy dietary patterns for the prevention of depression.

8.4.2 Macronutrients

8.4.2.1 Proteins

The consumption of milk less than once per day or eating eggs less than once per week was linked to an elevated risk of depression in the National Health and Nutrition Examination Follow-Up Study. Similarly, fewer-than-once-a-week consumption of buttermilk or cheese was linked to a lower incidence of depression. Legumes were the only protein source linked to depression in women. A prospective examination of data from the Women's Health Initiative, on the other hand, found no link between legume consumption and risk of depression. Furthermore, those who consume fish had a lower incidence of depression. Overall, a protein-rich diet is more likely to prevent or protect against depression.

8.4.2.2 Fats

There is mixed evidence regarding the ability of n-3 PUFA to prevent or treat depression.

The higher intake of the omega-3 PUFA, α-linolenic acid, is associated with reduced risk of depression in patients with or without medical comorbidities. Multiple studies have shown the effectiveness of n-3 PUFA supplementation, either as monotherapy or adjuvant treatment (Liao et al. 2019),

In 2010, the American Psychiatric Association and the International Society for Nutritional Psychiatry Research recommended that practitioners should consider n-3 PUFA monitoring and supplementation as the standard of care during the treatment of depression (Freeman et al. 2006). Supplementation with these molecules decreases the levels of key inflammatory cytokines (Adkins and Kelley 2010). Essential fatty acid supplementation has also been shown to improve depressive symptoms in people suffering from treatment-resistant depression. Food sources high in long-chain n-3 fatty acids should be consumed as part of a healthy dietary pattern to help prevent depression. Furthermore, patients with MDD benefited from the addition of n-3 PUFA supplements to antidepressant treatment. Also, the replacement of saturated fats with unsaturated fatty acids, including monounsaturated and polyunsaturated sources, may assist with the prevention and management of depression (Arnett et al. 2019).

8.4.2.3 Carbohydrates

Carbohydrates solely contribute to the dietary glycemic index. Dietary glycemic index has a close association with depression. Evidence suggests a negative correlation of prevalence of depression with intakes of total fiber, vegetable fiber, and breads/cereal fiber (Gopinath et al. 2016). Some recent evidences suggest that it is the dietary glycemic index, not the glycemic load, that is associated with depression (Minobe et al. 2018). Hence, preventive measure should focus in modifying diets as per their glycemic index for a healthy mental well-being.

8.4.3 Vitamins and Trace Elements

8.4.3.1 Vitamins

Higher intake of vitamin B (Gougeon et al. 2016; Skarupski et al. 2010) and vitamin D (Bertone-Johnson et al. 2011) reduces the risk of depression. The outcomes of treatment studies involving vitamins as a preventive and adjunctive therapy for depression have been mixed, depending on the dosage levels used and the health conditions of participants (Fava and Mischoulon 2009; Ford et al. 2008). Folate status affects the antidepressant medication efficacy; specifically, low folate status

appears to attenuate antidepressant response. Unlike folate, vitamin B12 does not appear to alter antidepressant response. Further, the high-level vitamin D supplementation is associated with significant improvement in depressive symptoms (Jorde et al. 2008).

8.4.3.2 Trace Elements

Higher intake of zinc (Das et al. 2021) and total flavonoids (Chang et al. 2016) reduces the risk of depression. Zn as an adjunct to standard antidepressant therapy reduced depressive symptoms and other mood components (e.g., anxiety, fatigue, confusion) in a nonhospitalized population (Nowak et al. 2003).

Se has reported improvement in mood and cognitive function among patients with depression. However, in the majority of studies, the role of Se was investigated in conjunction with other antioxidants (vitamins A, C, and E) (Benton and Cook 1991).

Iron supplementation has improved the depressive symptoms in anemic mothers among South African postpartum women. Furthermore, magnesium supplementation (120 mg/day) has shown to be effective as a monotherapy or adjunct therapy for improving depressive symptoms.

Overall, the adoption of a healthy eating pattern that meets food-based dietary recommendations and nutrient requirements is important to prevent, slow the progression of, or manage depressive symptoms, as well as promote optimal mental and physical health.

8.5 Depressive Disorders Among Other Groups

Specific populations may be more vulnerable to nutrient deficiency and may require supplementation to achieve repletion (e.g., vitamin B12 deficiency among vegetarians or vegans, elderly, or pregnant women).

8.5.1 Geriatric Depression and Nutrition

Elderly represents a special population in the eating pattern for many reasons, including reduced hunger and thirst, increased risk of metabolic diseases, increased cravings for sweets, and reduced physical activity (Naitoh and Burrell 1998). This leads to a considerable correlation between the intakes of vitamin B and a decrease in the prevalence of depressive symptoms. Moreover, sufficient nutrient intake of tryptophan derived from diet appears to be an important factor in terms of nutrition and serotonin levels in the body, contrasting depressive symptoms (Klimova et al. 2020). Late-onset depression affects approximately half of the older adults with

depression (Brodaty et al. 2001). Lifestyle changes made at a younger age have an effect on the risk of depression later in life. Dietary recommendations may lower the incidence of depression in this age group.

8.5.2 Child and Adolescent Depression and Nutrition

Growing evidence indicates a robust relationship between unhealthy dietary patterns and suboptimal mental health outcomes among children and adolescents. However, due to lack of prospective data, inferences about a causal association between diet and depression in this group should be done with caution. A poor-quality diet may trigger depression by modulating various biological and regulatory mechanisms such as oxidative stress and immune-inflammatory pathways that may predispose to depression among those who are vulnerable. Malnutrition and resultant micronutrient depletions can negatively impact the physical and mental health development of children. Diet and nutrition offer modifiable targets for preventive and therapeutic interventions in this group (Khanna et al. 2019; O'Neil et al. 2014). A recent systematic review confirms as overall there is a strong correlation between healthy dietary patterns or consumption of a high-quality diet and lower depression incidence and severity, and overall better mental health. On the other hand, authors found a connection between unhealthy diet and low-quality diet consumption and depressive symptoms in children (Khalid et al. 2016).

8.5.3 Postpartum Depression and Nutrition

Pregnancy represents a peculiar phase in a woman's life, during which healthier lifestyles are generally adopted (e.g., quitting smoking and drinking), hormonal status changes, and diet is modified (food intake of raw and undercooked or uncleaned crustaceans and preserved meat is suspended), with some potential implications to the postpartum phase (Gawlińska et al. 2021). n-3 PUFA depletion occurs during pregnancy and lactation. Maternal stores can drop by half during pregnancy and do not return to prepregnancy levels until 6 months after birth. Postpartum depression is strongly linked with lower rates of seafood consumption and lower concentrations of breast milk DHA (De Vriese et al. 2003).

8.6 Limitations of Existing Evidence on Nutrition and Depression

Summarizing the evidence presented hereby, published research indicates that pro-inflammatory diets are associated with an increased risk of depression, and a healthy diet or dietary nutrients may be used to prevent and treat depression. However, the current literature should be interpreted with caution and in light of several limitations listed below.

First, as the majority of studies use a cross-sectional design, it is difficult to establish a cause/effect/comorbid relationship for various nutrients in a longitudinal view. The lack of data from prospective studies with repeated measures makes it difficult to determine the directionality and causality of observations. Second, most of the studies failed to adjust for confounding factors (such as geographic areas, local eating behaviors, smoking, cardiovascular diseases, and personal diet/exercise) and focused on middle-aged or older adults. However, underlying patterns and mechanisms are not consistent across the life span.

Third, the interventional studies are of short duration ($\leq$12 months) and based on participants with specific medical conditions. Furthermore, methodological issues (such as blinding, adherence associated with long-term dietary interventions, expectation bias, and high dropout rates (>30%)) were not adequately addressed. Therefore, evidence is derived from observational studies. Fourth, most studies may have classified depression status inconsistently because it was determined using a variety of depression scales and diagnostic tools, self-report of diagnosis, or antidepressant use rather than a structured diagnostic interview led by an expert clinician. Further, unvalidated tools (e.g., dietary assessment tool, different methods to define dietary patterns) were used to assess diet. Thus, criteria for assessing diet and depression are required for research and clinical decision-making. Fifth, broad-spectrum nutritional interventions have a greater impact than single-nutrient interventions (prescribed diet, nutritional counseling, etc.). Single-nutrient interventions may even be harmful. Finally, it should be considered that.

8.7 Future Directions

The varied measures of diet and depression were found in most of the studies, and therefore results are inconclusive and need further investigation. Nowadays, the attention that is paid to the diet and nutritional balance of patients affected by depression is still strongly neglected. More high-quality intervention, cohort studies, studies involving low- and middle-income countries, comparison between different types of diets in distinct areas of the world, and usage of clinical diagnosis of depression are required to increase the robustness and replicability of the studies. This should allow for more detailed analysis and, potentially, more detailed dietary recommendations.

8.8 Conclusion

Although there is still insufficient evidence to support nutrient supplementation for the prevention of depressive disorders, some studies indicate that the Mediterranean diet and other healthy dietary patterns may aid in the prevention and management of depression, as well as other severe physical and mental diseases. Furthermore, adequate amounts of vitamins, n-3 essential fatty acids, and trace minerals are required for normal physiological functioning, and the deficiencies of these nutrients are associated with increased risk of depression. Treating these deficiencies often improves depressive disorders. For the future, a more comprehensive therapeutic and clinical approach including knowledge about dietary patterns, specific foods, and biological mechanisms of action of critical nutrients is desirable to develop sound and feasible clinical practice guidelines integrating attention to patients' nutrition.

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Chapter 9
Nutritional Deficiencies in Obsessive-Compulsive Disorder and Possible Treatment Interventions

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Contents

Abstract Obsessive-compulsive disorder (OCD) is a neuropsychiatric disorder characterized by intrusive distressing thoughts, images, or impulses (obsessions) and/or repetitive excessive behaviors performed in response to these obsessions (compulsions). The recommended treatment for OCD is medications with serotonin

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reuptake inhibitors and/or cognitive behavioral therapy using exposure and response prevention. In recent years, an increasing body of evidence has investigated nutrition and nutritional deficiencies in OCD. This chapter reviews and summarizes the current knowledge about the potential role of nutritional elements, including amino acids, plants and herbal supplements, vitamins, trace minerals, and other nutrients in the pathophysiology and treatment of OCD. Nutrition-based interventions need to be supported by more rigorous research. Greater attention to this type of treatment is warranted given that nutrients can be of low cost, safe, and acceptable.

Keywords Obsessive-compulsive disorder · Nutrition · Deficiency · Treatment

9.1 Introduction

Obsessive-compulsive disorder (OCD) is a chronic and debilitating condition (Schruers et al. 2005). Having a lifetime prevalence of 2–3%, OCD is the fourth most frequent mental health disorder after major depressive disorder, alcohol use disorder, other substance use disorders, and social phobia (Karno et al. 1988; Kessler et al. 2005). In the past, individuals with OCD were considered to be the exception rather than the rule. This concept gradually evolved until OCD has become recognized as one of the most common and incapacitating medical conditions (Murray et al. 1996; Weissman et al. 1994). It is characterized by constant and disturbing thoughts or pictures (obsessions) that trigger anxiety and distress. Obsessions are usually associated with ritualistic behaviors (compulsions) to relieve anxiety (Abramowitz and Jacoby 2014).

First-line treatment options for OCD comprise pharmacological (serotonin reuptake inhibitors) and nonpharmacological management. Among nonpharmacological interventions, exposure and response prevention, a subtype of cognitive-behavioral therapy, is the most validated treatment (Schruers et al. 2005). Unfortunately, about one-third of all affected individuals do not adequately respond to these interventions and are deemed as treatment-resistant (Rasmussen et al. 1993). Augmentation approaches with medications, deep brain stimulation, and electroconvulsive therapy show promising effects in this group of individuals (Schruers et al. 2005).

As nutritional deficiencies have been associated with various psychiatric and neurological disorders (Nawaz et al. 2020; Pfaender and Grabrucker 2014; Rucklidge and Kaplan 2016), looking into the role of nutritional and herbal supplements in OCD has become of interest (Kuygun Karcı and Gül Celik 2020). This chapter provides a summary of the research about nutrients and their potential therapeutic role in OCD. The chapter particularly reviews evidence relating to amino acids, plants and herbal supplements, vitamins, and trace minerals, among other nutrients.

9.2 Obsessions and Compulsions

The Diagnostic and Statistical Manual of Mental Disorders (DSM) has revised the diagnostic criteria of OCD in its DSM-5 version to emphasize that compulsions might be visible behaviors or mental rituals (Abramowitz and Jacoby 2014). The DSM-5-TR did not make any further changes to the criteria (Table 9.1).

An obsession is identified as a persistent and undesirable intrusive idea, doubt, picture, or drive that enters one's mind impulsively, repeatedly, and uncontrollably (Abramowitz and Jacoby 2014). *Distressing* and *ego-dystonic* are the two terms used to describe obsessions. In most cases, the affected individual considers the intrusions to be unwarranted or excessive and makes an effort to fend them off (Veale 2002). Obsessions can be followed by compulsions. These are repetitive behaviors or mental activities that an individual feels compelled to perform in reaction to the obsession. They are largely involuntary and are only rarely resisted by the subject (Veale and Roberts 2014). A compulsion can manifest itself as either an overt activity that is visible to others (for example, double-checking that a door is properly closed) or a hidden action that is not visible or cannot be witnessed (for example, repeating a particular word or counting numbers) (Stein 2002). In general, mental compulsions are more difficult to resist or monitor than overt ones, since they are more "portable" and easier to conduct (Stein et al. 2019). One distinction between OCD and other impulsive behaviors is that compulsions are not rewarding, whereas

Table 9.1 DSM-5-TR criteria and specifiers for obsessive-compulsive disorder

Criteria		Specifiers
Presence of obsessions, compulsions, or both	Obsessions are defined as (1) recurrent and persistent thoughts, urges, or impulses that are intrusive and unwanted, and (2) the individual attempts to ignore, suppress, or neutralize them by performing a compulsion	**With good or fair insight**: The individual recognizes that OCD beliefs are definitely/probably not true or may/may not be true
	Compulsions are defined as (1) repetitive behaviors or mental acts that the individual feels driven to perform in response to an obsession, and (2) the compulsions are aimed at preventing or reducing distress	
Symptoms are time consuming (take more than 1 h per day) or cause clinical distress or impairment		**With poor insight**: The individual thinks that OCD beliefs are probably true
Symptoms are not attributable to a substance or another medical condition		**With absent insight/delusional beliefs**: The individual is completely convinced that OCD beliefs are true
The disturbance is not better explained by another mental disorder		**Tic related**: The individual has a current or history of a tic disorder

impulsive behaviors, such as shopping, gambling, or paraphilias, relate to immediate satisfaction (Stein et al. 2019).

Obsessions include fear of contamination, doubt, and thoughts about sexuality, violence, or religion. Compulsions encompass excessive washing and checking behaviors (Schruers et al. 2005). A cluster of symptoms related to symmetry concerns and arranging rituals has been identified, along with another cluster related to hoarding (Leckman et al. 2001a, b). Feelings connected with OCD include disgust (particularly in contamination OCD), shame (especially in the presence of sexual, religious, or forbidden ideas), and an unpleasant sensation of "incompleteness" until things seem "exactly right" (Leckman et al. 2001a, b). Many diseases, such as autism spectrum disorder, Tourette's syndrome, and frontal lobe lesions, are characterized by obsessive-compulsive or stereotypic symptoms as an integral part of their symptomatology. In contrast, other disorders have a narrow focus of obsessions and compulsive behaviors; body dysmorphic disorder (concerns about imagined ugliness) and illness anxiety disorder (concerns about an imagined disease) are examples of those who suffer from somatic obsessions and compulsions. Disorders that have traits and psychobiology that are similar to OCD are classified as being on a spectrum of obsessive-compulsive disorders (Hollander et al. 1996).

OCD is equally common in both genders, although during childhood, it predominantly affects males. Over 85% of affected individuals will develop OCD symptoms before the age of 35 (Schruers et al. 2005). Symptomatology presents with a wide range of severity, from slight interference with everyday functioning to severe handicap. A chronic course of illness is also typical, with periods of remission occurring now and then. Symptoms are reported to last on average 10–12 years, with many enduring severe symptoms for a lengthy period before finding relief (Rasmussen and Tsuang 1984).

9.3 Nutritional Deficiencies and Obsessive-Compulsive Disorder

OCD has been established as a polygenic disorder, with evidence showing clusters in families, specific involved candidate genes, and single-nucleotide polymorphism-based heritability (refer to (Mahjani et al. 2021) and (Szejko et al. 2021) for a discussion of genetics, epigenetics, and genomics in OCD). Genomics of OCD could help unravel pathophysiological pathways contributing to the disease and, subsequently, develop personalized treatment plans. At this level, the role of nutrigenomics arises. Nutrigenomics refers to the study of the impact of nutrients on the expression of genetic makeup. Similar to pharmacogenomics where one medication will have various effects on different members of the population, nutrigenomics implies that only certain individuals will positively respond to specific nutritional interventions (Mead 2007). Moreover, the relationship between nutrigenomics and mental disorders remains in its infancy (Dauncey 2012). One

should keep this in mind while examining the literature about nutritional deficiencies in OCD.

9.3.1 Amino Acids and Derivatives

This section describes the role of glutamate, glycine, and N-acetyl cysteine (NAC) in the pathophysiology and treatment of OCD. Table 9.2 provides a concise summary of the characteristics of each element and their possible role in OCD.

9.3.1.1 Glutamate

Glutamate, the most abundant amino acid in the central nervous system (CNS), accounts for 5–15 mmol/kg of brain tissue, depending on the area (Danbolt 2001; Sanacora et al. 2004; Schousboe 1981; Snyder and Ferris 2000). More than 50 years of research have yielded a wide range of activities for glutamate in the CNS. Glutamate has a crucial role in the brain's metabolic processes: it is the primary excitatory neurotransmitter and a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) (Krebs 1935; Roberts and Frankel 1950; Sundaram et al. 2012). All circuits in the CNS, including intracortical and subcortical ones, are connected by glutamatergic projections (Shepherd 2004).

The excitotoxicity of glutamate may contribute to the pathophysiology of several neurological conditions, including Huntington's (Van Raamsdonk et al. 2005), Alzheimer's (Parameshwaran et al. 2008), and Parkinson's (Helton et al. 2008) diseases. Along the same lines, numerous neurologic illnesses can be alleviated by the development of selective glutamate receptor antagonists (Lipton 2004).

Recent data suggest that glutamate is dysregulated in OCD. In particular, OCD may be exacerbated by anomalies in the homeostasis and neurotransmission of glutamate in the cortico-striato-thalamo-cortical circuitry (Carlsson 2000, 2001; Chakrabarty et al. 2005; Pittenger et al. 2006; Rosenberg and Hanna 2000;

Table 9.2 Amino acids, derivatives, and their potential role in OCD

Nutrient	Alternative name(s)	Molecular formula	Appearance	Supplementation in OCD
Glutamate	Glutamic acid	$C_5H_9NO_4$	White crystalline powder	Possible therapeutic effect mediated by glutamate-modulating agents, such as memantine and riluzole. More evidence is available for the former agent
Glycine	Amino acetic acid	$C_2H_5NO_2$	White solid	Possible efficacy, yet limited by the profile of side effects
N-acetyl cysteine	Mucomyst (generic name)	$C_5H_8NO_3S$	Oral or intravenous formulation	Can be efficacious as an adjunct treatment in OCD and other related disorders

Rosenberg et al. 2000; Ting and Feng 2008). When it comes to pathophysiology, genetic studies provide the strongest evidence that glutamate homeostasis has an essential role in OCD. For instance, the role of the glutamate transporter gene Slc1A1 has been well established (Arnold et al. 2006; Dickel et al. 2006) and replicated (Kwon et al. 2009; Shugart et al. 2009). In patients diagnosed with schizophrenia who carried the Slc1A1 haplotype, antipsychotic treatment induced OCD symptoms, demonstrating a complex interplay between glutamate and dopamine circuits in OCD (Kwon et al. 2009). The Slc1A1 locus polymorphism interacts with a locus on chromosome 14, determining susceptibility for compulsive hoarding behaviors (Liang et al. 2008). Another haplotype at the Slc1A1 region, made of three single-nucleotide polymorphisms, was found to be about twice more common in individuals with OCD in comparison to healthy counterparts (Wendland et al. 2009). Polymorphisms in the Sapap3 gene, which codes for a glutamate-regulating family of proteins, have also been linked to OCD and other related conditions such as trichotillomania (Bienvenu et al. 2009; Boardman et al. 2011; Züchner et al. 2009).

Glutamate-modulating drugs have been investigated in the management of treatment-resistant OCD. Growing evidence points to the possibility of riluzole, memantine, and NAC as being efficacious. The latter is discussed in detail below. There are glial cells, specifically astrocytes, that remove most of the glutamate in the body, and the glutamate-modifying medication riluzole showed promise in treating refractory OCD by targeting these astrocytic glutamate transporters (Coric et al. 2005; Pittenger et al. 2006). The efficacy of the N-methyl-D-aspartate (NMDA)-blocking medication memantine was established in the animal models of OCD (Egashira et al. 2008; Wald et al. 2009). Clinical research also showed promising results for memantine in the treatment of OCD. Multiple case reports of patients with treatment-resistant OCD showed improvement in symptoms following memantine addition (Hezel et al. 2009; Pasquini and Biondi 2006; Poyurovsky et al. 2005). In an open-label study, patients with refractory OCD ($n = 14$) were given memantine augmentation for 12 weeks. About half (42%) showed a response, with at least 25% improvement on the Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) score (Aboujaoude et al. 2009). Another open-label study looked at the efficacy of 12-week memantine supplementation in patients with OCD ($n = 10$) and generalized anxiety disorder ($n = 7$). Those with OCD showed a statistically significant improvement in their symptomatology, with a 40.6% reduction in Y-BOCS scores (Feusner et al. 2009). Another single-blinded case-control study included 44 individuals with OCD receiving standard intensive inpatient treatment, of whom 22 also received memantine augmentation. Y-BOCS scores significantly improved in the memantine group (27%) compared to controls (16.5%) (Stewart et al. 2010).

Further insights into the function of glutamate in the pathophysiology of OCD may allow prediction of treatment response. Glutamate-modulating drugs have shown promising results in early clinical trials, but more research is needed before they can be considered safe and effective.

9.3.1.2 Glycine

Glycine is an amino acid produced by animals, microbes, and plants but is not required for survival. It is one of the most basic amino acids present in animal proteins. Glycine is found in nearly all tissues and has a significant function in the metabolism of one-carbon fragments, peptides, proteins, and nucleotides, among other molecules. Glycine acts as an inhibitory neurotransmitter in the CNS, spinal cord, and retina. It also has a role in mediating excitatory glutamatergic neurotransmission; it is a necessary co-agonist of glutamate at NMDA receptors (Betz et al. 2006; Bowery and Smart 2006; López-Corcuera et al. 2001).

Psychiatric and neurological disorders may benefit from drugs that increase the potency of glycine-mediated effects. Schizophrenia, for instance, has been linked to glutamatergic transmission dysfunction, mediated by NMDA receptors (Deutsch et al. 1989). The loss of glycinergic input has been considered to be a contributing factor in diseases of muscular tone control (Simpson Jr. et al. 1995). Consequently, many studies looked into the possible role and effects of glycine in various settings, such as schizophrenia (Heresco-Levy et al. 2004; Javitt et al. 2001), depression (Altamura et al. 1995), alcohol use disorder (Harvey and Yee 2013), and cognitive functioning (Peyrovian et al. 2019).

In OCD, a 12-week randomized controlled trial provided patients on stable treatment regimens with adjunct glycine (titrated to 60 g/day) or placebo. The glycine-treated group had a high dropout rate (7 out of 12 participants) due to unpleasant taste and significant nausea. The remaining 5 participants, in comparison to placebo ($n = 9$), displayed a statistically significant 6-point decrease on their Y-BOCS (Greenberg et al. 2009). A case report provided anecdotal evidence for the efficacy of glycine supplementation (50–66 g/day) in a young adult with treatment-resistant OCD and comorbid body dysmorphic disorder (Cleveland et al. 2009). These findings highlight a possible therapeutic effect of glycine in OCD, yet clinically limited due to its profile of side effects.

9.3.1.3 N-acetyl Cysteine

NAC, an amino acid-based nutraceutical, has been found to modify the release of glutamate in the synapses of subcortical brain regions. This is mediated through the modulation of the cysteine-glutamate antiporter. NAC is usually safe and well tolerated; gastric intolerance is its most reported side effect (Miller and Rumack 1983). As NAC has the potential to regulate numerous neuropathological pathways, including those associated with glutamate homeostasis, inflammation, and oxidative stress, it has been explored as adjunctive therapy for many psychiatric conditions, such as mood disorders, OCD, substance use disorders, and schizophrenia (Ooi et al. 2018).

The therapeutic effect of NAC on OCD has been well studied. A systematic review looking at the role of NAC in the management of OCD and related disorders

found positive results from 4 clinical trials and 5 case reports (Oliver et al. 2015). More specifically, a dose range of 2400–3000 mg/day of NAC reduced the severity of OCD symptoms and showed good tolerance to the medication (Oliver et al. 2015). Another study included nine clinical trials on the treatment effects of NAC in OCD and related disorders such as trichotillomania, excoriation, onychophagia, and Tourette's syndrome, and found NAC use to be most promising in excoriation (Minarini et al. 2017).

More recently, a 20-week open-label study provided 28 participants with treatment-resistant OCD with an adjunct purpose-formulated combination of nutraceuticals containing NAC among other elements (L-theanine, zinc, magnesium, pyridoxal-5′ phosphate, and selenium). The researchers reported a significant mean reduction on the Y-BOCS total score (by −7.13 average points) from baseline till the end of follow-up. At 20 weeks, one-quarter of participants (23%) were considered "responders," defined as Y-BOCS ≥35% reduction and "very much" or "much improved" on the Clinical Global Impression-Improvement scale. In addition, a statistically significant improvement was observed on other scales assessing for anxiety, depression, and quality of life. Particularly, treatment response on OCD was more prominent in those with lower baseline symptom levels, while it was reduced in those with more severe symptomatology (Sarris et al. 2021).

Current evidence, therefore, supports the use of NAC as a possible adjunct therapy for OCD among other psychiatric conditions, with a suggested dose of 2000–2400 mg/day.

9.3.2 Plants and Derivatives

This section describes the role of borage, curcumin, milk thistle, St. John's wort (SJW), and valerian root in the treatment of OCD. Table 9.3 provides a concise summary about the characteristics of each element and their possible benefit in OCD. Research about the role of herbs and plants in this field remains limited, and more studies are required to establish their efficacy and safety in OCD.

9.3.2.1 Borage

Borage is a Persian thymoleptic plant with medicinal properties. Animal models revealed that it has anxiolytic and sedative properties similar to diazepam (Rabbani et al. 2004). One randomized controlled trial showed that borage has antidepressant effects (Sayyah et al. 2006).

One study assessed the efficacy of 6-week supplementation of borage (500 mg/day) versus placebo in the treatment of 44 patients with OCD. Results showed a significant decrease in Y-BOCS and Hamilton Anxiety Rating Scale (HAM-A) scores in those receiving borage at weeks 4 and 6 of treatment. At week 6, Y-BOCS and HAM-A scores in participants receiving the intervention decreased

Table 9.3 Plants, derivatives, and their potential role in OCD

Plant	Alternative name (s)	Nativity	Flower's color	Supplementation in OCD
Borage	*Echium amoenum*, starflower	Mediterranean region and Europe	Blue	One randomized placebo-controlled trial showed possible benefit for borage supplementation in OCD
Curcumin	Diferuloylmethane	South-east Asia (from Curcuma longa)	Yellow	No clinical trials for curcumin in OCD
Milk thistle	*Silybum marianum*, Saint Mary's thistle	Mediterranean region and Europe	Purple	One randomized placebo-controlled trial showed no benefit for milk thistle supplementation in OCD
SJW	*Hypericum perforatum*, Klamath weed	Europe, North Africa, and Southwest Asia	Yellow	Mixed and limited evidence for SJW efficacy in OCD
Valerian root	*Valeriana officinalis*	Europe and Asia	White	One randomized placebo-controlled trial showed possible benefit for valerian root supplementation in OCD

by 6 and 10 points from baseline, respectively. There was no difference between treatment groups in terms of adverse effects (Sayyah et al. 2009).

9.3.2.2 Curcumin

Curcumin, the active ingredient in turmeric, is a yellow spice extracted from the roots of *Curcuma longa* (Aggarwal et al. 2007). Curcumin has the potential to regulate tumor growth (Larasati et al. 2018). It modulates oxidative stress and inflammatory cytokines (Ayati et al. 2019; Miao et al. 2021) and can cross the blood-brain barrier (BBB) (Hoppe et al. 2013). Curcumin also increases serotonin levels in the brain (Kulkarni and Dhir 2010). It was shown to have neuroprotective effects in several neurological and psychiatric disorders, including traumatic brain injury (Sharma et al. 2009), Alzheimer's disease (Yang et al. 2005), Parkinson's disease (Wang et al. 2010), bipolar disorder (Gazal et al. 2014), and epilepsy (Farooqui 2012).

No clinical studies looked into the role of curcumin in OCD. In preclinical models, one study investigated curcumin supplementation in a quinpirole-induced rat model of OCD. Rats were divided between controls, negative controls, two groups receiving curcumin (5 mg/kg and 10 mg/kg), and one group receiving paroxetine (1.8 mg/kg) for 35 days. Results showed a significant improvement in the compulsive checking and ritualistic behaviors in the curcumin groups. An increase in serotonin and a reduction in dopamine levels were noted in the

curcumin-treated rats. Curcumin had a shielding effect on the memory task and was comparable to the selective serotonin reuptake inhibitor paroxetine (Chimakurthy and Murthy 2010). Another preclinical study assessed the effect of curcumin in Swiss albino mice and found that 40 mg/kg significantly attenuated compulsive behaviors. This effect was mediated by neuromodulation with serotonin 5-HT receptors (Mishra et al. 2021).

9.3.2.3 Milk Thistle

Milk thistle is a plant with medicinal properties that grows in the Persian and Mediterranean regions. Silymarin, a key constituent of milk thistle, has antioxidant, anti-inflammatory, immune-modulatory, and antidepressant effects (Katiyar 2005). It inhibits monoamine oxidase enzyme and increases cortical serotonin levels (Mazzio et al. 1998; Osuchowski et al. 2004). It also ameliorates reductions in serotonin and dopamine in the hippocampus and prefrontal cortex, observed with stimulant misuse (Lu et al. 2010).

One randomized controlled trial compared the efficacy of milk thistle (600 mg/day) to fluoxetine (30 mg/day) in 35 patients diagnosed with OCD. Participants, followed for 8 weeks, had a baseline average Y-BOCS score > 21. Results showed no difference between treatment groups in Y-BOCS scores at the end of treatment. Milk thistle supplementation was not associated with notable side effects (Sayyah et al. 2010).

9.3.2.4 St. John's Wort

SJW is a spreading leafy plant found in open regions throughout most of the temperate world. It has been widely employed in the manufacture of teas and tinctures to cure anxiety, melancholy, insomnia, water retention, and gastritis. It is mostly composed of chemical elements such as hypericin and hyperforin (Klemow et al. 2011). SJW blocks the reuptake of serotonin, norepinephrine, and dopamine at neural synapses. It also prevents GABA from attaching to GABA receptors (Peterson and Nguyen 2022). SJW has established evidence in the treatment of depression and other psychiatric disorders (Apaydin et al. 2016; Sarris and Kavanagh 2009).

Two studies assessed the effectiveness of SJW in OCD. An open trial investigated the efficacy of a 12-week treatment with SJW (450 mg twice per day—0.3% hypericin) in 12 patients diagnosed with OCD. Results showed a significant decrease in the mean Y-BOCS score from baseline to endpoint (Taylor and Kobak 2000). A subsequent randomized controlled trial compared a 12-week treatment with SJW (flexible dose of 600–1800 mg/day) to matching placebo. However, no difference was found between groups on the total Y-BOCS score or its subscales at the end of treatment (Kobak et al. 2005).

9.3.2.5 Valerian Root

Valerian root is a 3–5-foot-tall perennial plant found in North America, Europe, and Asia (Kinrys et al. 2009). Sesquiterpenes of the volatile oil (containing valeric acid), iridoids (valepotriates), lignans, alkaloids, and furanofuran are found in valerian roots. All varieties of the root contain amino acids such as GABA and glutamine (Hadley and Petry 2003). Several mechanisms of action of valerian root have been described, including enhancement of GABA transmission (Yuan et al. 2004) and modulation of serotonin via 5-HT5A receptors (Dietz et al. 2005).

Valerian root extracts were shown to improve sleep quality and decrease sleep latency (Hiller and Zetler 1996). They are often used to treat insomnia (Beaubrun and Gray 2000) and, in a recent meta-analysis, were found to be safe and effective in promoting sleep and preventing associated disorders (Shinjyo et al. 2020). They were also found effective in the treatment of other psychiatric disorders (Müller et al. 2003; Roh et al. 2019). One 8-week randomized placebo-controlled trial looked at the efficacy of valerian root extract (765 mg/day) in 31 adults with OCD. Those treated with the extract had significantly lower scores on the Y-BOCS scores at weeks 4, 6, and 8 as compared to the placebo group (Pakseresht et al. 2011).

9.3.3 Vitamins

This section describes the role of vitamins in the treatment of OCD. Table 9.4 provides a concise summary of the characteristics of each vitamin and its possible role in OCD. More research into the efficacy of vitamin supplementation in OCD is needed.

9.3.3.1 Vitamin B9

Vitamin B9 aids in DNA and RNA synthesis, as well as in the metabolism of proteins. It is crucial for the breakdown of homocysteine, an amino acid which when present in excessive concentrations can have deleterious effects on the body. Folate is necessary for the functioning of the CNS. Ample studies have shown that individuals deficient in vitamin B9 can present with psychological symptoms, particularly depression and impaired cognition (Bottiglieri et al. 2000; Reynolds 2002).

In one study, mean folate levels in patients admitted to a psychiatry ward were substantially lower compared to healthy patients. A positive association was also found between decreased vitamin B9 levels and depression (Lerner et al. 2006). Folate level, along with other types of vitamin B, was found to be significantly lower in individuals diagnosed with attention-deficit hyperactivity disorder compared to healthy individuals (Landaas et al. 2016).

Table 9.4 Vitamins and their potential role in OCD

Vitamin	Alternative name(s)	Molecular formula	Adult normal range	Solubility	Supplementation in OCD
B9	Folate, folacin	$C_{19}H_{19}N_7O_6$	2.7–17.0 ng/mL	Water soluble	Not effective
B12	Cobalamin	$C_{63}H_{88}CoN_{14}O_{14}P$	160.0–950.0 pg/mL	Water soluble	Anecdotal evidence for efficacy in OCD
C	Ascorbic acid	$C_6H_8O_6$	0.6–2.0 mg/dL	Water soluble	No clinical trials for vitamin C in OCD
D	Calciferol, sunshine vitamin	$C_{28}H_{44}O$	20.0–40.0 ng/mL	Fat soluble	No clinical trials for vitamin D in OCD
E	Tocopherol	$C_{29}H_{50}O_2$	5.5–17.0 μg/mL	Fat soluble	No clinical trials for vitamin E in OCD

One study assessed folate and homocysteine levels in the blood of patients with OCD ($n = 23$) in comparison to a matched number of healthy controls. Folate levels were significantly decreased in the OCD group, whereas homocysteine levels were significantly elevated. In addition, there was a statistically significant and unfavorable relationship between vitamin B9 level and Y-BOCS scores (Atmaca et al. 2005). However, other studies did not find evidence for folate deficiency in individuals with OCD (Esnafoğlu and Yaman 2017; Hermesh et al. 1988; Türksoy et al. 2014). One double-blind, placebo-controlled, 12-week study assessed the efficacy of using folic acid (5 mg/day) as an adjunct to fluoxetine (40 mg/day) in patients with OCD ($n = 36$). Over the treatment period, no differences were found between groups in Y-BOCS scores and other scales assessing for comorbid depression and anxiety (Tural et al. 2019). One open-label two-phase study compared aripiprazole, olanzapine, and L-methyl folate (a metabolite of folic acid) in patients with treatment-resistant OCD ($n = 60$). Those in the olanzapine and aripiprazole groups showed a significant improvement on their Y-BOCS and Clinical Global Impression-Severity scale scores. However, there were no changes in the L-methyl folate group. L-methyl folate, although effective in treatment-resistant depression, was therefore not useful in treatment-resistant OCD (Dar et al. 2021). Thus, evidence for the efficacy of vitamin B9 supplementation in patients with OCD seems to be limited.

9.3.3.2 Vitamin B12

Vitamin B12 is found in beef, eggs, and dairy products. Individuals consume nearly 2.4 g of vitamin B12 each day, of which only 50–60% is absorbed (Shipton and Thachil 2015). Vitamin B12 is important for DNA synthesis, CSN development, neuronal myelination, and cognitive activity, among other processes (Venkatramanan et al. 2016). Symptoms of vitamin B12 deficiency include negativism, insomnia, impaired concentration and attention, disorientation, and amnesia (Tufan et al. 2012). Its deficiency has been linked to a variety of psychiatric illnesses (Berry et al. 2003), including depression, bipolar disorder, panic disorder, phobias, and neurocognitive disorders (Eastley et al. 2000; Lachner et al. 2012).

Few studies investigated the role and level of vitamin B12 in patients with OCD. One study found a statistically significant decreased level of cobalamin in patients diagnosed with OCD ($n = 35$) as compared to controls ($n = 22$). In particular, deficiency was detected in 31.4% of participants in the former group, while no deficiency was observed in controls (Türksoy et al. 2014). These results replicated an older study that described a lower level of vitamin B12 in patients with OCD ($n = 30$) in comparison to healthy individuals ($n = 30$) (Hermesh et al. 1988). Sharma and Biswas described a case of a young adult man who presented with symptoms of OCD and was found to have a decreased vitamin B12 level and positive family history of cobalamin deficiency. Interestingly, his symptoms resolved upon methylcobalamin supplementation (Sharma and Biswas 2012). Another case report suggested a causality between OCD presentation and vitamin B12 deficiency (Valizadeh and Valizadeh 2011), but it was later refuted (Upadhyaya and Sharma 2012).

9.3.3.3 Vitamin C

Oxidative stress and free radical formation have been associated with the pathogenesis of many psychiatric disorders, including OCD. Ultraviolet light, cigarette smoking, and some pollutants are well-known determinants of free radical-induced toxicity to the CNS. Malondialdehyde, a product of membrane lipid peroxidation that represents free radical-mediated damage, has been significantly increased among patients with OCD (Shohag et al. 2012b). As such, vitamin C, a well-known antioxidant, was suggested to have a role in the pathophysiology of this disorder (Ersan et al. 2006).

Vitamin C is an essential vitamin available in fruits and vegetables, including oranges, broccoli, spinach, and tomatoes. Most of vitamin C intake comes from daily food resources. Despite this, deficiency is common, with a prevalence of 7.1% in the United States (Schleicher et al. 2009). Deficiency has been linked to many conditions, including infectious diseases and COVID-19 infection, cardiovascular diseases, severity of diabetes mellitus, stroke recovery, and sepsis (Lykkesfeldt and Tveden-Nyborg 2019). Severe vitamin C deficiency, or scurvy disease, has been

associated with symptoms of low mood, inattention, decrease in concentration, and cognitive impairment (Plevin and Galletly 2020).

A recent meta-analysis found a significant reduction in vitamin C level in individuals with OCD (Balandeh et al. 2021). Another meta-analysis had comparable results, with a significant association between low ascorbic acid levels and OCD. This was attributed to a surge of the oxidant markers 8-hydroxydeoxyguanosine and malondialdehyde, and the antioxidants glutathione peroxidase and superoxide dismutase (Maia et al. 2019). Otherwise, no studies looked into the efficacy of vitamin C supplementation for the management of OCD; assessing the therapeutic effects of ascorbic acid in this disorder is warranted.

9.3.3.4 Vitamin D

Vitamin D is invaluable to the human body for calcium and phosphorus homeostasis, immunity, and muscle performance (Cuomo et al. 2019). The role of vitamin D in the pathogenesis of psychiatric and neurological disorders has been steadily gaining traction in the medical community. For example, vitamin D deficiency was found to be associated with autism spectrum disorders, mood disorders, psychotic disorders, Alzheimer's disease, multiple sclerosis, and Parkinson's disease (Cuomo et al. 2019).

In its active form, 1,25-dihydroxy-vitamin D3 regulates both tryptophan hydroxylase and tyrosine hydroxylase. These two hormones are responsible for the synthesis of serotonin, dopamine, epinephrine, and norepinephrine. Vitamin D deficiency, by interfering with the production of these neurotransmitters, may contribute to the pathophysiology of OCD (Cui et al. 2015; Kaneko et al. 2015). Moreover, vitamin D may have a neuroprotective role through its antioxidant effects, mediated by inhibiting nitric oxide synthase, an enzyme responsible for nitric oxide synthesis. An increase in nitric oxide level has been linked to the pathogenesis of OCD (Behl et al. 2010).

At a clinical level, studies looking at vitamin D in patients with OCD are restricted to children and adolescents. One study described a case report where vitamin D supplementation alleviated OCD symptoms in a 7-year-old boy whose symptomatology was associated with streptococcal infection. This pointed to vitamin D deficiency as a potential cause of his symptoms (Celik et al. 2016). One other study by the same group of researchers compared serum vitamin D level in patients with OCD associated with streptococcal infection ($n = 33$) and control subjects ($n = 20$). Although there was no significant difference in vitamin D between groups, vitamin D deficiency (level of <15 ng/mL) was significantly more common in the patient group (Çelik et al. 2016). Another study also found no difference in vitamin D level between adolescents with OCD and healthy controls, although a negative correlation was observed between level and scores on the children's Y-BOCS (Yazici et al. 2018). Alternatively, one study did show significantly lower vitamin D levels in 52 adolescents diagnosed with OCD as compared to controls ($n = 30$)

(Esnafoğlu and Yaman 2017). These mixed results warrant further investigation of the function of calciferol in the pathogenesis of OCD.

9.3.3.5 Vitamin E

Vitamin E is a common nonenzymatic antioxidant that plays a crucial role in balancing the production of free radicals in the CNS (Rabe-Jabłońska and Dietrich-Muszalska 2015). It is mostly available in plant-derived products, such as seed oils (Mène-Saffrané 2017). Vitamin E deficiency is common in developing countries and typically affects extremes of age including children and the elderly (Dror and Allen 2011).

In preclinical models, vitamin E deficiency is associated with heightened anxiety-like behaviors in rats (Desrumaux et al. 2018; Terada et al. 2021). Clinically, supplementation with vitamin E has neuroprotective effects, and high plasma levels were found to be possibly linked to a decreased risk of Alzheimer's (Mangialasche et al. 2010). Vitamin E can potentially be used as an adjuvant for the management of depressive symptoms (Manosso et al. 2020). It may also have benefits in reducing antipsychotic-induced tardive dyskinesia (Soares-Weiser et al. 2018).

In OCD, two meta-analyses established a significantly lower vitamin E level in patients with OCD as compared to healthy individuals (Balandeh et al. 2021; Maia et al. 2019). This was attributed to increased malondialdehyde levels, a marker of oxidative stress and oxidation-mediated cellular injury, and decreased serotonin levels in the brain (Maia et al. 2019). These findings hint towards the potential role of vitamin E in OCD.

9.3.4 Trace Minerals

This section describes the role of trace elements in the treatment of OCD. Table 9.5 provides a concise summary of the characteristics of each trace element and their possible role in OCD.

9.3.4.1 Zinc

Zinc (Zn) is the second most abundant trace mineral in the human system. Zn is involved in a range of biochemical and physiological processes (Weiss et al. 2000). It has been linked to growth and development, cellular differentiation, immune response, DNA and protein synthesis, gene expression, enzymatic catalysis, inflammation and oxidative stress, neurotransmission, and cognitive functioning (Bhowmik and Kumar 2010; Plum et al. 2010). Zn dyshomeostasis causes increased permeability of the BBB. This is mediated by an increase in oxidative stress (Qi and Liu 2019). Typically, Zn protects the BBB from oxidative stress via its

Table 9.5 Trace elements and their potential role in OCD

Trace element	Molecular formula	Appearance	Adult normal range	Supplementation in OCD
Zinc	Zn +2; atomic number 30	Silver-gray	0.66–1.10 mcg/mL	One randomized placebo-controlled trial showed possible benefits for zinc supplementation in OCD
Selenium	Se; atomic number 34	Gray metallic	70.00–150.00 ng/mL	One randomized placebo-controlled trial showed possible benefits for selenium supplementation in OCD

membrane-stabilizing and antioxidant activities, assisting in the maintenance of metabolic homeostasis in the CNS (Fu et al. 2014). Zn is also involved in neurogenesis (Levenson and Morris 2011). Loosely bound Zn is found in high concentrations in the dentate gyrus and olfactory bulb synaptic vesicles, where neurogenesis and migration are most active in the adult brain (Kumar et al. 2021). Additionally, Zn is needed for the formation of Zn finger proteins, which participate in the regulation of gene expression, DNA binding to transcription factors, and protein-protein interactions (MacDonald 2000). Numerous studies showed that zinc supplementation, when given throughout pregnancy, effectively reduces lipopolysaccharide-induced upregulation of pro-inflammatory factors, for example interleukin 6 and tumor necrosis factor, in the prefrontal cortex (Mousaviyan et al. 2021).

Alterations in serum Zn level have been described in several psychiatric disorders. For instance, one meta-analysis found depression to be associated with reduced Zn plasma level (Swardfager et al. 2013). In OCD, one study compared serum levels of trace elements between healthy controls ($n = 48$) and patients with OCD ($n = 48$). Results showed significantly decreased level of zinc in the latter group, along with significantly low levels of iron and magnesium. Patients with OCD also displayed an imbalance in trace element homeostasis and element-to-element interrelationship pattern (Shohag et al. 2012a). An 8-week randomized placebo-controlled study assessed the efficacy of fluoxetine plus Zn supplementation in patients with OCD. Twelve patients were given fluoxetine (20 mg/day) plus Zn (440 mg/day), while the control group ($n = 11$) received fluoxetine plus placebo. Both groups showed a reduction in the mean Y-BOCS score. However, at the end of treatment, patients treated with fluoxetine plus Zn had significantly lower scores in comparison to placebo (Sayyah et al. 2012).

9.3.4.2 Selenium

Selenium (Se) is present in the body as selenoproteins, which characteristically are oxidoreductases. It regulates the antioxidant properties of several enzymes, including the glutathione peroxidase enzyme (Wołonciej et al. 2016). Se modulates the

production of active thyroid hormone and is required for the functioning of the immune system (Rayman 2000).

The role and effects of Se in psychiatric illnesses are not very well established. One cross-sectional study showed a lower prevalence of depression in individuals consuming high doses of Se, even after adjusting for sociodemographic and lifestyle variables (Ferreira de Almeida et al. 2021). One randomized placebo-controlled trial did not find a benefit from Se on mood symptoms and quality of life in elderly volunteers (Rayman et al. 2006). Alternatively, co-supplementation of Se and probiotics in diabetic people with coronary heart disease, as compared to placebo, significantly improved depression and anxiety symptoms (Raygan et al. 2019).

Serum Se levels were noted to be significantly reduced in 28 individuals with OCD as compared to matched healthy controls ($n = 28$) (Ozdemir et al. 2009). One randomized placebo-controlled study recruited 30 patients with treatment-resistant OCD and a baseline Y-BOCS>21 and then divided them into two equal groups: selective serotonin reuptake inhibitor with Se (200 mcg/day) or with placebo. After 6 weeks, the former group displayed a statistically significant decline in the Y-BOCS scores in comparison to the placebo group, with no substantial side effects (Sayyah et al. 2018).

9.3.5 Others

9.3.5.1 Myoinositol

Myoinositol (MI) is a stereoisomer of inositol, a C6 sugar alcohol (Bizzarri et al. 2016). MI is the precursor of inositol triphosphate, an intracellular second messenger that regulates thyroid-stimulating hormone, insulin, and follicle-stimulating hormone (Di Paolo and De Camilli 2006). In neural cells, MI is mainly produced by three pathways: (1) receptor-mediated salvage mechanism, (2) de novo synthesis using glucose 6-phosphate as a precursor, and (3) dietary myoinositol uptake via myoinositol transporters (Downes and Macphee 1990).

MI has shown clinical efficacy in panic disorder (Benjamin et al. 1995) and depression (Levine et al. 1995), among other psychiatric conditions (Sarris et al. 2010). Its role in the neurobiology of OCD has been noted in the literature. MI may regulate the reuptake of serotonin and enhance 5-HT2 receptor density, contributing to a potential therapeutic role in OCD (Harvey et al. 2002). MI level was also observed to be significantly reduced in the prefrontal cortex of individuals diagnosed with OCD, as compared to healthy controls (Batistuzzo et al. 2015).

Several studies investigated the advantages of MI supplementation in OCD. Early research documented a significant decrease in Y-BOCS scores in patients with OCD ($n = 13$) who received MI (18 g/day) for 6 weeks as compared to matched controls (Fux et al. 1996). However, a follow-up study conducted by the same investigators using the same protocol failed to replicate this finding (Fux et al. 1999). Similarly, Seedat and Stein did not find any benefit of MI (18 g/day) augmentation of selective

serotonin reuptake inhibitors in ten patients with OCD who were treated for 6 weeks (Seedat and Stein 1999). Alternatively, 14 patients with treatment-free OCD were provided with MI (18 g/day) and followed for 12 weeks in an open-label trial. Participants showed a significant decrease in their Y-BOCS scores. In addition, using single-photon emission computed tomography, lower cerebral perfusion in the prefrontal cortex, temporal lobe, and parietal cortex was found to be associated with a clinical response after MI (Carey et al. 2004). Due to the limitations of sample size and open-label design, further studies are needed to properly establish the efficacy of MI supplementation in OCD.

9.3.5.2 Omega-3 Fatty Acids

Omega-3 fatty acids have long been studied for their benefits in vascular health. Examining the adult brain composition, polyunsaturated fatty acids—eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)—are found in high concentrations and have a major role in neuronal membrane functioning. The beneficial effects of omega-3 fatty acids in mental health have been postulated owing to this contribution. Clinical studies associate a diet rich in fish with a low incidence of psychiatric disorders; this has proven to be directly linked to omega-3 fatty acid intake from fish (Lakhan and Vieira 2008). The accepted daily dose of omega-3 fatty acid for healthy individuals is 1–2 g. However, for individuals with mental disorders, up to 9.6 g is safe and efficacious (Eritsland 2000; Stoll et al. 1999; von Schacky 2006).

Only one study assessed the efficacy of EPA supplementation in OCD. This was a 6-week, placebo-controlled, two-phase crossover randomized controlled trial administering EPA (2 g/day) to 11 individuals with OCD. Patients maintained their selective serotonin reuptake inhibitor medication throughout the study. There was neither a treatment effect for any of the clinical outcomes, including OCD, depression, and anxiety symptoms, nor a significant drug-by-time interaction. The researchers concluded that adjunctive EPA is ineffective for the management of OCD symptoms (Fux et al. 2004).

9.4 Conclusions

Nutritional status may contribute to the pathogenesis of OCD and have a role in the treatment of this condition. Despite the available literature, research into the potential role of various nutrients in OCD remains in its infancy. Most conducted studies are limited by their small samples and, at times, mixed findings. While some nutrients were assessed as monotherapy, others were investigated as an add-on to antidepressants. Mental health professionals treating patients with OCD should be mindful of possible nutritional interventions, their proper dosages, and potential side effects. This is clinically relevant in patients seeking alternative and complementary

treatment avenues. Whenever prescribed, similarly to any pharmacological treatment, nutritional therapy should be overseen, and doses should be changed as needed to attain optimal outcomes without side effects. Some supplements should also not be used in conjunction with certain medications, for instance, SJW with antidepressants owing to the possible risk of serotonin syndrome.

More research in this field is needed. Longitudinal follow-up studies with large population-based samples should be conducted to determine whether nutritional status at baseline predicts subsequent OCD symptoms. The dietary habits of individuals should be taken into account when designing protocols for treatment interventions. Furthermore, double-blind randomized controlled studies with structured diagnostic tools and larger sample sizes are required. Possible confounders of the nutrition–OCD relation, including gender, race and ethnicity, socioeconomic level, body mass index, dietary habits, physical activity and exercise, dietary supplement use, and comorbid medical and psychiatric conditions, should be considered and addressed.

Although more studies are required to clarify the role of nutrition and nutritional deficiencies in the pathogenesis and treatment of OCD, the potential for dietary changes to improve symptomatology is compelling as nutritional interventions are generally inexpensive, safe, and acceptable to patients.

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Chapter 10
Caffeine, Mental Well-Being, and Psychiatric Disorders

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Abstract Caffeine is the most consumed substance in the world. It is well known to affect alertness and interfere with sleep. Caffeine acts as an adenosine antagonist and indirectly affects other neurotransmitters. DSM-V lists four disorders directly related to caffeine intake. Caffeine interferes with anxiety and sleep disorder. Studies have shown positive effect of caffeine on neurocognitive function, such as Alzheimer's and Parkinson's disease. Caffeine is found to improve some elements of depressive disorder, such as amotivation symptom, and it is widely used during the electoral convulsive therapy to lower seizure threshold. It can decrease the lithium level, which might precipitate switch to manic or hypomanic episode and bipolar disorder. Further research and randomized control trials are needed to establish the relationship between caffeine and psychiatric effects.

Keywords Caffeine · Coffee · Adenosine · Anxiety · Depression · Insomnia · Alzheimer · Parkinson · DSM-V

10.1 Introduction

Bitter in taste and considered the world's most widely used drug, caffeine is typically consumed to wake up and reenergize our bodies to take on the day's challenges and hardships, or as testified by 80% of the world's population which consumes a caffeinated product every single day (Petre 2020). Caffeine is naturally found in seeds and leaves and within fruits (Heckman et al. 2010). These include coffee beans, tea leaves, cocoa beans, yerba mate leaves, guarana berries, and kola nuts (Reyes and Cornelis 2018). It is also commonly added in many other foods and beverages for its benefits on mood, alertness, and increased energy (Heckman et al. 2010). Scientific literature has defined caffeine in many ways; chemically, it is known as methylxanthine (1,3,7-trimethylxanthine), but most commonly it is described as a natural stimulant or a psychoactive drug (van Dam et al. 2020). That is because caffeine's main impact is on the brain where it blocks the chemical adenosine (Baehr and Welsh 2014). The way it works is simple; adenosine is a neurotransmitter in our brains, which is responsible for sending chemical messages of tiredness and relaxation (Petre 2020). However due to caffeine's similar molecular structure, it binds to adenosine receptors instead, hence preventing adenosine's function and reducing the feeling of tiredness (van Dam et al. 2020). Caffeine also exerts its energizing effects through increasing levels of the fight or flight hormone, adrenaline, in the blood and increasing the activity of dopamine and norepinephrine neurotransmitters in the brain, which play a role in how good or bad we feel (Petre

2020). It is also worth mentioning that caffeine's popularity is also due to its quickness in delivering alertness as it takes less than 20 min to make it into the bloodstream and is almost completely absorbed within 45 min after consumption, reaching its full potency (Petre 2020).

While the science of how caffeine works has been thoroughly studied and proven, the same cannot be said for the history of the drug. The origins of caffeine are unknown and surrounded by myths, similarly to tea and coffee. It is speculated by anthropologists that plants containing caffeine such as tea leaves and coffee beans were discovered as early as 700,000 B.C. and directly eaten by humans in the early Paleolithic Stone Age (Weinberg and Bealer 2001). However, the infusion of caffeine-containing plants with hot water came centuries after that (Weinberg and Bealer 2001). Tea was first discovered in ancient China. Legend has it that in 2732 B.C., Emperor Shen Nung discovered tea by coincidence as some leaves made their way into his pot of boiling water; intrigued by the pleasant smell, he decided to drink the brew and sparked the tea culture in the country (DeWitt 2000). Tea's popularity spread across China throughout the fourth and eighth centuries, and it was not only used for medicine but also as an everyday refreshing beverage (DeWitt 2000). On the other hand, coffee is said to be discovered in 850 C.E. by a herdsman. According to Ethiopian folktale, a goatherd named Kaldi first discovered coffee as he noticed his goats' unusual hyperactivity and refusal to sleep at night after consuming coffee berries (National Coffee Association USA n.d.). Kaldi told the local monastery about his discovery, which turned the beans into a drink, realizing that its stimulating effects affect humans as well (National Coffee Association USA n.d.). This revelation quickly spread out to the Arabian Peninsula, which actively began the cultivation and trade of coffee in the fifteenth century from today's Yemen and popularized it around the world. It made its way to Persia, Egypt, Syria, India, North Africa, Turkey, and the Balkans (Myhrvold 2021). Coffee's popularity in the Arab region created a culture of public coffee houses called *qahveh khaneh*—to enjoy not only coffee, but also various social activities including listening to music, enjoying performances, playing chess, and keeping up with current news (Myhrvold 2021). Coffee made it to Europe in early 1615 and was eventually introduced to the United States, becoming a global phenomenon (Myhrvold 2021).

Today, 99% of the coffee we drink is derived from two species, *Coffea arabica* (arabica), cultivated by Latin America, Eastern Africa, Asia, and Arabia, and *Coffea canephora* (robusta) produced mainly by Western and Central Africa, Southeast Asia, and (de Mejia and Ramirez-Mares 2014). Despite tea and coffee's relative early discovery, caffeine was not extracted until the beginning of the nineteenth century (Weinberg and Bealer 2001). Friedlieb Ferdinand Runge, a young physician, met the poet Johann Wolfgang von Goethe, who was impressed by Runge's skills in chemical extractions; hence, he asked him to analyze a small box of rare Arabian mocha beans (Weinberg and Bealer 2001). In a few months' time, Runge was successful in isolating and purifying caffeine as a white crystalline substance for the first time in 1819 (Baratloo et al. 2016). As stated in the book "The World of Caffeine" by authors Weinberg and Bealer, "it was a result of an encounter between

Table 10.1 Average caffeine content of common products

Drink	Caffeine content
Brewed coffee	100 mg/cup
Instant coffee	60 mg/cup
Black tea	45 mg/cup
Green tea	20–30 mg/cup
Energy drinks	80 mg/can (other energy drinks may contain substantially more)
Soft drinks	25–50 mg/can

a scientist and a poet that caffeine was first revealed to the world; a curiously symbolic origin when one considers the vast panorama of the drug's history, encompassing, as it does, so much of the disparate worlds of science and culture" (Weinberg and Bealer 2001).

While caffeine is usually associated with coffee and tea, the drug is present in many of our foods and drinks like chocolate, soft drinks, and even chewing gum (Alexis 2021). On average, adults in the United States consume 135 milligrams of caffeinated products daily, which is the equivalent of 1.5 cups of coffee a day (1 cup = 8 ounces) (The Nutrition Source n.d.). According to the U.S. Food and Drug Administration, it is safe for healthy adults to consume 400 mg (roughly amounts to 4 cups of coffee) of caffeine daily (Petre 2020). Considering this, it is worth mentioning the amount of caffeine present in our foods and beverages to avoid the risks of excess consumption. Coffee, energy drinks, caffeine supplements, yerba mate, and guarana-containing drinks have the highest concentrations of caffeine (Heckman et al. 2010). Starting off with brewed coffee, a typical serving of a cup or 8 ounces amounts to 95 mg caffeine, while the same quantity in instant coffee has 60 mg of caffeine. As for decaffeinated coffee, 4 mg of caffeine is typical in a cup. For espresso, although it is high in concentration of caffeine, it is served as a shot or 1.5 ounces containing 65 mg, but 8 ounces of espresso would amount to 240 mg (Petre 2020; The Nutrition Source n.d.). On the other hand, energy drinks have 85 mg of caffeine a cup, but typically they are produced in 16-ounce bottles which have 170 mg. There are also energy shots—2 ounces—that come in higher concentrations of 200 mg caffeine, equivalent to 2 cups of coffee. Similarly, caffeine tablets are of high concentrations containing 200 mg caffeine (van Dam et al. 2020). Yerba mate has 85 mg caffeine per cup, while guarana drinks can have up to 125 mg of caffeine (Petre 2018). Tea is considered to have a medium concentration of caffeine. An average cup of black tea brew has 47 mg, but green tea has less with 28 mg, and chamomile or peppermint tea contains no caffeine at all, hence both considered low in caffeine. Soft drinks, chocolate, and chewing gum are also regarded as low in caffeine. Sodas or soft drinks are at an average of 40 mg for 12-ounce cans. While chocolate varies in caffeine amounts from type to type, dark chocolate has more with 24 mg caffeine in 1 ounce and milk chocolate much less with 7 mg. Chewing gums containing caffeine typically have 25 mg per piece (Alexis 2021; Petre 2020; The Nutrition Source n.d.). Given this information, caffeine consumption takes a new light in our dietary lifestyle and puts importance on the caffeinated products we choose to consume and mix (Table 10.1).

10.2 Caffeine Pharmacodynamic

Caffeine as a drug belongs to the methylxanthine class. It has a stimulant effect on the central nervous system (CNS). This naturally occurring stimulant can be found in coffee, tea, chocolate, and other substances. In addition to those, it can also be found in energy drinks, soda, and other supplements where caffeine is artificially added. This abundance of sources, along with general social and cultural acceptance, contributes to caffeine being the most used psychoactive substance worldwide (Ribeiro and Sebastião 2010).

There are numerous uses for caffeine. Many people use it to stay awake and alert for various activities. It is approved by the Food and Drug Administration (FDA) as a treatment for some medical conditions, such as apnea of prematurity and bronchopulmonary dysplasia. Some of the non-FDA-approved uses of caffeine include treatment for migraine headaches and post-dural puncture headaches, as well as to boost athletes' performances. There are ongoing trials examining the usage of caffeine for the treatment of depression and neurocognitive disorders, such as Alzheimer's and Parkinson's disease (Evans et al. 2022).

Caffeine acts on several neurotransmitters and receptors in the body. However, it exerts most of its effects by antagonizing adenosine receptors specifically. Being both fat and water soluble, caffeine can readily penetrate the blood-brain barrier, allowing it easy access to the CNS. There are four adenosine receptors: A1, A2a, A2b, and A3. Caffeine acts on all of them, yet the antagonism of A2a receptors is what causes the wakeful effects of caffeine. Adenosine receptors exist throughout the body. In the heart, for instance, antagonism of A1 receptors in the cardiac muscle causes positive inotropic effect. Adenosine has an inhibitory effect on the CNS and other parts of the body. It is by antagonizing this inhibitory effect can caffeine induce its stimulatory effect. Caffeine stimulates the release of catecholamines, which further increase the heart rate and inotropic effect. It does that by, again, antagonizing adenosine receptors (Spriet 2014).

Caffeine has a complex effect on vascular tone. On the one hand, it antagonizes vascular adenosine receptors, causing vasodilation. It also stimulates endothelial cells to release nitric oxide, which promotes smooth muscle relaxation and further vasodilation. On the other hand, caffeine causes indirect vasoconstriction through the catecholamine release with increased sympathetic tone as a result. Caffeine appears to elevate systolic blood pressure by 5-10 mmHg in infrequent users; however, there is no such effect on individuals who use caffeine regularly. In addition to adenosine receptor antagonism, caffeine also acts to inhibit the phosphodiesterase (PDE). Inhibiting PDE-5 can cause further vasodilation (Ribeiro and Sebastião 2010).

As mentioned earlier, adenosine receptors are present in many parts of the human body; hence, antagonism of adenosine receptors may also result in the stimulation of respiratory drive. This stimulation occurs by increasing medullary response to CO2, stimulating central respiratory drive, and enhancing diaphragm contraction. Caffeine also increases diuresis by increasing blood flow to kidneys, increasing glomerular

filtration, and increasing sodium excretion. Caffeine can trigger calcium release from intracellular stores, which has an application in contracture test for the diagnosis of malignant hyperthermia. Caffeine also targets GABA-A receptors and suppresses them, which may cause neurobehavioral effects (Evans et al. 2022).

10.2.1 Caffeine Pharmacokinetics

Caffeine is metabolized mainly in the liver by the cytochrome P450 oxidase system, enzyme CYP1A2 to be exact. Caffeine is metabolized to one of these three metabolites: paraxanthine, theobromine, or theophylline. These metabolites, before being further metabolized and then excreted in urine, have the following biological effects:

1. Paraxanthine: increases lipolysis, which results in higher levels of glycerol and free fatty acids in the blood
2. Theobromine: has a vasodilatory effect and leads to increased urine volume
3. Theophylline: causes bronchodilation and is used in the treatment of asthma

Caffeine has a short half-life of about 5 h. However, this half-life largely varies depending on different factors. Pregnancy, for example, can extend it three times. Smoking, on the other hand, can halve caffeine's half-life. In infants, the half-life is approximately 8 h, while in premature infants, this number jumps to 100 h due to an immature cytochrome P450 system. Patients taking cytochrome inhibitors and those with liver disease will experience a prolonged half-life of caffeine (Evans et al. 2022).

Caffeine is readily available when taken orally with 100% oral bioavailability. It usually takes about 45–60 min after oral intake for the onset of action and lasts about 3–5 h. Taking caffeine with food tends to slow its absorption. In medical settings, caffeine can be administered parenterally. Some of the parenteral routes used are rectal, insufflation, or inhalation. Inhalation and insufflation are generally used with an intention of getting high. These routes bypass the first-pass metabolism and lead to a much faster absorption (i.e., within minutes). Resulting bioavailability and duration, on the other hand, are less than those of an oral route (Evans et al. 2022).

While there are no absolute contraindications for using caffeine, there are some conditions for which caution is necessary, which include cardiovascular disease and arrhythmias, peptic ulcer disease and gastroesophageal reflux disease, hepatic disease, seizure disorder, pregnancy, and severe anxiety (Spriet 2014; Evans et al. 2022). There are studies that suggest that consuming high doses of caffeine (more than 400 mg/day) can lead to intrauterine growth restriction and miscarriage. The American College of Obstetricians and Gynecologists (ACOG) considers 200 mg of caffeine a day to be safe during pregnancy.

10.3 Caffeine and Addiction

Coffee is one of the most popular drinks in the world. Only in the United States, 87% of both children and adults regularly consume food and drink that contain caffeine. On average, an adult consumes around 200 mg of caffeine a day in the United States. However, a good percentage of people exceed the 500 mg mark daily. Regular use of caffeine along with its integration in daily routines and social events makes it significantly more difficult to recognize caffeine-associated disorders. Having a caffeine-related disorder places the person at an increased risk of other substance-use disorders. Indeed, two-thirds of people who use caffeine heavily also use sedative and hypnotic drugs (van Dam et al. 2020).

Generally, people report a sense of improved well-being, increased energy, and better focus with low doses of caffeine. These effects are usually seen in the dose range of 20–200 mg (Cappelletti et al. 2015). Consuming larger quantities, in the range of 300–800 mg, leads to people reporting being anxious and nervous. In regular users, caffeine suppresses the mild withdrawal symptoms that occur after a whole night without caffeine. This in turn acts as a reinforcer for continued use (Petre 2020).

Investigation reports high concordance rate in monozygotic twins for various caffeine use aspects like total consumption, tolerance, withdrawal, intoxication, and heavy use. There may be a common genetic factor underlying the use of caffeine, alcohol, and cigarette smoking. People who smoke cigarettes tend to use more caffeine than their nonsmoker counterparts. There are few reasons that might explain this: first, common genetic predisposition as mentioned earlier; second, smoking increases caffeine elimination from the body; and third, caffeine enhances the effects of nicotine. Numerous studies have shown an increased intake of caffeine among psychiatric inpatients (Sadock et al. 2015).

The most recent edition of the Diagnostic and Statistical Manual (DSM-V) contains new sections for caffeine-related disorders. Caffeine-use disorder is not a specific diagnosis in the DSM-V, but it has been classified as a condition requiring further research. This category comprises problems that appear to have some evidence of effects on psychological well-being but do not have a significant enough research basis to justify placement in the list of classifiable disorders. Due to this use, many people do not feel severe personal suffering or a major decline in functioning in any part of their lives. These two criteria are mentioned as prerequisites for almost every disorder included in the DSM-V; caffeine intoxication and caffeine withdrawal, on the other hand, are both included as disorders in the DSM-V (American Psychiatric Association 2013; Sadock et al. 2015).

Caffeine-use disorder was included in DSM-V as a disorder for further study rather than as a recognized diagnosis due to a lack of data on its prevalence and clinical importance in general population samples. There are three DSM-V diagnostic criteria for caffeine-use disorder that are necessary and sufficient: (1) a persistent urge or unsuccessful attempts to reduce or restrict caffeine intake; (2) caffeine usage that continues despite knowledge of an ongoing or recurring physical or

psychological problem that is likely to have been caused or worsened by caffeine; and (3) withdrawal, as manifested by the characteristic withdrawal syndrome for caffeine, or caffeine or a closely related substance is taken to relieve or avoid withdrawal symptoms (American Psychiatric Association 2013).

Beyond the three primary criteria for caffeine-use disorder, six additional diagnostic criteria included in other substance-use disorders, such as craving, tolerance, and using caffeine in higher amounts or for a more extended period than planned, were included as markers for greater severity. To reduce the risk of overdiagnosis given the prevalence of caffeine usage, the recommended diagnostic strategy for caffeine is more conservative than for other substances, which need fulfillment of any 2 of 11 diagnostic symptoms to meet the criteria for mild substance-use disorder. Most studies on the prevalence of substance-use disorder criteria as applied to caffeine were done among special populations such as heavy or treatment-seeking caffeine consumers or psychiatric patients; they preceded the proposed DSM-V criteria or had very small sample sizes (American Psychiatric Association 2013).

Caffeine intoxication presents a significant health risk and can result from excessive caffeine use. Some cases have warranted hospitalization. According to the DSM-V, caffeine intoxication requires a recent intake of caffeine well above 250 mg, as well as the presence of five or more of the following symptoms either during or shortly after caffeine ingestion: restlessness, nervousness, excitement, insomnia, facial flushing, gastrointestinal disturbances, tachycardia or cardiac arrhythmias, periods of inexhaustibility, diuresis, muscle twitching, rambling flow of thought and speech, and psychomotor agitation. The detected symptoms must cause significant distress or impairment in social, occupational, or other essential areas of functioning. The signs and symptoms must not be caused by another medical condition or explained better by a mental disorder, including intoxication from a different substance (American Psychiatric Association 2013).

The withdrawal symptoms occur after the abrupt cessation of prolonged daily caffeine use. The withdrawal syndrome includes fatigue, headache, drowsiness, low mood, irritability, poor concentration, and flu-like symptoms. The detected symptoms must cause significant distress or impairment in social, occupational, or other essential areas of functioning. The signs and symptoms must not be caused by another medical condition or explained better by a mental disorder, including intoxication or withdrawal from a different substance (American Psychiatric Association 2013). Unspecified caffeine-related disorder is a diagnosis that applies when symptoms caused by caffeine use led to distress or impairment in social, occupational, or other aspects of patient's functioning; however, they do not meet the criteria for any specific caffeine-related disorder (American Psychiatric Association 2013).

There are other caffeine-induced disorders such as anxiety and sleep disorder (American Psychiatric Association 2013). Further explanation of these two previous disorders is beyond the scope of this chapter.

10.4 Caffeine and Sleep Disorder

Caffeine is a stimulant that works as an adenosine receptor antagonist, specifically receptors that influence sleep, arousal, and cognition. Adenosine is a substance in our body that promotes sleepiness. When its receptors are blocked by caffeine, we remain vigilant and alert.

Caffeine also interferes with circadian melatonin rhythms, which are physiological patterns, that operate on a 24-h clock, like our sleep-wake cycle (Chaudhary et al. 2021; O'Callaghan et al. 2018).

There is evidence of psychological factors that contribute to the stimulating effect of caffeine, so the stimulating effect is partly due to placebo effect and expectancy from caffeine. Although caffeine has the potential to improve alertness and performance, it may cause sleep deprivation, which is opposite to the main point of consuming caffeine (O'Callaghan et al. 2018). Sleep deprivation and poor sleep quality can cause many problems including decrease in cognition, alertness, attention, vigilance, and speed of motor functions (Chaudhary et al. 2021).

The effect of caffeine on sleep is a vicious cycle. Excessive caffeine consumption will lead to not getting enough sleep, which likely causes tiredness and fatigue, which will lead to reaching several cups of coffee to make it through the day and will again affect the sleep quality. There is a relationship between dose and timing-response. The sleep of some age groups, like the old-age group, may be more sensitive to caffeine than others. Also (Carskadon 2011; Petre 2020; van Dam et al. 2020), there is evidence of some individual differences due to functional polymorphism of genes implicated in adenosine neurotransmission and metabolism (Ribeiro and Sebastião 2010).

Caffeine delays the onset of sleep, increases the sleep latency, reduces the total sleep hours, and reduces the quality of sleep. It affects the normal sleep stages; it was found to reduce slow-wave sleep (SWS) and rapid eye movement (REM) sleep. Sleep fragmentation can also be an effect of nocturnal sleep caffeine administration. Caffeine has a significant disruptive effect on both subjective and objective sleep even if taken 6 h before bedtime (Aurora et al. 2012; Carskadon 2011; O'Callaghan et al. 2018). There is evidence that people who consume an excessive amount of coffee (60 cups or more per year) have less volume of pineal body, especially parenchyma (melatonin-producing area), by 20% than those people who consume less than 60 cups per year (Park et al. 2018).

Caffeine is linked to some disorders. It can cause caffeine-induced sleep disorder, insomnia type, or it may exacerbate preexisting insomnia disorder. It may cause circadian rhythm sleep-wake disorder because it may interfere with the melatonin system as mentioned above. It can cause non-rapid eye movement sleep arousal disorder indirectly through sleep deprivation. Because caffeine is considered a powerful psychoactive substance, it can lead to nightmares by stimulating the brain activity directly and can cause nightmare disorder indirectly through affection of sleep quality (American Psychiatric Association 2013). Caffeine has also been linked to obstructive sleep apnea, especially the caffeinated soda for unclear reasons

(Aurora et al. 2012), and has been linked to worsening the symptoms of restless leg syndrome (Batool-Anwar et al. 2016). For appropriate sleep hygiene, it is recommended to avoid caffeine close to bedtime. However, evidence is less clear regarding caffeine consumption at earlier times of the day. The recommended cutoff time is 6 h before sleep (O'Callaghan et al. 2018).

10.5 Caffeine and Attention Deficit/Hyperactivity Disorder (ADHD)

Attention deficit/hyperactivity disorder (ADHD) is a disorder that decreases attention and/or hyperactivity and impulsivity. It is a chronic condition that affects children and may continue into adulthood (American Psychiatric Association 2013). The most effective treatment for ADHD is stimulant medication, which improves the attention span and has a role in controlling impulsive behavior (Sadock et al. 2015).

Caffeine has a positive influence on attention, working memory, and alertness. It raises the amount of dopamine in the brain, which is linked to attention, pleasure, and movement.

Studies show that caffeine alone is less effective than stimulant medications such as amphetamine in controlling ADHD symptoms (Barclay 2019). Some studies show evidence that caffeine may work as an adjuvant along with prescribed stimulants in children with ADHD and it can amplify the therapeutic effect. However, it is not recommended to prescribe caffeine to children, especially those who are taking stimulant medications, because they may be more vulnerable to side effects and caffeine can also affect the development of the brain in growing children. In addition, children with ADHD are known to have more sleep problems than other children, which may be exacerbated by caffeine (Konstantinovsky 2021). Caffeine and stimulant drugs, when combined, may cause synergy effects, which means that they are more powerful and effective, but also have greater side effects. Both drugs can cause sleeping problems, anxiety, irritability, appetite affection, nausea, and stomach pain (Cipollone et al. 2020; Ioannidis et al. 2014).

10.6 Caffeine and Anxiety Disorders

Anxiety is one of the most common psychiatric problems, and caffeine has been linked to it. Caffeine works as an antagonist to A1 and A2A receptors, which are found in both brain and peripheral tissues. These receptors are related to anxiety, and some of their anxiogenic mechanisms are regulation of coronary blood flow and myocardial oxygen; regulation of activities of other neurotransmitters like GABA, glutamate, dopamine, serotonin, and acetylcholine; vasoconstriction in the blood

vessels of the brain; and decrease in the blood supply, which can increase stress and anxiety. Caffeine may also affect some nutrients in our body, like magnesium level and some B vitamins, which are important in fighting stress and anxiety (Klevebrant and Frick 2022; van Calker et al. 2019).

Caffeine consumption can lead to some physical symptoms that may mimic anxiety symptoms, including palpitations, tremors, irritability, restlessness, rapid breathing, and twitches. These symptoms may trigger anxiety or exacerbate it. Also, quick quitting for caffeine and its withdrawal from the body can cause some anxiety symptoms like irritability, tremors, headache, and restlessness. So, it is not recommended to quit caffeine suddenly in people who have anxiety disorder (Preidt 2019).

There is evidence that caffeine is linked to some anxiety disorders. Yet, moderate caffeine consumption is safe and may have benefits for most people. Caffeine is known to have a panicogenic effect. However, its effect on anxiety and panic attacks has no evidence of dose-response relationship. Caffeine-induced anxiety disorder is a DSM-V diagnosis that falls under anxiety disorders and not substance-related disorders. Patients with this disorder present with either anxiety or panic attacks that must be due to caffeine intake. It has been linked to social anxiety disorder, and the relationship can go both ways; caffeine may increase social anxiety symptoms, and people who have this condition may use caffeine to cope with the social anxiety symptoms. The relationship between caffeine and obsessive-compulsive disorder is not clear, but generally excessive caffeine consumption is not recommended for people with anxiety disorder (American Psychiatric Association 2013; Sadock et al. 2015).

Caffeine can interact with a variety of psychiatric medications, including antipsychotics, antidepressants, anxiolytics, and sedative agents. It is metabolized by CYP1A2 enzyme and acts as a competitive inhibitor for it, so it may increase the side effects of some medications and may complicate the treatment plan and alter the medication response. Also, fluvoxamine, which is used mostly in OCD treatment, is known to enhance the effect of the caffeine, so patients who receive these medications should be educated to avoid excessive caffeine consumption (Broderick et al. 2005; Culm-Merdek et al. 2005).

10.7 Caffeine and Alzheimer's Disease

As mentioned early in this chapter, it takes around 30–60 min for caffeine to reach the peak in blood after intake. Caffeine has a hydrophobic nature, which allows it to quickly cross the blood-brain barrier. Caffeine is found to have a neuroprotective effect. According to the Three-City Study (Ritchie et al. 2007), caffeine has reduced the risk of cognitive decline in women, especially at higher ages and when the caffeine consumption is more than three cups a day. It is interesting to say that the study has shown that the case is not the same with men. Another study (Eskelinen et al. 2009) found that the consumption of more than three cups of coffee per day

in men and women decreases the risk of developing dementia compared to the consumption of less than two cups of coffee per day.

Caffeine consumption helps to reduce neurotoxicity, which promotes the neurocognitive disorder, such as Alzheimer's disease. Caffeine has almost the same chemical structure as the adenosine, both competing on the same adenosine receptors, which decrease the overall effect of the adenosine. This will result in decrease in the influence of extracellular calcium and decrease in glutamate. As a result, it will decrease the neuroexcitatory level. In addition, activation of the adenosine A2A receptor will activate and upregulate the microglia cells in the brain, which might initiate the inflammatory cascade. Caffeine blocks the A2A adenosine receptor and decreases the level of inflammation and apoptosis, which are among the mechanisms of cell degeneration (Eskelinen and Kivipelto 2010; Kolahdouzan and Hamadeh 2017).

10.8 Caffeine and Parkinson's Disease

Caffeine intake is found to reduce the risk of having Parkinson's disease in men and women. Liu et al. (2012) found that consuming high amounts of caffeine (more than 5 cups of coffee) was inversely associated with developing Parkinson's disease. The exact mechanism for this is still unknown. The effect of caffeine on the adenosine A2A receptor and decreasing of the inflammatory cascade could be one of the mechanisms (Chen and Schwarzschild 2020; Ren and Chen 2020).

In summary, caffeine has positive effects on promoting cognitive function and delaying neurocognitive disorder. Consuming high amounts of caffeine (300–500 mg/100 kg/day) is found to lower the risk of Alzheimer's and Parkinson's disease. The exact mechanism is unknown; one mechanism is the antagonizing effect of adenosine receptors, which decreases the activation of microfilm and inhibits the inflammatory cascade.

10.9 Caffeine and Mood Disorder

Mood disorder can be classified into unipolar or depressive disorder and bipolar related disorder. Fatigue, insomnia, poor concentration, and decreased motivation are among the symptoms of depressive disorder. On the other hand, having excessive levels of energy, a decreased need for sleep, and increased activities are among the symptoms of bipolar related disorder. Caffeine has shown to interfere with these previous symptoms. For example, caffeine increases alertness and might interfere with the sleep cycle, which would increase insomnia or decrease the need for sleep.

10.9.1 Bipolar Related Disorder

In the literature, although there was no strong evidence, a link was made between excessive caffeine consumption and bipolar related disorder (mania, hypomania, mixed episode). This link might be explained in patients with established diagnosis of bipolar disorder who are treated with lithium. Lithium is renally metabolized, and its level is affected through the interaction with different drugs. Caffeine is a diuretic substance, which increases the exertion of lithium and leads to the decrease in the lithium level, which precipitates relapse and switches to manic-hypomanic mixed episodes. Also, caffeine is a stimulant; it affects sleep and energy levels, which could precipitate the episode or interfere with symptomatic treatments of bipolar disorder. There are no current guidelines about the limit of using caffeine for patients with bipolar disorder or patients who are receiving lithium (Frigerio et al. 2021).

10.9.2 Depressive Disorder

Depressive disorder is commonly presented with fatigue, lack of motivation, and poor concentration. Fatigue and energy loss are the most reported symptoms after the depressed mood, and they could be linked with resistance to treatment. Treatment of resistant depression may warrant the need to add medications that have stimulant effects, such as bupropion, methylphenidate, and modafinil (Asil et al. 2021; Kang et al. 2018). In the literature, there are a few studies about the relation between depressive disorders and caffeine intake. Some of these studies suggest that consuming caffeine could prevent depression; others suggest that it could help with treating existent depression. However, a study finds that a high dose of caffeine increases the prevalence of major depressive disorder in women with multiple sclerosis. López-Cruz et al. (2018) concluded that caffeine consumption at intermediate levels (300–550 mg/day) appears to have positive effects in patients with depressive disorder. However, that is not the case with higher consumption and with people with some neurological pathology.

10.9.3 Electroconvulsive Therapy (ECT)

One of the most well-established effective treatments for resistant depression and refractory depressive disorder is electroconvulsive therapy. ECT can be prolonged by parenteral caffeine prior to the ECT session. Different formulations have been used including caffeine, sodium benzoate (CSB) injections (250–500 mg of caffeine), caffeine citrate, and theophylline (one of the three primary metabolites of caffeine). Oral administration of these products can result in an inconsistent absorption, and hence clinical effect. Case reports and case series, small trials, retrospective

designs with heterogeneous patients' population, small sample sizes, and inconsistent protocols have reported the effectiveness of this practice. An increase of caffeine is considered safe, tolerable, and cost effective. Thus, it has been suggested to increase electroencephalography (EEG) or motor seizure duration and to minimize amnesia, especially for patients who are not achieving the ideal EEG seizure duration (at least 30 seconds) (Bozymski et al. 2018).

10.10 Caffeine and Psychotic Disorder

The literature on caffeine and psychosis is limited (mainly case reports), and the prevalence of caffeine-induced psychotic disorders is unknown. Despite caffeine being a psychoactive stimulant substance, it has not been recognized as a clinical diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) or in the International Classification of Diseases (ICD-11th) to cause or induce psychotic disorders like amphetamines or cocaine. Psychotic symptoms are not recognized among the signs and symptoms of caffeine intoxication or withdrawal. By examining the onset, temporal course, and other factors, a substance-induced psychotic disorder can be distinguished from a primary psychotic disorder. Moreover, intoxication symptoms are differentiated from caffeine-induced disorders, which appear during intoxication (American Psychiatric Association 2013; Sadock et al. 2015).

Several case reports have suggested that an increased caffeine consumption is associated with worsening psychotic symptoms. The onset and offset of these aggravated symptoms and the consumption and discontinuation of caffeine in a close temporal relationship suggest that caffeine could be the culprit in vulnerable patients (Caykoylu et al. 2008).

There have been few studies that have examined the effects of caffeine use on psychotic symptoms in psychiatric patients despite caffeine being commonly used among them. It has been suggested that high intake of caffeine (intoxication) may worsen existing psychotic symptoms and low intake may improve cognitive and extrapyramidal side effects of medication (Adolfo et al. 2009). It was also reported that a healthy individual presented with psychosis after consuming large amounts of caffeine for an extended period. During the caffeine withdrawal state, there is no evidence of associated psychotic symptoms (Cerimele et al. 2010).

Caffeine and its metabolites affect multiple neuronal functions depending on the amount consumed, and it has the opposite effects of adenosine. It alters the adenosinergic activity predominantly by antagonizing the adenosine receptors. Adenosine is well known to inhibit the release of several neurotransmitters including dopamine, glutamate, serotonin, GABA, and norepinephrine. Positive symptoms of psychosis are thought to result from changes in the dopaminergic activity in the mesolimbic pathway, especially with high intakes of caffeine (Huang and Sperlágh 2021; Ribeiro and Sebastião 2010).

Although caffeine has been implicated in causing psychosis in some cases, the stimulant's dopamine agonist effects on patients with schizophrenia are heterogeneous. Caffeine competitively inhibits CYP1A2, which might increase some of the antipsychotic medications' plasma levels (e.g., clozapine, olanzapine). Additionally, there is an association between higher caffeine intake and smoking nicotine among patients with schizophrenia, partly due to the nicotine-inducing effect on the cytochrome P450 1A2 enzyme (the main enzyme responsible for the metabolism of caffeine), which induces caffeine metabolism and reduces its effect (Bissonnette et al. 2021).

Due to the development of tolerance, high levels of caffeine intake may not lead to intoxication. The exact caffeine dose that may have produced the psychotic symptoms is not known, and the duration of increased caffeine consumption preceding psychotic symptoms varies between people. There seems to be a wide range of doses from 200 to 4600 mg of caffeine/day that might precipitate psychotic symptoms, and the duration ranges from a few hours to several months or years. A double-blind, placebo-controlled study investigated the effect of regular caffeine consumption (10 mg/kg) on the psychotic symptoms of patients with schizophrenia and found that caffeine has aggravated their symptoms. The treatment is usually limiting caffeine consumption for a couple of weeks, and the aggravated psychotic symptoms would subside and improve after that time (Huang and Sperlágh 2021).

10.11 Caffeine and Psychiatric Medication Interactions

Caffeine can affect other psychotropic medications in different ways. Caffeine is metabolized by the CYP1A2, and it inhibits CYP1A2 competitively. Fluvoxamine, a selective serotonin reuptake inhibitor, inhibits CYP1A2 and can increase the effects of caffeine. On the other hand, cigarette smoking is a CYP1A2 inducer, which increases caffeine metabolism and decreases the effect of caffeine (Culm-Merdek et al. 2005). Excessive caffeine intake can increase the risk of serotonin syndrome (Shioda et al. 2004). On the same mechanism, caffeine may increase clozapine plasma concentration by up to 60% (Carrillo et al. 1998). Also, it can affect other psychotropic medications such as olanzapine, clomipramine, and imipramine. Lastly, by stimulating effect, caffeine in high dose can decrease the efficacy of benzodiazepine (Sawynok 1995).

Caffeine is a diuretic substance; it can affect the medications that are renally metabolized. Excessive consuming of caffeine can decrease the effect of lithium and decrease the lithium level in the blood. Also, decreased consuming of caffeine can increase the lithium level and precipitate lithium toxicity. Some case reports correlate lithium level with caffeine consumption. There is no current recommendation about the daily dose of caffeine when using lithium (Baethge et al. 2009).

10.12 Conclusions

Caffeine is the most consumed substance in the world. It acts on adenosine receptors and affects other neurotransmitters. Caffeine has various effects on mental health well-being and mental illness. It might worsen anxiety and sleep disorder. Studies have shown positive effect of caffeine on neurocognitive function, such as Alzheimer's and Parkinson's disease. Caffeine improves some elements of depressive disorder, such as amotivation symptom, and it is widely used during the electoral convulsive therapy to lower seizure threshold. It interferes with other drugs, such as lithium and fluvoxamine. Further research and randomized control trial are needed to establish the relationship between caffeine and psychiatric effects.

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Chapter 11
Biopsychology of Chocolate Craving

Laura Orsolini, Angelica Cicolini, Virginio Salvi, and Umberto Volpe

Contents

Abstract Chocolate is the most desired food in the world, and it has always been considered as a pleasant food, sought after both for hedonistic reasons and for its role as a "panacea" for mood and affectivity. Multiple features of "the food of Gods" can explain how it is induced/increased to induce/increase the desire to eat it. Its unique orosensory qualities (i.e., taste, smell, aroma, and texture) mostly contribute to explaining the commonly shared acceptability of chocolate craving. Furthermore, chocolate determines a peculiar brain activity, activating analogous brain areas and

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neurobiological mechanisms than substances of abuse. Chocolate contains various biologically active components such as methylxanthine, biogenic amines, and cannabinoid-like fatty acids, all of which arguably own both biological and emotional activity. Chocolate may be consumed as a form of self-medication for dietary lacks or to compensate low levels of neurotransmitters implicated in the regulation of mood, appetite, and behavior. Chocolate consumption and cravings are often parossistic and vary along with hormonal fluctuations related to the menstrual cycle, which suggests a hormonal relationship. This chapter focuses on chocolate characteristics, by focusing on their relationships with the neurobiological mechanisms, which may contribute to maintaining chocolate addiction and craving.

Keywords Addiction · Biogenic amines · Chocolate · Craving · Methylxanthines · Polyphenol · Social drug

11.1 Background

Chocolate and cocoa originate from Mexico. Their history began with the pre-Columbian civilization who were able to create cocoa tree crops (*Theobroma cacao*) since 450 B.C. The Aztecs considered cacao beans as a "*Gift of God*" and consumed them not only as a food and/or due to medical intents but also as a form of currency. Chocolate was also believed to have aphrodisiac properties and donate power and strength to humans (Verna 2013). The explorer Hernán Cortés after drinking *xocoatl* (a beverage based on cocoa, hot water, and corn), at the Aztec emperor Montezuma's court, led to the Spanish court the beans and implements required to replicate "*the drink that builds up resistance and fights fatigue*" (Trivino 2013). It was 1528, and since then chocolate has slowly become one of the most palatable and sought-after foods. Cocoa is produced following a fermentation process of the seeds obtained from the pods of the cacao tree. The beans are desiccated and roasted and then separated into nibs and shells; the nibs are grinded to make the cocoa liquor, which is made from nonfat cocoa solids and cocoa butter.

From the cocoa beans, the food industry makes several types of chocolate with a specific composition and different qualities (Borchers et al. 2000):

- Dark chocolate consists of cocoa mass (>80% of the whole weight) and cocoa butter.
- Gianduja chocolate, which is a blend of hazelnuts, cocoa, and sugars.
- Milk chocolate, which contains milk powder in addition to cocoa butter, sugar, lecithin, and cocoa.
- White chocolate is made from cocoa butter, milk, and sugar with no cocoa mass.

11.2 Chocolate Composition and Psychopharmacologic Active Components

11.2.1 Overview

Chocolate is a complex food and contains several biological compounds, many of which may induce physiological and emotional effects, which may determine chocolate craving.

Cocoa, which represents the core component in chocolate, contains a considerable quantity of fat: being constituted by cocoa butter in 45–50%, oleic acid in 33%, palmitic acid in 25%, and stearic acid in 33% (Rusconi and Conti 2010).

Chocolate also contains polyphenols, a group of heterogeneous bioactive compounds characterized by the presence of a polyphenol structure. Polyphenols are about 10% of the total bean's dry weight. In particular, three types of polyphenols can be identified in cocoa beans: (a) proanthocyanidins or flavonoids (58%); (b) catechins (37%); and (c) anthocyanidins (4%) (Zugravu and Otelea 2019). It has been well known that polyphenols display an elevated antioxidant activity and a positive interaction with the brain and nervous system (Fusar-Poli et al. 2021a, b).

Cocoa beans also contain caffeine (0.06–0.4% of total weight), a renowned psychostimulant. Dark chocolate contains variable amounts of caffeine (35–200 mg/50 g), while milk chocolate contains comparatively low quantity of caffeine (14 mg/50 g).

The chocolate is also a source of theobromine, another methylxanthine. Unlike caffeine, theobromine has only a modest stimulatory action on the central nervous system (CNS). The amount of theobromine varies with the final product. Dark chocolate contains more theobromine than milk chocolate: 50 g milk chocolate contains about 75 mg theobromine, while 50 g of dark chocolate contains up to 220 mg of theobromine. The impact of the methylxanthines on cognition and mental performance has been extensively investigated, particularly their role on age-related cognitive deterioration and neurodegenerative processes (Nehlig 2013).

Cocoa is also wealthy in minerals: e.g., phosphorus, copper, iron, zinc, potassium, and magnesium (Latif 2013). Additionally, cocoa also contains other compounds, such as biogenic amines (i.e., serotonin, tryptophan, phenylethylamine, tyrosine, and tryptamine). Chocolate has also been reported as a significant source of dietary magnesium and has been hypothesized as a balancing substance for the altered levels of mineral macroelements (Balboa-Castillo et al. 2015). Furthermore, a few other constituents with biological action can be found in cocoa beans and obtained products: such as anandamide, an endogenous binder for the cannabinoid receptor (Smit 2011), and tetrahydroquinoline alkaloids, such as salsolinol, that may interact with the dopaminergic system (Melzig et al. 2000).

The nutritional values of cocoa and two categories of chocolate (dark and milk) appear in Table 11.1 (Urbanska and Kowalska 2019).

Table 11.1 Nutritional values per 100 g of cocoa and dark and milk chocolate

Chemical composition	Cocoa	Dark chocolate	Milk chocolate
Water (g)	2.5	0.5	0.8
Protein(g)	20.4	6.6	7.3
Lipid (g)	25.6	33.6	36.3
Cholesterol (mg)	0	0	10
Carbohydrate (g)	11.5	49.7	50.5
Sugar (g)	Traces	49.7	50.5
Total fiber (g)	–	8	3.2
Sodium (mg)	–	11	120
Potassium (mg)	–	300	420
Iron (mg)	14.3	5	3
Calcium (mg)	51	51	262
Phosphorus (mg)	685	186	207
Phenolics (mg)	996–3781	579	160
Flavonoids (mg)	–	28	13
Theobromine (mg)	–	802	125

11.2.2 Polyphenols

Cocoa beans are an important source of antioxidants, especially polyphenols, with the flavonoids and compounds derived from them which are being present in high concentration (Gu et al. 2004). The polyphenols, due to vasodilatation, enhance cerebral blood flow (CBF). The mechanism that determines vasodilatation is nitric oxide (NO) dependent. Vasodilatation and increased CBF provide oxygen and glucose to the neurons, due to an increased formation of blood vessels, particularly in the hippocampus (Wasik and Antkiewicz-Michaluk 2017). Several studies reported an association between CBF and cognitive function in humans. For example, a randomized, single-blind study reported an acute improvement of cognitive function due to the intake of cocoa flavonoids. The study was performed on 30 healthy adults who were offered dark chocolate containing 720 mg flavonoids. Cognitive performance was evaluated using a visual spatial working memory for location task and a choice reaction time task, created to engage procedures of sustained attention and inhibition. Compared with the control group, cocoa flavonoids raised up visual contrast sensitivity and reduced the necessary time to detect motion direction (Field et al. 2011). The polyphenols also reduce neurodegenerative processes and neuro-inflammation and stimulate neurogenesis (Fusar-Poli et al. 2021a, b). All this occurs thanks to two mechanisms. Firstly, polyphenols interact with signaling cascades that prevent neuronal death induced by apoptosis and caused by neurotoxins and free radicals (Barrera-Reyes et al. 2020). Secondly, cocoa polyphenols can activate the cascade pathways of rapamycin that have a relevant role in neuronal growth, memory mechanism, and synaptic function (Dubner et al. 2015). However, it is worth underlining that the effects of polyphenols on antioxidant capacity are observed only after a longer intake of cocoa (Scholey and Owen

2013). Last but not least, flavonols appear to play a crucial role in increasing beneficial gut microbes (e.g., Lactobacillus) and decreasing less beneficial ones (e.g., Clostridia) that follow cacao intake (Tzounis et al. 2011). Cocoa antioxidant, anti-inflammatory, and potential health-promoting properties could represent the reason for implementing trials examining the effect of cocoa-derived products on human health.

11.2.3 Biogenic Amines

The biogenic amines behave like sympathomimetic substances. Many of them can be found in chocolate, especially phenylethylamine (PEA), tyramine, serotonin, and tryptophan (Hurst et al. 1982). PEA is a neuromodulator which acts on mood regulation, implicated in the pathogenesis of depression. PEA is chemically and pharmacologically comparable to catecholamines and amphetamines, and it is heterogeneously distributed in the CNS. PEA is produced by brain tissues, and it is quickly metabolized by monoamine oxidase and aldehyde dehydrogenase to phenylacetic acid, the major metabolite. Reduced levels of both PEA and its metabolite were found in the tissues and biological fluids of subjects with depressive disorders. Moreover, the administration of PEA or its precursor has been demonstrated to improve depressive symptomatology (Sabelli and Javaid 1995). PEA is found in generous amounts in chocolate (0.4–0.6 μg/g), and some researchers have suggested that chocolate craving may be a consequence of a necessary self-regulation of PEA levels in the brain. However, many other foods contain large quantities of PEA and tyramine, but these, like sausages or cheese, are not sought after as chocolate.

Liebowitz and Klein (1982) defined an affective disorder, named "*hysteroid dysphoria*," and hypothesized that it was due to an aberrant control of PEA levels in the brain. The "*hysteroid dysphoria*" is characterized by frequent depressive episodes caused by feeling inadequate or not socially accepted, which may culminate in bulimic attacks for chocolate foods. The authors did not report any scientific references and supported the thesis that depressed episodes, hysteroid dysphoria, accompanied with chocolate-binging episodes may be loaded with PEA. Moreover, in this regard, animal experiments performed through intracranial administration of PEA demonstrated how administering PEA may increase euphoria, courtship, and sexual activity of the experimental animals (Crenshaw 1996). Evidently, oral consumption and cerebral injection are completely distinct ways of administration, and the concept that people eat chocolate to appear "sexier" or more "sensual" because eating chocolate determines an increase of endogenous PEA is more likely a legend (Smit 2011).

Serotonin is a neurotransmitter in the CNS and peripheral nervous system that has a relevant function in the control of mood and behavior. It can be found in a number of foods, like bananas, pineapples, and chocolate. Overall, 100 g of chocolate contains approximately 2.7 mg of serotonin (Hurst and Toomey 1981). Like all

the biogenic amines, serotonin is also metabolized rapidly after oral intake, and eating foods that contain serotonin will not have a direct increase in brain amounts of serotonin. However, cocoa-derived food contains tryptophan, which is a precursor of serotonin not subjected to deamination (Silva 2010). Guillen-Casla et al. (2012) supposed that chocolate consumption could be a behavioral mechanism for homeostatic control of neurotransmitters, especially serotonin. Low CNS levels of serotonin have been linked with depression, addiction disorders, and obsessive-compulsive disorders (Maes and Meltzer 1995; Young et al. 1988; Van Dijk et al. 2008). Moreover, the ingestion of chocolate has been supposed to raise tryptophan intake and, hence, serotonin production by the brain.

11.2.4 Methylxanthines

A different group of compounds contained in chocolate are methylxanthines, which are mainly represented by caffeine and theobromine, both having stimulant properties (Smit 2011). In particular, theobromine is the primary component of chocolate, with chocolate and other products based on cocoa being the primary fount of theobromine in the Western diet. However, it can also be found in small quantities in tea, guarana, and yerba mate (Camandola et al. 2019). Table 11.2 summarizes the content in theobromine present in various chocolate and cocoa products (Smit 2011).

The central mechanism of action for methylxanthines is represented by the inhibition of adenosine receptors. Adenosine is a presynaptic inhibitory neuromodulator. Methylxanthines eliminate its inhibitory action and cause arousal. Adenosine receptors are G protein-coupled receptors found in several organs, such as muscles, heart, and brain tissues. In the CNS, adenosine receptors guide sleep/wakefulness, synaptic plasticity, and neural signaling (Fredholm et al. 2005). Methylxanthines have been demonstrated to bind both adenosine subtype receptors A1 and A2A present in brain tissues. The antagonism of adenosine receptors A1 enhances neurotransmitter release, level of alertness, and vasoconstriction, while the antagonism of adenosine receptor A2 enhances synaptic plasticity and cognition (Camandola et al. 2019). The selective antagonism of adenosine receptors can also regulate hippocampal long-term potentiation (LTP), a type of synaptic plasticity implicated with the learning process and memory (Costenla et al. 2010). Compared to caffeine, theobromine is a low-affinity ligand and a weaker adenosine receptor antagonist. Mumford et al. (1996) furnish one of the most significant researches in this sense. They administered theobromine in capsule form, to weed out possible

Table 11.2 Theobromine content in chocolate and cocoa products

Product	Portion size	Concentration (mg/per portion)
Dark chocolate	50 g	378
Milk chocolate	50 g	95
Cocoa powder	10 g	189

orosensory effects. They showed that significant changes in mood or behavior occurred in only a few participants in the study. Conversely, participants who received the coffee capsules showed interesting changes in mood and behavior. This apparently confirms theobromine's relatively weak psychoactive effects. Different to theobromine, the effects of caffeine have been thoroughly studied. Consumption of disproportionate quantity (more than 1 g/day or more than ten cups of strong coffee per day) can induce tachycardia, dyspepsia, irritability, and insomnia, also collectively referred to as "*caffeinism*." Being a psychostimulant substance, caffeine increases energy (the consumer exhibits greater vigilance and is less tired) and enhances other aspects of mood and psychomotor and cognitive efficiency (Smit 2011). So, it has been hypothesized that only the addition of theobromine and caffeine might be involved in the psychopharmacological features of cocoa and chocolate, instead of the substances taken individually (Tuenter et al. 2018).

11.2.5 Cannabinoid-Like Fatty Acids

Devane et al. (1992) detected a category of biologically active components in chocolate that appear to target the endogenous cannabinoid system of the brain. Anandamide is a brain phospholipid that binds competitively with cannabinoid receptors with a high affinity and simulates the psychoactive action of cannabinoid drugs, such as euphoria and "heightened sensitivity." It is produced and released by brain neurons and is rapidly catabolized by a selective enzyme activity. Anandamide acts principally in the nucleus accumbens, where most cannabinoid receptors (especially CB1-R) act by augmenting the activity of the mesolimbic dopamine reward system (Lucchichini and Pistis 2012). Chocolate, which is plentiful in fat, contains lipids molecularly and pharmacologically linked to anandamide. Di Tomaso et al. (1996), subjecting samples of cocoa powder to chromatography, isolated two compounds that are related to anandamide: N-oleyl-ethanolamine and N-linoleoyl-ethanolamide. These lipids simulate cannabinoid ligands both directly, by stimulating cannabinoid receptors, and, indirectly, by rising anandamide levels (by inhibition of anandamide hydrolysis in microsomes). Therefore, it would seem that these cannabinoid-like fatty acids, similar to anandamide, may be at the basis of the chocolate craving (Mahler et al. 2007; Higgs et al. 2003). However, the presence of these two compounds was not confirmed in white chocolate. Moreover, with the bioavailability of these compounds usually not being more than 5% of the product, due to the first-pass effect determined by the activity of both intestinal and hepatic enzymes, the amount of anandamide actually usable and able to reach the CNS is very low and not sufficient for exerting a therapeutic effect (Nehlig 2013). In fact, according to Rogers and Smit (2000), on average, a 70 kg person would need to eat about 25 kg of chocolate to ingest enough anandamide to have a significant cannabimimetic behavior.

11.2.6 Magnesium

Chocolate is one of the foods with the greatest amount of magnesium. Dark chocolate contains approximately 90–100 mg magnesium/100 g, while milk chocolate contains lower magnesium quantity (43–50 mg/100 g) (Fusar-Poli et al. 2021a, b). Some researchers have speculated that chocolate consumption may also be due to a magnesium deficiency (Bruinsma and Taren 1999; Balboa-Castillo et al. 2015). However, although a magnesium supplementation has been proven to decrease chocolate craving, specific foods containing significant quantities in magnesium are not necessarily sought after as chocolate (Michener and Rozin 1994).

Stress induces magnesium deficiency by acting on multiple levels: stress induces secretion of mineralocorticoids and glucocorticoids, which causes an increase in renal excretion and a decrease in intestinal assimilation of magnesium. Magnesium deficiency leads to selective depletion of CNS levels of dopamine, a core component neurotransmitter of the neuronal circuit of pleasure and satisfaction, which is also involved in the addictions (Botturi et al. 2020; Yamanaka et al. 2019). Moreover, for the abovementioned reason, it has also been hypothesized that the stress-induced magnesium deficiency may contribute to an increased chocolate craving (Rozin et al. 1991). Although the evidence that chocolate selection might be based on magnesium unbalance is marginal and few studies have investigated this question in humans, no definitive conclusions can be drawn up for confirming the etiopathogenesis of chocolate craving. In fact, the causes may be numerous and not necessarily limited to the deficit of only a single nutrient or mineral. Therefore, further studies are needed to resolve this dilemma.

11.2.7 Concluding Remarks

Although most of the pharmacologically active compounds present in chocolate and cocoa have been demonstrated to display potential psychopharmacological activity, it has also been supposed that they might not necessarily determine a beneficial effect in humans, mainly due to the extremely low concentrations, the inability to cross the blood–brain barrier, the enzymatic inactivation, and so forth. Among the abovementioned compounds, caffeine appears to play a significant role in mood and behavioral regulation and currently appears to provide the clearest evidence of its action. However, theobromine represents a really promising "candidate," which has been demonstrated to synergistically act with caffeine in mood regulation. Moreover, also biogenic amines may play a significant role as pharmacologically active compounds. Therefore, some compounds contained in chocolate and cocoa products may potentially exert a pharmacological and psychological role, which should be furtherly and extensively investigated in more clinical trials.

11.3 Chocolate Intake Patterns

11.3.1 Chocolate Addiction

Chocolate is presumed to be the most craved food in the world (Montagna et al. 2019). Scientists distinguish between chocolate wanting, liking, and craving. Liking is a "*hedonic reaction to the pleasure of a reward*" (Berridge 2009). Wanting is the term used for indicating the psychological process of "incentive salience." Incentive salience is assigned to rewards and their predictive signs, which assists in determining their motivational significance. Those signs become triggers for wanting. Beyond the terminology definitions, liking and wanting are neurally distinguishable, with the liking being an opioid-based process while the wanting a mesolimbic generated process (Salamone and Correa 2002). Instead, craving is defined by Baker et al. (1987) as that "*motivational state in which an individual feels compelled to seek and ingest a particular substance*." Food craving has also been identified by a severe desire or urge to eat a particular class of food.

Moreover, the term "addiction" is commonly used to intend such craving (Bruinsma and Taren 1999), even though the addiction is a complex concept and may include several components, not all necessarily present in those subjects addicted to chocolate (APA 2013; Kalon 2016; Sussman and Sussman 2011). In this regard, Rozin et al. (1991) coined the terminology "*chocoholic*" and "*chocoholism*," to compare the addiction to chocolate with the addiction to alcohol (alcoholism) or tobacco (tabagism).

However, those individuals who define themselves as "chocolate cravers" are extremely heterogeneous in terms of patterns of craving and general attitudes towards chocolate (Hetherington and Macdiarmid 1993; Cartwright and Stritzke 2008). For instance, some "chocolate cravers" may not experience the feelings of intense urges preceding the chocolate consumption, which may resemble craving feelings experienced by those subjects with a substance and/or alcohol-use disorder. However, many "chocolate cravers" might sneak up on eating chocolate or do it with a binge eating modality similar to behaviors experienced by those individuals who abuse/misuse other substances. Those "chocolate cravers" who show a sensation of well-being during chocolate eating may also experience some socio-family-work impairment due to chocolate addiction (Bruinsma and Taren 1999).

Rogers and Smit (2000) introduced the concept of the ambivalent behavior towards chocolate craving experienced by those subjects with a chocolate addiction. The subject may experience the conflict between the wish to consume it and the concomitant wish to get away from it or to limit its intake. In fact, chocolate is a greatly palatable food, usually consumed as a complimentary meal, considered as a "threat" or a "reward," more than a substance with its dietary value and/or beneficial properties. Thus, chocolate has not been largely considered as an essential food but rather negatively connoted, being mainly considered a food able only to evoke pleasant orosensory addictive sensations, risky to the health and, hence, to be parsimoniously consumed or eaten with severe restraints, at least in Western

countries (Rogers and Smit 2000; Cartwright and Stritzke 2008). However, some authors argue that when the individual tries to resist the wish to eat chocolate, this mechanism may indeed encourage the development of a more prominent desire to chocolate (i.e., the *salience*) (Benton 2004). For example, there is evidence that early parental food control may make those limited foods, such as chocolate, more salient to children, resulting in greater consumption of them (Brown 2004). Therefore, craving for chocolate can be conceptualized as "*a net action disposition*," resulting from the interaction of concurrent inclinations to approach chocolate and to avoid it (Bechara et al. 2006). From this perspective, craving is conceptualized as the result of a struggle between opposing motivational behavioral forces. Prominent approach inclinations will facilitate consumption, while prominent avoidance inclinations will facilitate abstinence. This vision of chocolate craving is in agreement with the results of studies that described how different neural substrates are activated, depending on whether individuals are motivated to approach or avoid eating chocolate (Small et al. 2001). Furthermore, the ambivalence may also be manifested due to the feelings of guilt that may arise previous to eating chocolate. Feelings of guilt are an effective response following the resolving of ambivalence in favor of a decision to eat chocolate. This feeling may also occur after eating chocolate, when the wish to not have eaten comes out (Benton 2004).

Finally, Michener and Rozin (1994) supported the hypothesis that the composite sensory experience associated with chocolate intake may be more likely responsible for chocolate liking or craving rather than determining appetite and satiety processes. In fact, the authors argued that the sensory experiences associated, rather than specific pharmacological constituents of cocoa products and chocolate, may determine a chocolate craving. The critical elements include aroma, sweetness, and texture of chocolate.

11.3.2 Assessing Chocolate Craving: How to Discriminate Between Chocolate Cravers and Non-cravers?

So far, only two scales have been frequently used to investigate the core components of chocolate cravings: the Attitudes to Chocolate Questionnaire (ACQ) (Benton et al. 1998) and the Orientation to Chocolate Questionnaire (OCQ) (Cartwright et al. 2007).

Benton et al. (1998) developed the ACQ, a 24-item, 5-point Likert questionnaire able to measure chocolate craving in three domains: (a) craving, (b) guilt feelings, and (c) cravings for functional use (e.g., eating chocolate to curb hunger) (Appendix 11.1).

Cartwright et al. (2007) developed the OCQ, a 14-item, 9-point Likert questionnaire investigating the attitudes to chocolate in the last month. According to Cartwright et al. (2007), the craving experience is defined along a spectrum ranging from weak to extreme. The OCQ contains three subscales: (a) a 6-item approach

subscale, (b) a 6-item guilt subscale, and (c) a 2-item avoidance subscale (Appendix 11.2).

11.4 Chocolate as Social Drug

Chocolate craving shares some features with drug addiction, such as the same shared neurotransmitters and neuronal pathways involved (Alonso-Alonso et al. 2015), even though the literature so far published mainly refers more generally to sugar rather than to chocolate addiction (Avena et al. 2008; Ahmed et al. 2013; DiNicolantonio et al. 2018). Substances of abuse and some palatable foods (e.g., chocolate) display similarities in terms of the type of involvement of the reward circuitry, capability in inducing craving and pleasure, as well as modifying mood (DiNicolantonio et al. 2018). In fact, it has been well documented that those substances able to induce an addiction usually act by activating those neurons containing dopamine (DA) and situated in those brain areas implicated in the process of behavior reinforcement (Berridge 2001). The mesolimbic DA projections from the ventral tegmental area (VTA) to the nucleus accumbens (NAc) have a role in the reinforcement system. Moreover, the NAc is also fundamental for several components of the reward, such as food searching, reinforcement of learning, incentive motivation, and stimulus salience (Kringelbach 2004). Most substances of abuse stimulate DA cell bodies in the VTA and determine the DA release to the NAc.

In this regard, some researchers demonstrated, using neuroimaging studies, that a lot of palatable foods (including chocolate) can release DA in the NAc (Rada et al. 2005; Small et al. 2001). Moreover, Nader et al. (2006) demonstrated that the intake of palatable foods may increase the individual's predisposition in consuming more foods due to the development of tolerance, which is resulted by plasticity changes in the dopaminergic ways with downregulation of D_2 receptors and upregulation of D_1 receptors, as already documented in subjects with an addiction to substances of abuse (Johnson and Kenny 2010; Kalivas and O'Brien 2008. Ahmed et al. 2002). As already mentioned above, chocolate, sugar, and substances of abuse are able to stimulate both DA and opioid neurotransmitter systems (Berridge 2009). In particular, it has been already mentioned that DA neurotransmitter system induces the "*wanting*" (i.e., the incentive to eat the food), while the opioid neurotransmitter system modulates the consumption of a desired food by magnifying the "*liking*" (i.e., the hedonic value of the wanted food) (Berridge 2009).

Opioid peptides are found throughout the limbic system and display some of their actions in reinforcement processing by cooperating with DA systems (Levine and Billington 2004). Repeated use of opiates or similar substances can result in μ-opioid receptor sensitization in numerous areas, including the NAc. A μ-receptor antagonist injected into the NAc attenuates the rewarding consequences of heroin (Vaccarino et al. 1985). The ingestion of palatable foods may affect the opioid system in a variety of sites, and the injection of μ-opioid agonist in the NAc appears to increase the intake of palatable foods rich in sugar (Mercer and Holder 1997). Conversely,

opioid antagonists appear to decrease the intake of sweet foods. Therefore, sugar and chocolate may provoke drug-like effects that may augment the risk for drug (and chocolate) addiction (Avena et al. 2008). In fact, Avena et al. (2008) documented in animal models that those rats with sweetness preference more likely self-administer themselves cocaine at a greater frequency. The authors argued that this mechanism may be due to the effects induced by the sugar on DA, cholinergic, and opioid systems (Avena et al. 2008). Similarly, in a clinical study recruiting bariatric patients, Fowler and Saules (2014) reported that those individuals who reported difficulties in the management of high-palatable foods (including chocolate), before the bariatric surgery, are those who more probably will develop a *de novo* substance-use disorder after surgical procedure.

11.5 The Effects of Chocolate on Mood

Overall, several studies demonstrated a positive and beneficial effect of chocolate on depressed mood, with similar findings reported in men and women (Rose et al. 2010; Lua and Wong 2012; Martin et al. 2012; Meier et al. 2017; Jackson et al. 2019). Chocolate is often accompanied by a beneficial emotional consolation, and this seems to be related to the ability of chocolate to release multiple gut and brain peptides, which are responsible for this psychological effect (Parker et al. 2002). A recent systematic review and meta-analysis, aimed at investigating whether coco-rich products may improve affective dimensions in adults without a psychiatric disorder, demonstrated a significant positive short-term effect on depressive and anxiety symptomatology (Fusar-Poli et al. 2021a, b). However, longer term trials are so far poor and generally did not report significant positive effects of cocoa-rich products and chocolate on the mood. The short-term effects produced by the intake of cocoa-derived food on mood can be explained by the interaction with several neurotransmitter systems and by the presence of several compounds, such as the tryptophan, serotonin, N-acylethanolamines, methylxanthines, and polyphenols (Bruinsma and Taren 1999; Parker et al. 2006; Fusar-Poli et al. 2021a, b). Firstly, cocoa-derived food increases the levels of tryptophan, and, consequently, this may increase the synthesis of serotonin in CNS, which is implicated in the mood regulation (Silva 2010). Secondly, cocoa-rich products contain tyramine, which is a precursor of DA, the "pleasure neurotransmitter," which may be responsible for mood improvement (Macht and Simons 2011). Moreover, chocolate contains also two compounds similar to anandamide that, through the binding to the same brain sites of cannabinoids, may be responsible for sense intensification and euphoria sensations as well as they may cooperate with other components of chocolate in the production of transient feelings of well-being (Bruinsma and Taren 1999). Caffeine and theobromine also have additive and mutually reinforcing outcomes on cognition and vigilance (Scholey and Owen 2013). Cocoa-rich products also contain a great quantity of polyphenols, which may act as anti-inflammatory and antioxidant agents,

being likely implicated also in mood and anxiety improvement (Felger 2018; Fusar-Poli et al. 2021a).

Overall, not all types of chocolate would seem to produce the same effects on mood (Parker et al. 2006; Martin et al. 2012). Indeed, Martin et al. (2012) investigated two groups with low and high levels of anxiety trait, randomly assigned to consume (a) milk chocolate snack ($n = 16$ high anxiety trait, $n = 14$ low anxiety trait), (b) dark chocolate snack ($n = 13$, $n = 17$), and (c) cheese and crackers ($n = 15$, $n = 15$). The authors evaluated mood alterations immediately and up to 1 h after eating the snacks. The milk chocolate snack resulted in the reduction of anxiety in high-anxiety-trait participants. These results were not obtained with dark chocolate or cheese and crackers. Dark chocolate and cheese and crackers, specifically, increased the anxiety and the energetic status of low-anxiety-trait participants.

11.6 Is Chocolate Craving Gender Driven?

Chocolate cravings are approved by over 90% of US women (Osman and Sobal 2006). In about half of female cravers, the periodicity and severity of chocolate craving considerably increase particularly in proximity to the recurrence of menstrual period (Osman and Sobal 2006). In this regard, some researchers suggested that a physiological basis for chocolate craving underpinned the abovementioned temporal pattern between chocolate craving and peri-menstruum (Bruinsma and Taren 1999). In particular, the authors supposed that the physiological changes premenstrually occurring might provoke a need state in which some compounds contained in chocolate (e.g., magnesium and serotonin) are wanted by women. Moreover, with some compounds contained in chocolate being able to induce pleasant feelings, the same authors suggested that women may look for chocolate more perimenstrually due to their transient deficiencies in the premenstrual period, either directly (e.g., anandamide, a cannabinoid) or indirectly through neurotransmitter release (e.g., endogenous opioids) (Tarasuk and Beaton 1991). In fact, some evidence suggested that serotonin levels are low perimenstrually and maybe premenstrual chocolate craving is the process induced to physiologically increase CNS concentration of tryptophan and serotonin (Guillen-Casla et al. 2012). Moreover, chocolate eating and craving among women may be guided by variable hormone levels (Zellner et al. 2004). In fact, the episodic nature of chocolate craving in women may support the hypothesis of the inclusion of some internal/physiological states, most likely due to the hormonal fluctuations which are more evident during the perimenstrual period (Dye 2001). In fact, the craving tends to be overstated just ahead of the menses when estrogen concentrations are moderate and progesterone concentrations are high (Alonso-Caraballo et al. 2020). Progesterone induces fat storage, which may provoke a concurrent increment in cravings for fatty foods, including chocolate (Alonso-Caraballo et al. 2020).

However, other researchers do not support the abovementioned hypothesis, with these findings being not so relevant and significantly reported in low–middle-income

countries or disadvantaged countries with limited economic resources (Parker et al. 2003; Osman and Sobal 2006). For instance, only 6% of Egyptian women endorse craving chocolate (Parker et al. 2003). Similarly, only 28% of Spanish women are reported to suffer menstrual cravings. Therefore, some authors argued that these differential geographical distributions can be more likely determined by internal cultural norms (Osman and Sobal 2006).

11.7 Concluding Remarks

Overall, there is evidence that chocolate craving may reflect a drug-like biological response to some constituents of chocolate and cocoa-rich products. More specifically, chocolate craving seems to be more likely determined by taste and various psychological processes induced by chocolate rather than by biological/physiological mechanisms. Chocolate contains a range of compounds that would display psychotropic properties when taken in appropriate (and therapeutic) doses. These compounds specifically include caffeine, theobromine, phenylethylamine, and anandamide. However, chocolate and cocoa-rich products usually contain the abovementioned compounds in doses lower than the therapeutic threshold level, and, hence, it was hypothesized that chocolate and cocoa products may not completely exert their beneficial and therapeutic effects as at these doses they are probably inactive. In this regard, Rogers and Smit (2000) calculated that an individual would need to eat at least 25 kg of chocolate to receive a psychoactive dose of anandamide. These data demonstrate that it is unlikely that chocolate is able to induce a "drug-like" reaction. Conversely, with chocolate being a pleasant food with a good taste, it is highly likely that we are more motivated to eat chocolate as we physiologically prefer foods that are both sweet and rich in fats. In fact, chocolate appears to reveal a perfect combination of sweetness and fat, giving it an exceptionally attractive taste. Therefore, the uniquely attractive combination of sweetness, flavor, and mouthfeel of chocolate makes it more positively reinforcing than other foods, resulting in a chocolate craving.

Further open questions regard whether the researchers should adequately use the term "addiction" to chocolate consumption at higher quantities from a scientific point of view. The definition of drug addiction reflects the presence of a compulsion, loss of control, unpleasantness after drug (or food) withdrawal, a positive psychological response when the drug (or food) is consumed, and a physical dependence when the drug (or food) is not consumed. However, so far, there has been no scientific evidence demonstrating that eating chocolate may lead to physical dependence, despite there is evidence that chocolate is often consumed to enhance mood. Most people eat chocolate every day without any signs of tolerance or dependence. However, one could argue that the individuals are culturally instructed that chocolate is a food that should be moderately eaten, due to their potential detrimental effects on health. However, it has been well documented that inhibiting a subject who desires

eating foods that taste good may significantly increase his/her desire to eat it much more.

Finally, despite several researches demonstrating that chocolate and drug consumption may significantly differ in several processes, there has been, so far, some evidence which supports the need to implement further studies aimed at investigating similarities and potential shared neurotransmitter pathways in addictions and chocolate craving.

Appendix 11.1 Attitudes to Chocolate Questionnaire (ACQ) (Benton et al. 1998)

Choose the response that best describes your attitude	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
1. I eat chocolate to cheer me up when I am down	1	2	3	4	5
2. My desire for chocolate often seems overpowering	1	2	3	4	5
3. I feel unattractive after I have eaten chocolate	1	2	3	4	5
4. I often feel sick after eating chocolate	1	2	3	4	5
5. I eat chocolate as a reward when everything is going really well for me	1	2	3	4	5
6. I am often on one kind of diet or another	1	2	3	4	5
7. The thought of chocolate often distracts me from what I am doing (e.g., watching TV)	1	2	3	4	5
8. I usually find myself wanting chocolate during the afternoon	1	2	3	4	5
9. I consider chocolate to be high in fat and to be of poor nutritional value	1	2	3	4	5
10. After eating chocolate, I often wish I hadn't	1	2	3	4	5
11. I feel guilty after eating chocolate	1	2	3	4	5
12. I eat chocolate only when I am hungry	1	2	3	4	5
13. Chocolate often preys on my mind	1	2	3	4	5
14. I feel unhealthy after I have eaten chocolate	1	2	3	4	5
15. I always look at the caloric value of a chocolate snack before I eat it	1	2	3	4	5

(continued)

Choose the response that best describes your attitude	Strongly agree	Agree	Neither agree nor disagree	Disagree	Strongly disagree
16. If I resist the temptation to eat chocolate, I feel more in control of my life	1	2	3	4	5
17. Nothing else but chocolate will satisfy my chocolate	1	2	3	4	5

Appendix 11.2 Orientation to Chocolate Questionnaire (OCQ) (Cartwright and Stritzke 2008)

This questionnaire relates to your attitudes towards chocolate in the last month. Please indicate how much you agree with the statements below by circling the number corresponding most closely to your attitude during the last month. Your answers may range from agree not at all (1) with the statement to agree very strongly (9) with the statement.

I agree with this statement									
1. I wanted to eat chocolate as soon as I had the chance	1	2	3	4	5	6	7	8	9
2. I deliberately occupied myself so I would not want chocolate	1	2	3	4	5	6	7	8	9
3. I liked to indulge in chocolate	1	2	3	4	5	6	7	8	9
4. I felt guilty after eating chocolate	1	2	3	4	5	6	7	8	9
5. I considered myself weak when I gave in to my chocolate cravings	1	2	3	4	5	6	7	8	9
6. My desire to have some chocolate seemed overwhelming	1	2	3	4	5	6	7	8	9
7. I felt unhealthy after I had eaten chocolate	1	2	3	4	5	6	7	8	9
8. I felt unhealthy after I had eaten chocolate	1	2	3	4	5	6	7	8	9
9. I did things to take my mind off chocolate	1	2	3	4	5	6	7	8	9
10. I felt dissatisfied with myself after eating chocolate	1	2	3	4	5	6	7	8	9
11. I was thinking about chocolate a lot of time	1	2	3	4	5	6	7	8	9
12. After eating chocolate, I often wished I hadn't	1	2	3	4	5	6	7	8	9
13. I usually found myself wanting chocolate in the afternoons	1	2	3	4	5	6	7	8	9
14. I felt unattractive after eating chocolate	1	2	3	4	5	6	7	8	9

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Chapter 12
Food Addiction

Samer El Hayek, Vanessa Padilla, Mario Eid, and Andrés Jovel

Contents

Abstract For years, the concept of food addiction has been gaining increased attention in the scientific literature and the media. A conceptualization of the condition from a substance use disorder and behavioral addiction perspective has emerged. Even though food addiction remains a controversial diagnosis, with research being in the nascent stages, this condition can have a devastating impact on the lives of those afflicted. In this chapter, the authors provide a comprehensive review of the literature targeting food addiction. Topics for discussion include epidemiology and risk factors, pathophysiology and neurobiology, symptomatology framework based on the diagnostic criteria of behavioral and nonbehavioral

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addictions, physical and psychiatric comorbidities, and proposed treatment avenues of food addiction.

Keywords Food · Hyperpalatable · Addiction · Nutrition · Eating · Mental health

12.1 Introduction to Food Addiction: Is Food Addiction a True Medical Disorder?

Food addiction is a controversial construct and proposed medical diagnosis. Back in 1956, Theron Randolph was the first to introduce the term "food addiction" in the scientific literature. However, earlier in the twentieth century, "eating addiction" was used to refer to individuals with binge eating patterns. Nowadays, the scientific community still debates the validity of food addiction as a medical diagnosis. The use of objective tools, such as the Yale Food Addiction Scale (YFAS), has allowed researchers to better assess and describe the concept of food addiction (Penzenstadler et al. 2019). Furthermore, over the past decade, an increased number of studies have tried to describe the phenomenology of this condition, epidemiology, neurobiology, symptomatology, and the impact it has on affected individuals, as well as its possible treatment avenues. Although ample research has investigated the intricate relationship between food addiction and substance use, eating disorders, and obesity, much more is yet to be understood.

Certain foods, primarily processed foods, refined carbohydrates, and high-fat foods, can contribute to an increased addictive potential. One recent systematic review supports the notion that food addiction is a unique entity that meets similar criteria to other substance use disorders (SUDs) (Gordon et al. 2018).

In this chapter, the authors explore the current evidence about food addiction and provide clinical guidance on its assessment and treatment. First, the epidemiology and risk factors of food addiction will be discussed, followed by a review of research findings of its neurobiology and the conceptualization of food addiction from a SUD perspective. Food addiction symptomatology framework based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) criteria will be explored. Key comorbid or associated physical and mental health conditions, encountered among individuals with food addiction, will also be described. Objective tools used to assess food addiction will be highlighted, as well as the role of society and the mainstream media in shaping this condition. Finally, a comprehensive review of available evidence-based treatment interventions will be discussed, with recommendations for future research.

12.2 Epidemiology and Risk Factors of Food Addiction

According to the YFAS, the adult prevalence rates of food addiction range between approximately 5 and 10% in nonclinical samples, 15 and 25% in obese samples, and 30 and 50% in morbidly obese bariatric patients or obese individuals with binge eating disorder (Oliveira et al. 2021). Among children and adolescents, the estimated prevalence of food addiction is estimated to be around 15% (12% among community samples and 19% among overweight/obese samples) (Yekaninejad et al. 2021).

Food addiction is a multifactorial construct that is postulated to emerge secondary to the interplay between biological, genetic, psychological, and social factors.

Biological factors include hormonal imbalances, abnormalities in brain structures, side effects to certain medications, and genetic inherited factors (Liu et al. 2010; Murray et al. 2014). The genetic influence on the risk of becoming overweight or obese is substantial. Changes in gene expression occurring during intrauterine development, or epigenetics changes, can significantly impact an individual's subsequent risk of developing obesity (Rhee et al. 2012; Şanlı and Kabaran 2019). The relationship between genetics and food addiction, on the other hand, is certainly complicated and not yet clear. A recent review described the intricate association of genetic and epigenetic research related to addictive tendencies toward food (Davis and Bonder 2019). A genome-wide association study of 9314 females of European ancestry who were diagnosed with food addiction did not identify a significant association with single nucleotide polymorphisms or genes already implicated in drug addiction (Cornelis et al. 2016). However, a review of neurogenetic evidence in obesity implicated a relationship between obesity and gene polymorphisms that code for dopamine receptor types 2, 3, and 4; the dopamine active transporter; and enzymes associated with dopamine degradation such as catechol-o-methyltransferase, monoamine oxidase A, and monoamine oxidase B (Stanfill et al. 2015).

Biological factors interact with lifestyle and psychosocial factors. For instance, physical exercise can reduce the genetic effects on obesity measures, such as body mass index (BMI) and weight circumference (Lin et al. 2019). Psychological factors that can mediate food addiction include emotional distress and behavioral difficulties associated with weight gain, such as feelings of guilt and weight stigmatization (Adams et al. 2019). Compulsive eating patterns are thought to occur secondary to ineffective self-control schemes (Kayloe 1993), as a means to treat negative emotions triggered by depressive symptoms (Dêbska et al. 2011), or due to psychosocial factors such as high stress, low coping mechanisms, and low emotional support (Mazur et al. 2011). Certain character traits have also been implicated in the development of food addiction. A recent systematic review of 45 studies assessed the role of impulsivity and reward sensitivity in food addiction. While self-reported impulsivity was found to be consistently associated with food addiction, this was not the case with reward sensitivity. The latter, defined as the degree to which an individual's behavior is motivated by reward-relevant stimuli, was inconsistently associated with food addiction. Along the lines of impulsivity, food addiction was

consistently associated with negative and positive urgency (the tendency to act impulsively when experiencing extremely negative and positive emotions, respectively) and lack of perseverance (the tendency to quit when a task becomes difficult or boring) (Maxwell et al. 2020). Lastly, social factors including family dysfunction, peer pressure, social media influence, social isolation, and lack of a support system can also trigger or worsen food addiction. A 2019 review illustrates a biopsychosocial model of risk factors and triggers of food addiction (Adams et al. 2019).

The interplay among the above-described risk factors has been proposed to likely drive the development of food addiction. Food addiction can, therefore, be defined as an entity caused by the interplay between several factors that encourage or stimulate food cravings to reach a state of heightened pleasure or stress relief. Further understanding of these different elements is necessary to identify and implement individualized, targeted, holistic, patient-centered treatment interventions.

12.3 Neurobiology of Food Addiction

Three reviews provide an in-depth discussion about the neurobiology of food addiction. In 2010, Blumenthal and Gold reviewed the similarities in the physiology of addiction and food consumption, the published evidence of food addiction, and the freshly developed tools to better characterize pathological appetitive behaviors (Blumenthal and Gold 2010). Before then, in 2009, Dagher provided an overview of the signaling networks that regulate food consumption and the similarities between drug use and food addiction (Dagher 2009), while Wang et al. reviewed the neurobiology underlying food consumption, including the interactions between peripheral and central signaling systems involved in eating and the mediating role of dopamine (Wang et al. 2009).

At a structural level, four central nervous system (CNS) regions are involved in the regulation of eating: the amygdala/hippocampus, insula, orbitofrontal cortex, and striatum (Dagher 2009). Other implicated brain structures include the hypothalamus and arcuate nucleus, which have also been particularly involved in weight regulation (Wang et al. 2009). To further delineate the role of these structures in food addiction, one study compared functional magnetic resonance imaging (fMRI) in 39 healthy young women ranging from lean to obese. Results showed that participants with higher scores on food addiction scales had significantly greater activation in the dorsolateral prefrontal cortex and the caudate in response to anticipated receipt of food (i.e., a highly caloric and sweet drink). Participants also showed decreased activation in the lateral orbitofrontal cortex in response to receipt of food (Gearhardt et al. 2011). The findings of this study are similar to patterns of neuronal activation observed in SUDs. The activation of these brain regions stimulates implicit learning about “food rewards”, allocating efforts toward maximizing them, and integrating information about bodily energy stores and gut contents with information from the

outside world, such as food types and availability (Blumenthal and Gold 2010; Dagher 2009; Wang et al. 2009).

At a hormonal level, there is growing recognition of the involvement of hormones in food addiction (Blumenthal and Gold 2010). In the CNS, dopaminergic pathways regulate the motivation to consume food and the pleasurable feelings after eating (Dagher 2009; Wang et al. 2009). These dopaminergic pathways interact with other systems including opioid-mediated, GABAergic, and serotonergic circuits. Moreover, orexin and melanin play important signaling roles in hypothalamic circuits, whereas neuropeptide Y and alpha-melanocyte-stimulating hormones regulate neuronal signaling in the arcuate nucleus (Wang et al. 2009).

Disruption of the hypothalamic-pituitary-adrenal axis and levels of corticotropin-releasing factor have been described as mediators of food addiction. Cottone and colleagues demonstrated that rats withdrawn from access to a high-sucrose diet exhibited an increase in mRNA and peptide expression of corticotropin-releasing factor in the central nucleus of the amygdala. Rats also displayed anxious behaviors when unable to access their diet. Upon access to the hyperpalatable food, overeating was noted. Interestingly, these findings in rats were mitigated by pretreatment with a selective corticotropin-releasing factor antagonist (Cottone et al. 2009).

Peripherally, many signaling pathways are involved in regulating hunger and satiety. These pathways are highly interconnected with the central circuits. In particular, four gut- and fat-derived hormones mediate this complex homeostatic regulation: ghrelin, leptin, insulin, and peptide YY. Ghrelin, or the "hunger peptide," is released by the stomach and acts on the hypothalamus to stimulate the dopaminergic reward pathways, leading to an increase in food consumption. Ghrelin typically rises during a fasting period and falls following meal intake. In contrast, leptin acts on the hypothalamus to decrease food intake and increase metabolic rate, inhibiting dopaminergic circuits. Leptin relays information about available fat reserves to the CNS, therefore playing a significant role in long-term energy homeostasis. Insulin and peptide YY, secreted from the pancreas and small intestine, respectively, relay information to the brain about acute changes in energy levels (Wang et al. 2009).

12.4 Food Addiction Conceptualized from a Substance-Use Disorder Perspective

The recent expansion in the food industry allowed the creation of food products with increased rewarding properties. These products typically have a low nutritional value and are saturated with carbohydrates, sugars, fat, and additives. They are referred to as hyperpalatable food and have been described in the literature as "addictive" (Dimitrijević et al. 2015). This paved the way for a framework of food dependence as an analog to SUDs, characterized by the three stages of addiction: binge/intoxication, withdrawal/negative affect, and preoccupation/anticipation.

The binge/intoxication stage involves the dopamine and opioid pathways in the nucleus accumbens and dorsal striatum. The innate reinforcing nature of food is a result of dopamine release in the striatum (Wang et al. 2004, 2009). However, food is found to activate dopaminergic pathways differently than drugs of abuse. In particular, hyperpalatable food causes a delayed increase in dopamine level as a function of increased glucose and insulin. Meanwhile, the opioid system exerts a synergistic effect with dopaminergic pathways to promote food intake. In contrast, drugs of abuse typically increase dopamine through direct pharmacologic effects or, indirectly, through opioid, GABAergic, and cannabinoid systems (Barbano and Cador 2007; Volkow et al. 2008). Interestingly, both food and drugs activate the endogenous opioid system. As such, naltrexone, an opioid receptor antagonist, is used in both weight loss and SUD treatment (Colantuoni et al. 2001; Gearhardt et al. 2009a). The withdrawal/negative affect stage activates the extended amygdala and medial part of the nucleus accumbens, whereas the preoccupation/anticipation stage engages the prefrontal cortex, hippocampus, and insula (Koob and Volkow 2016). Dopamine pathways in these brain structures were found to be modulated in food addiction, as will be discussed below.

Food addiction can be conceptualized from the lens of SUDs. At a physiological level, a hyperpalatable food product activates the reward system. At a behavioral level, this previously neutral stimulus (i.e., hyperpalatable food product) becomes paired with a rewarding effect (i.e., satisfaction or relief) via dopamine and other rewarding brain circuits, leading to conditioned reinforcement. Subsequently, the neutral stimulus becomes a reinforcer of the behavior, leading to an "urge" to consume the food product to achieve the rewarding effect.

Findings from brain imaging studies validate the presence of similarities in central processes between individuals with food addiction and SUDs (Lindgren et al. 2018). Clinical studies of positron-emission tomography imaging in alcohol, stimulant, and opioid use disorders show that a defining trait of SUDs is a reduction in dopamine release and a decrease in dopamine receptor D2 (DRD2) availability in the nucleus accumbens and dorsal striatum (Martinez et al. 2005, 2007). To assess whether food addiction has a comparable pattern, several studies examined dopamine release and availability of DRD2 in the brains of individuals with obesity. Studies have shown that, compared to individuals with low BMI, those with high BMI had less striatal dopamine release in response to consuming glucose (Wang et al. 2014), and reductions in striatal DRD2 availability correlated with increasing BMI (Wang et al. 2001). The lack of dopamine-induced signaling results in decreased functional modulation of reward brain regions, which is thought to mediate the compulsive administration of hyperpalatable food or drugs (Wang et al. 2004).

Imaging studies indicate similar changes in regional brain glucose metabolism in individuals with either food addiction or SUDs. In both groups, an association is seen between DRD2 availability and glucose metabolism in the orbitofrontal cortex and anterior cingulate gyrus (Volkow et al. 2001, 1993). Reduced glucose metabolism in these prefrontal brain regions was found to be correlated with reduced striatal dopamine availability and signaling in individuals with obesity (Volkow et al. 2001).

Decreased glucose metabolism in the executive control centers reflects a decrease in their functioning, which appears to contribute to the lack of inhibitory control over food/drug-taking behaviors observed in these individuals (Volkow et al. 2008). One major difference between addiction to food and drugs is glucose metabolism changes observed in the somatosensory cortex, which is associated with the subjective perception of taste. Individuals with obesity had increased glucose metabolism in the postcentral gyrus in the left and right parietal cortex of the somatosensory cortex (Wang et al. 2002). Given this enhanced activity, palatability is thought to be increased in individuals with obesity, which potentiates the reinforcing properties of food, the intense desire to consume high-calorie meals, and the subsequent risk of developing food addiction (Wang et al. 2004).

In terms of regulation of μ-opioid receptors, individuals with obesity share features similar to those with opioid use disorder. One study showed that compared to lean individuals, those with obesity have significantly lower availability of μ-opioid receptors in brain regions of reward processing, including the ventral striatum, insula, and thalamus. This may promote overeating to compensate for a blunted μ-opioid receptor response (Karlsson et al. 2015).

Another hormone possibly involved in food addiction is norepinephrine. Imaging results in individuals with morbid obesity show a decrease in norepinephrine transporter availability in the thalamus compared to healthy controls (Li et al. 2014). Also, higher emotional eating patterns in individuals with obesity, defined as increased food consumption in response to negative emotions, correlates with lower norepinephrine transporter availability in the locus coeruleus and higher availability in the left thalamus (Bresch et al. 2017). Similar alterations are described in SUDs. In comparison to healthy controls, individuals with cocaine use disorder have significant upregulation of norepinephrine transporters in the thalamus (Ding et al. 2010). Collectively, these findings suggest that fluctuations in norepinephrine availability in the brain are present in individuals with obesity, emotional eating, and SUDs.

Numerous brain imaging studies have elucidated neurostructural correlates between obesity and SUDs. Drug cues have consistently produced activation of the ventral striatum, amygdala, prefrontal cortex, anterior cingulate cortex, orbitofrontal cortex, and insula (Courtney et al. 2016). A similar response is seen when individuals with obesity are exposed to food-related cues in comparison to controls (Rothemund et al. 2007) and upon consuming high- versus low-calorie beverages (Feldstein Ewing et al. 2017). Furthermore, an overlap in activated brain regions was described following the provision of food and drug cues in individuals with cocaine use (Tomasi et al. 2015). Alternatively, BMI was found to be positively correlated with response in CNS regions implicated in reward and attention, including the lateral orbitofrontal and ventrolateral prefrontal cortex, during the initial provision of food cues (Yokum et al. 2011). This suggests that, following exposure to food cues, individuals with higher activation of reward and attention regions might be at greater risk of obesity. Conversely, gains in body weight and fat were found to be associated with an increase in the responsivity of reward and attention brain regions to food cues, including putamen and mid-insula (Stice and Yokum

2016). Individuals with obesity also show, compared to individuals with normal BMI, differences in the activation of regions of food reward and salience before and after food intake (Hogenkamp et al. 2016) and after a 48-h fasting period (Wijngaarden et al. 2015). Finally, higher levels of body fat were found to be associated with frontal gray matter atrophy, particularly in the prefrontal cortex (Willette and Kapogiannis 2015). These findings hint at the loss of executive function and inhibitory control, which are common themes in SUDs, as processes associated with obesity (Lindgren et al. 2018).

12.5 Food Addiction and DSM-5-TR Criteria

Food addiction is a multidimensional and complex condition. Whether or not it has an inherently addictive quality similar to drugs of misuse or it represents a behavioral addiction, similar to gambling disorder, continues to be debated (Lindgren et al. 2018). In this section, the authors explain food addiction from both perspectives.

One of the original conceptualizations of food addiction was to compare it to the DSM criteria of SUDs. The DSM-5 was the first version to include the diagnosis of binge eating disorder, which emphasized the presence of escalated ingestion of food (in amounts larger than what most people would eat in a discrete period) and loss of control over overeating as core symptoms of the illness. This parallels the description of food addiction as a compulsive "food-seeking" behavior (Koob and Volkow 2010). However, the DSM-5 may still fail to capture the full pathology and spectrum of symptoms behind food addiction (Lindgren et al. 2018). There is disagreement about the needed criteria for diagnosing this condition (Meule and Gearhardt 2014b), as the translation of the DSM SUD criteria to food addiction is not straightforward. Empirical evidence for the applicability of some of these criteria, such as tolerance and withdrawal symptoms, is based on preclinical studies (Avena et al. 2008). Nevertheless, almost all symptoms can be found in and applied to humans (Gearhardt et al. 2009a). Cassin and von Ranson showed in their cross-sectional study that all participants with binge eating disorder received a diagnosis of SUD when, in a diagnostic interview, the word "substance" was substituted with "binge eating" (Cassin and von Ranson 2007).

Table 12.1 is an application of the DSM-5-TR criteria of SUDs to food addiction (Dimitrijević et al. 2015; Meule and Gearhardt 2014b). Previous studies showed that the most common symptoms of food addiction are eating large amounts of food over a long period, an attempt to reduce consumption, and continued use despite negative consequences. Rare symptoms include tolerance and time spent on the purchase and consumption of food. Alternatively, the least common or inapplicable symptoms are intoxication, withdrawal, and reduction of social, occupational, or recreational activities secondary to food consumption (Dimitrijević et al. 2015; Meule and Gearhardt 2014b).

The diagnosis of SUDs requires at least two symptoms of the DSM criteria and a clinically significant functional impairment. In food addiction, distress has been

Table 12.1 Food addiction conceptualized as a DSM-5-TR substance use disorder

DSM-5-TR substance use disorder criterion	Food addiction equivalent	Evidence and explanation
Substance often taken in larger amounts or over a longer period than was intended	Food often consumed in larger amounts or over a longer period than was intended	• Core feature in binge eating disorder and bulimia nervosa • Observed in nonclinical population, including individuals with normal weight • Characterized by eating faster than others, eating alone, when not hungry, and until becoming ill • Associated feelings of shame and guilt • Triggers include hyperpalatable food rich in sugar and fat, and pervasive marketing
Persistent desire or unsuccessful efforts to cut down or control substance use	Persistent desire or unsuccessful efforts to cut down or control food intake	• Core feature in binge eating disorder and bulimia nervosa • Recurrent, and commonly failed, engagement in fitness programs, diet plans, and medical intervention (including over-the-counter medications and surgeries) • Weight loss market in the United States achieved a record of 72 billion dollars in 2019 (LLC 2021)
Great deal of time is spent in activities necessary to obtain or use the substance or recover from its effects	Great deal of time is spent in activities necessary to obtain or overeat food or recover from its effects	• Criterion might not be applicable • Might consider engaging in dietary habits as a tool to recover from food addiction
Craving, or a strong desire or urge to use the substance	Craving or a strong desire or urge to eat specific types of food	• Concept of food cravings previously described in the literature (Hormes and Rozin 2010), with noted cultural differences in types of craved food (Komatsu 2008; Lawson et al. 2020; Weingarten and Elston 1991) • Neurostructural activation patterns in the setting of craving overlap across different substances, including food (Kühn and Gallinat 2011; Naqvi and Bechara 2009; Pelchat et al. 2004) • Craved food can be consumed in an addictive-like

(continued)

Table 12.1 (continued)

DSM-5-TR substance use disorder criterion	Food addiction equivalent	Evidence and explanation
		manner • Overeating can be associated with more intense and frequent experiences of food cravings: higher scores on self-reported food craving measures have been found in patients with binge eating disorder, bulimia nervosa, and obesity (Abilés et al. 2010; Van den Eynde et al. 2012) • Association of food consumption with external cues, such as advertisements, sights, smells, and sounds can trigger food cravings or increased preference for highly palatable foods (Corsica and Pelchat 2010)
Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home	Recurrent overeating resulting in a failure to fulfill major role obligations at work, school, or home	• Criterion might not be applicable • Might consider morbid obesity and reduced mobility secondary to food addiction as a culprit for failure to fulfill obligations
Continued use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance	Continued overeating despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of excessive or specific types of food	• Increased social isolation described in obese individuals compared to those with normal weight (Anderson et al. 2006) • Interpersonal problems such as interpersonal distrust, social insecurity, or hostility linked to binge eating behavior, independent of BMI (Fassino et al. 2003; Lo Coco et al. 2011)
Important social, occupational, or recreational activities are given up or reduced because of substance use	Important social, occupational, or recreational activities are given up or reduced because of overeating of food	• Criterion might not be applicable • Shame and guilt in the setting of unhealthy eating patterns can nonetheless trigger feelings that might interfere with social and recreational activities
Recurrent substance use in situations in which it is physically hazardous	Recurrent overeating in situations in which it is physically hazardous	• Criterion might not be applicable • Clinically, this can refer to

(continued)

Table 12.1 (continued)

DSM-5-TR substance use disorder criterion	Food addiction equivalent	Evidence and explanation
		inappropriate food consumption in the context of an acute health condition: eating excessive sugar despite living with a diagnosis of diabetes mellitus or eating excessively following bariatric surgery • Can be applied to eating while driving, as it impairs driving performance and increases the risk for crashes (Alosco et al. 2012; Stutts et al. 2005)
Substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance	Overeating is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by overeating	• In preclinical studies, rats exposed to hyperpalatable food continue to consume it despite negative consequences, such as electric shock (Novelle and Diéguez 2018) • Clinically, this can refer to inappropriate food consumption in the context of an acute health condition: eating excessive sugar despite living with a diagnosis of diabetes mellitus or eating excessively following bariatric surgery
Tolerance: the need for markedly increased amounts of the substance to achieve intoxication or desired effect; markedly diminished effect with continued use of the same amount of the substance	Tolerance: the need for markedly increased amounts of food to achieve the desired effect; markedly diminished effect with continued use of the same amount of food	• Evidence from preclinical studies: – Rats provided with intermittent or excessive access to sugar solutions significantly increase their intake over time and display neurochemical changes similar to those observed in drug use (Colantuoni et al. 2001; Rada et al. 2005) – Rats displayed voluntary tolerance for punishment by electrical shock to obtain a particular palatable food (Oswald et al. 2011) • Evidence from clinical studies: – Females who crave carbohydrates develop an increased preference for this food category and tolerance to

(continued)

Table 12.1 (continued)

DSM-5-TR substance use disorder criterion	Food addiction equivalent	Evidence and explanation
		its ability to ameliorate dysphoria (Corsica and Pelchat 2010) – Males provided with chocolate for 3 weeks gradually increased their chocolate intake while reporting a reduction in the pleasantness of taste and desire to eat the chocolate (Hetherington et al. 2002)
Withdrawal syndrome: differs by substance; substance is taken to relieve or avoid withdrawal symptoms	Withdrawal syndrome: when refraining from eating specific foods; specific foods are eaten to relieve or avoid withdrawal symptoms	• Evidence from preclinical studies: – Withdrawal symptoms (tremors, irritability, increased body temperature) occur when animals are deprived of their hyperpalatable food (Di Segni et al. 2014; Novelle and Diéguez 2018) • Evidence from clinical studies: – In a qualitative study, withdrawal-like symptoms were reported by youth attempting to reduce the intake of pleasurable food, including persistent cravings and irritability (Pretlow 2011)
Substance intoxication	Not applicable to food intoxication	• Criterion is not applicable

previously noted by Schwartz and colleagues. In their study of 4283 people, 46% of participants expressed that they would waive 1 year of their life rather than be fat, 15% would waive 10 years, 25% would agree to have no children, 30% would rather be divorced than obese, and 14% alcohol dependent rather than overweight (Schwartz et al. 2006).

Gambling disorder was added in the DSM-5 as a non-substance-related disorder. Similar to SUDs, some of the gambling disorder symptoms can conceivably be applied to food addiction, as denoted in Table 12.2 (Meule and Gearhardt 2014a).

Whether food addiction resonates more with the criteria of SUDs or with those of the non-substance-related gambling disorder remains to be eluded. Regardless, symptoms of food addiction seem to echo several features of both conditions. As such, it may represent a mixture of nonbehavioral and behavioral addictions and, therefore, constitute a separate and novel entity on the spectrum of potentially addictive disorders.

Table 12.2 Food addiction conceptualized as a DSM-5-TR gambling disorder

DSM-5-TR gambling disorder criterion	Food addiction equivalent	Evidence and explanation
Need to gamble with increasing amounts of money to achieve the desired excitement	Need to eat increasing amounts of food to achieve the desired satisfaction	• Equals the tolerance criterion in SUDs
Restlessness or irritability when attempting to cut down or stop gambling	Restlessness or irritability when attempting to cut down or stop overeating	• Equals the withdrawal criterion in SUDs
Repeated unsuccessful efforts to control, cut back, or stop gambling	Repeated unsuccessful efforts to control, cut back, or stop overeating	• Core feature in binge eating disorder and bulimia nervosa
Preoccupation with gambling	Preoccupation with food and eating	• Food addiction is strongly associated with a preoccupation with food, eating, and overeating when feeling distressed (Gearhardt et al. 2009a, 2012; Meule and Kübler 2012)
Gambling when feeling distressed	Eating/overeating when feeling distressed	• Food addiction is strongly associated with a preoccupation with food, eating, and overeating when feeling distressed (Gearhardt et al. 2009a, 2012; Meule and Kübler 2012)
After losing money gambling, often return another day to get even	After dieting or holding off from food intake, may return or relapse into overeating patterns	• Criterion might not be applicable • One can hypothesize that, in food addiction, failed attempts to decrease food intake can be counteracted by unhealthy eating patterns
Lying to conceal the extent of involvement with gambling	Lying to conceal the extent of involvement with overeating	• Core feature in binge eating disorder and bulimia nervosa • Characterized by feelings of shame and guilt associated with excessive eating and trying to conceal the behavior
Jeopardizing or losing a significant relationship, job, or educational or career opportunity because of gambling	Jeopardizing or losing a significant relationship, job, or educational or career opportunity because of overeating	• Criterion might not be applicable • Might consider morbid obesity secondary to food addiction as jeopardizing life opportunities. For instance, with stigma playing a role, human resource professionals underestimate the occupational prestige of obese individuals and are less likely to

(continued)

Table 12.2 (continued)

DSM-5-TR gambling disorder criterion	Food addiction equivalent	Evidence and explanation
		hire them (Giel et al. 2012) • In women, excessive weight is associated with an increased likelihood of taking sick leave days and long-term absenteeism from work (Reber et al. 2018)
Relying on others to provide money to relieve desperate financial situations caused by gambling	Relying on others to provide money to relieve desperate financial situations caused by overeating	• Money spent on binge eating was found to markedly affect the quality of life in individuals with binge eating disorder and bulimia nervosa, the former being particularly bothered by financial problems (Agras 2001)

12.6 Signs and Symptoms of Food Addiction

Food addiction is recognizable by the following cluster of symptoms:

- **Symptoms related to the amount of food consumed.** This includes food consumed in larger amounts or over a longer period than was intended, continuing to eat certain types of foods when no longer hungry, cravings, and persistent desire or repeated failures to reduce the amount of food intake.
- **Symptoms related to time spent on food-related activities.** This includes spending a great deal of time in activities necessary to obtain food, overeat, or recover from food's effects.
- **Symptoms related to consequences of food addiction.** This includes failure to fulfill major obligations at work, school, or home; continued overeating despite persistent or recurrent social or interpersonal problems and despite knowledge of having physical or psychological problems caused or exacerbated by overeating; giving up or reducing important activities; spending a significant amount of money on the behavior; and recurrent overeating in physically hazardous situations.
- **Associated physiological dependence.** This includes food tolerance and withdrawal symptoms.
- **Associated psychological symptoms.** This includes decreased energy, difficulty concentrating, sleep disturbances, restlessness, and irritability.
- **Associated physical symptoms.** This includes chronic fatigue, headache, and gastrointestinal symptoms.

12.7 Food Addiction Scales

In an attempt to provide a standardized measure for the diagnosis of food addiction, the YFAS was constructed in 2008 (Gearhardt et al. 2009b). It is a 25-item instrument that encompasses dichotomous and Likert scale questions. It measures the presence of food addiction symptoms based on the DSM-IV substance dependence criteria (7 items) and associated clinically significant impairment or distress (2 items). The former seven items include diminished control over consumption, persistent desire or repeated unsuccessful attempts to quit, consumption of large amounts of food over a longer period than intended, spending much time obtaining food, giving up important activities, withdrawal, and tolerance. When at least three out of the seven items are met *and* clinical impairment is present, a diagnosis of food addiction can be provided. The YFAS has shown good internal reliability and good convergent validity with measures obtained from similar constructs. Since its creation and validation, this scale has been used in almost all food addiction research and has been translated into several languages (Gearhardt et al. 2009b; Meule and Gearhardt 2014b; Oliveira et al. 2021).

In 2014, the modified YFAS (mYFAS) was created as a briefer assessment tool of food addiction (Flint et al. 2014). The mYFAS consists of nine self-report questions: seven that assess the DSM-IV SUD criteria and two that evaluate clinical impairment or distress. The mYFAS performed similarly on indicators of reliability and validity as the YFAS and yielded similar rates of food addiction symptoms and diagnostic threshold scores (Flint et al. 2014; Lemeshow et al. 2016).

Back in 2016, the YFAS 2.0 emerged to reflect the diagnostic criteria of SUD in the DSM-5 (Gearhardt et al. 2016). The YFAS 2.0 includes 35 items that assess food addiction based on the 11 criteria of SUD in DSM-5. It also lowers the diagnostic threshold of food addiction from three to two symptoms, along with clinically significant impairment or distress. To determine the severity of food addiction, the YFAS 2.0 uses mild, moderate, or severe specifiers. The updated scale appears to have better internal consistency but similar convergent, incremental, and discriminant validity with eating-related constructs compared to the original YFAS (Gearhardt et al. 2016; Schulte and Gearhardt 2017). The YFAS 2.0 has been translated and adapted to multiple contexts (Oliveira et al. 2021).

The YFAS 2.0 was later adapted into mYFAS 2.0, a 13-item measure, with good reliability and similar convergent, discriminant, and incremental validity compared to the full YFAS 2.0 (Schulte and Gearhardt 2017). It was translated into several languages such as French (Brunault et al. 2020) and Chinese (Li et al. 2021; Zhang et al. 2021). The French version of the mYFAS 2.0 was found to have close psychometric properties to the YFAS 2.0 in both nonclinical and clinical samples (Brunault et al. 2020).

12.8 Food Addiction and Impact on Physical Health

Food addiction has a direct impact on well-being. Individuals suffering from food addiction are at increased risk of physical and psychological consequences. Overeating can predispose to the early development of chronic metabolic diseases such as obesity, which may contribute to high cholesterol and glucose impairment, ultimately leading to increased risk of cardiovascular diseases and organ dysfunction. Gastrointestinal issues may also develop secondary to food addiction, possibly due to disruption of gut microbiota and brain-gut interactions, especially if an eating disorder is comorbid (Santonicola et al. 2019). Other debilitating physical consequences described in food addiction may be chronic fatigue, sleep disorders, reduced sex drive, lethargy, headaches, arthritis, kidney or hepatic disease, osteoporosis, malnutrition, and chronic pain. Directly or indirectly, the physical changes caused by food addiction may have an increased toll on the mental health of affected individuals (Wenzel et al. 2020).

Food addiction can occur in healthy individuals with no obesity, who are capable of maintaining normal body weight. Some of these individuals engage in behavioral modifications, such as increasing the intensity or the frequency of their physical activity, to counteract the potential effects of uncontrolled overeating. However, food addiction may still lead to obesity, defined as a BMI greater than or equal to 30. This can be largely considered a preventable disease. Worldwide, by 2016, over 650 million adults were obese (WHO 2021b). The presence of obesity is a major risk factor for stroke, heart disease, diabetes, musculoskeletal disorders, and neoplasms such as endometrial, breast, ovarian, prostate, liver, gallbladder, kidney, and colon cancer (Pi-Sunyer 2009). When obesity occurs in childhood, the individual is at increased risk of premature death and living with disability as an adult. As obesity can be a difficult disease to treat and overcome, some obese individuals may pursue bariatric surgery as a treatment option to improve health outcomes. A 2017 review of literature on food addiction and bariatric surgery found that presurgical food addiction was related to psychopathology (with mixed findings related to substance misuse), but not related to presurgical or postsurgical weight outcomes (Ivezaj et al. 2017). Still, further research is needed to examine any positive or negative, short- and long-term, effects of bariatric surgery on food addiction symptoms (Koball et al. 2020).

Unstable blood glucose levels or low insulin sensitivity as a result of food addiction can lead to diabetes. A study examining a sample of individuals with type 2 diabetes found a link between obesity and food addiction in this population, with impulsivity and food addiction significantly predicting higher BMI (Raymond and Lovell 2015). Although obesity and type 2 diabetes are treatable conditions, living with diabetes represents a management challenge requiring strict treatment, glucose monitoring, and lifestyle modifications to maintain adequate glucose control and prevent comorbid medical complications such as retinopathy, kidney failure, cognitive decline, depression, and neuropathy. A recent 2020 cross-sectional study exploring the relationship between food addiction and type 2 diabetes found that the

presence of food addiction in individuals with diabetes worsens glycemic control and increases BMI and hemoglobin A1C levels. Moreover, there was an increased presence of diabetic retinopathy, neuropathy, nephropathy, and depressive symptoms among individuals with type 2 diabetes and food addiction (Nicolau et al. 2020).

As many individuals suffer from cardiovascular disease, which is the leading cause of death globally (WHO 2021a), it is imperative to understand the role of unhealthy eating patterns in the risk of developing heart conditions. Addictive behaviors, such as smoking cigarettes and drug use, have been associated with an increased risk for premature heart disease (Mahtta et al. 2021; Thylstrup et al. 2015). To minimize the cardiovascular risk, in addition to promoting tobacco, alcohol, and drug use cessation, individuals should monitor and reduce their salt and red meat intake, eat more fruits and vegetables, and engage in regular physical activity. A cross-sectional study among Peruvian adults assessing food addiction, saturated fat intake, and BMI found no differences among men or women but identified a positive correlation between those with reported increased weight, food addiction, and higher saturated fat intake (Lopez-Lopez et al. 2021). Many longitudinal studies have demonstrated the association between the so-called unhealthy lifestyle (high-saturated-fat diet, high caloric intake, poor sleep, and physical inactivity) and cardiovascular disease. Alternatively, studies have suggested that a Mediterranean-type diet, with an emphasis on plant food sources, reduces the risk of obesity and cardiovascular diseases (Anand et al. 2015). Therefore, promoting a low-fat diet with minimally processed low-glycemic content may ultimately help prevent obesity and cardiovascular disease.

No data has been published on food addiction and infertility. However, among many factors, eating disorders and poor diet (lower intake of fruit and higher intake of fast food) have been associated with either longer time to pregnancy, infertility, or reproductive health negative outcomes such as increased risk of miscarriage (Grieger et al. 2018; Linna et al. 2013).

12.9 Food Addiction and Mental Health

An association between food addiction and a wide variety of mental health symptoms has been described in the literature (Burrows et al. 2018; Piccinni et al. 2021). Individuals with food addiction may experience comorbid psychiatric conditions, such as eating disorders, mood disorders, anxiety disorders, and SUDs (Piccinni et al. 2021). Food addiction has also been found to have a significant direct relationship with binge eating, depression, and anxiety (Burrows et al. 2018). This has also been established in adolescents (Skinner et al. 2021).

Common eating disorders are anorexia nervosa, bulimia nervosa, and binge eating disorder. Food addiction may lead individuals to develop any of these eating disorders given the unhealthy patterns of food restriction and binges. Excessive episodes of food restriction, either via reducing caloric intake, skipping meals, or

excessive fasting, may signal the body to perceive extreme hunger, eventually leading to binge episodes or overeating. A recent review article provided evidence that food addiction may be a completely distinct phenomenon separated from other eating disorders (Hauck et al. 2020). Meanwhile, an important criterion in eating disorders is experiencing thoughts of shame or guilt related to overeating after the excessive ingestion of food. As food addiction may lead to the development of eating disorders, it is worth pointing out that eating disorders can also occur in combination with other SUDs, major depression, and anxiety disorders, which may complicate the clinical assessment and management of individuals with food addiction.

Mood disorders are commonly encountered among individuals suffering from food addiction. Depression, isolation, and low self-esteem may occur secondary to food addiction. Food addiction may be highly mediated by mood and impulsivity, which can be affected by chronic stress exerting a negative effect on the hypothalamic-pituitary-adrenal axis function (Kalon et al. 2016). Moreover, as dopamine has been associated with reward, food intake, stress regulation, and gastrointestinal motility, one study explored the relationship of peripheral dopamine levels on depressed patients meeting YFAS criteria for food addiction. The study found that plasma dopamine levels positively correlated with eating behaviors in females and negatively with food addiction in males (Mills et al. 2020). The presence of obesity has been directly linked with the risk of developing depression, and a bidirectional relationship has been described as depressed individuals are also at elevated risk of developing obesity (Luppino et al. 2010). As a wide variety of factors can predispose an individual to develop mood disorders when struggling with food addiction, attention to the severity of any eating disorder is crucial. Binges may be perceived as temporary relief of depressive symptoms. Isolation, ensuing regret, shame, and guilt may precipitate a recurrence of depressive symptoms.

Regardless of the presence or absence of food addiction, it is well established that eating disorders are associated with the highest mortality rate among mental illnesses. Once an individual with food addiction struggles with major depression and/or eating disorder, self-harm behaviors and risk of suicide become potentially fatal complications. Adolescents living with eating disorders co-occurring with depression are at increased risk of suicidal ideations (Patel et al. 2021). Eating disorders remain the third most common chronic illness among adolescents. Adolescents struggling with comorbid depression and eating disorders were found to be at five times increased odds of experiencing suicidal ideations but lower odds of having a suicide attempt (Patel et al. 2021). As per the National Association of Anorexia Nervosa and Associated Disorders (ANAD), the mortality rate associated with anorexia nervosa is 12 times higher than the death rate of all causes of death for females aged 15–24 (ANAD 2021). In particular, suicide accounts for at least two-thirds of the nonnatural deaths among those diagnosed with eating disorders. Specifically, in anorexia nervosa, individuals are significantly more likely to engage in serious suicide attempts, exhibit a higher expectation of dying, and have an increased risk of disease severity, compared to individuals without an eating disorder or with bulimia nervosa (Guillaume et al. 2011).

Food addiction has also been associated with anxiety symptoms, especially in certain populations such as obese individuals and adolescents (Benzerouk et al. 2018; Parylak et al. 2011). Studies have described that individuals who struggle with food addiction and exhibit irrational beliefs (defined as "habitual affect-eliciting thought patterns leading to dysfunctional emotional and/or behavioral responses") show high trait anxiety, depression, and emotional eating patterns (Nolan and Jenkins 2019). Comorbid anxiety disorders in food addiction may add to the burden of the illness, with anxious individuals exhibiting more challenges and increased maladaptive mechanisms to cope with daily stressors.

Alternatively, efforts have been made to understand if there is any relationship between food addiction and cognitive dysfunction. The strength of cognitive inhibitory control exerted by the orbitofrontal, prefrontal, and parietal cortices appears to be weakened in food addiction (DiLeone et al. 2012). A meta-analysis found that adults with binge eating disorder or food addiction have difficulties with core executive functions, performing poorly when completing cognitive tasks related to cognitive flexibility, inhibitory control, attention, and planning (Iceta et al. 2021). When exploring the effects of food addiction on cognition, one study found that adolescents with food addiction exhibited a higher probability of making errors after an incorrect answer, a higher probability of false alarm, and a poorer target sensitivity. They also scored higher on self-reports assessing executive functioning difficulties, binge eating, depressive symptoms, and impulsivity levels compared to adolescents without food addiction (Rodrigue et al. 2020).

12.10 Mindful Eating Amid Fast Food Availability

Life in the twenty-first century is characterized by an unprecedented availability of ready-made foods as perhaps never seen before by our species. The discovery of refrigeration, which started thousands of years ago and has been progressively perfectioned, has helped our species to store and maintain edible organic foods for longer periods. Canning, mass production, and food preservatives are other important advancements toward storing and distributing nutrients (Guerrant et al. 1946; Jones and Jones 1937).

In the twentieth century, the world witnessed the beginning of a restaurant industry known as "fast food." Never had existed a restaurant that would produce warm, ready food with a preset menu before the consumer places their order. Developed nations and wealthy sectors of some developing countries also experienced the concept of "drive-in" restaurants, where one would consume fast food near or inside their car. A new relationship with food started to bud: one where our days and meals do not have to be significantly planned around the procurement and preparation of food with some time in advance. Eventually, many of these places went on to provide services 24 h a day.

Since the arrival of the "fast food revolution" in the United States, Europe, and most of the Western world, the mass production process has become significantly

more efficient (Kearney 2010). Developing countries have also seen an increase in fast food presence, and what some describe as an "obesity epidemic." There is growing concern that they are strongly correlated. The industry is regulated differently in each country, with some countries limiting advertisement and setting stricter nutritional standards in the name of population health.

As the Western civilizations have become more unequal, with the rising wealth gap between groups of people, those of lower socioeconomic status have become more drawn to consuming quick lower cost meals. These are typically heavily advertised in major media outlets, and recent studies showed significant associations of addictive phone use (Domoff et al. 2020) and both overall and commercial TV viewing (Domoff et al. 2021) with addictive eating in adolescents. These meals are mass-produced with low cost, lower quality ingredients (saturated fats, refined sugars, and overall low nutritional value), and increased risk of poor health outcomes, such as obesity, hypertension, coronary artery disease, diabetes mellitus, and metabolic syndrome (Fuhrman 2018). The fat, sweet, carbohydrate, and salt contents of many of these hyperpalatable foods produce a positive reward effect when consumed. As such, in many ways, fast, affordable, and hyperpalatable food has become a viable solution to food insecurity for many struggling families who cannot buy whole foods with high nutritional value or take the time to prepare them.

Eating is a physiological need for the human species, and this behavior can be understood as having biological, psychological, sociological, and cultural elements. Humankind has embraced different levels of ritualistic behaviors around meals. If seen on a spectrum, it could be poised as the simple act of feeding in response to hunger, a complex event that involves significant planning, preset rituals, and different layers of sophisticated sociocultural elements. However, for many, modern life has overall decreased the opportunity to experience communal meals (with a rich social and cultural aspect of eating) and decoupled eating with those aspects that are less about satisfying the hunger sensation and more about sharing resources to maintain family and community well-being.

In the last half a century, the concept of mindfulness has been more and more embraced by the Western world, initially by outliers incorporating Eastern philosophy (mainly from some forms of Buddhism) into their daily lives. Nowadays, mindfulness can be considered a more "mainstream" concept, used by an ever-growing number of mental health clinicians, life coaches, and other wellness or mental health paraprofessionals. Within mindfulness, there has been a modern push to practice "mindful eating," the act to redirect our attention to the present moment when our senses are being stimulated while engaged in food consumption (Nelson 2017). More broadly, some argue that mindful eating can be defined as being fully attentive to all that is related to the act of eating—as one buys, prepares, serves, and consumes food. This includes food-related experiences, cravings, and physical cues that may arise (Nelson 2017).

Mindfulness is a process-oriented, rather than an outcome-driven, behavior. When it comes to mindful eating, the purpose is not to lose weight. It is generally the case that, within a mindful approach, the person's choices often are to eat less, savor eating more, and select foods consistent with desirable health benefits. Studies

have shown that obese patients with binge eating disorder using eating-specific mindfulness-based meditation exercises experience a reduction of binging frequency and intensity, a reduction in depressive symptoms, and a subjective increase in sense of control (O'Reilly et al. 2014). Two recent narrative reviews provide a comprehensive summary of the evidence about the role of mindfulness, mindful eating, and intuitive eating in changing eating behaviors in general (Brewer et al. 2018; Warren et al. 2017). However, because food addiction is a relatively new concept and construct, the search for any studies directly exploring the effect of mindful eating on food addiction did not yield any results at the time of this publication. The following section provides a summary of the currently available treatment avenues for food addiction.

12.11 Evidence-Based Treatment Interventions for Food Addiction

To provide a comprehensive effective treatment plan for individuals struggling with food addiction, it is imperative to identify all comorbid medical conditions and understand the best available treatments for each of them. Collaboration among providers, such as primary care physicians, nutritionists, mental health providers, and counselors, who attempt to identify the best treatment options in their areas of expertise, may offer relief to individuals with food addiction. Unfortunately, there is a lack of clear clinical practice guideline recommendations to target food addiction. Moreover, there are no approved therapies for food addiction among obese individuals. Vella and Pai provide a narrative review of potential pharmacological and psychological treatment strategies for food addiction (Vella and Pai 2017).

A systematic review describing available treatments for food addiction found that the most effective interventions to reduce self-reported food addiction outcomes were a combination of psychotropic medications such as naltrexone and bupropion, bariatric surgery, and lifestyle modifications (Leary et al. 2021). Despite their effectiveness, it is important to properly evaluate and identify the individuals who most likely will benefit from each of these treatments. For example, bariatric surgeries may not apply to normal-weight individuals struggling with food addiction. Rather, these individuals may benefit from early, cost-effective, and practical lifestyle modifications by assessing and changing their diet patterns and physical activity level. The risks and benefits of medication use should be weighed in the medical decision-making while considering the proper indication for any prescribed medication. In the case of bupropion and naltrexone, this combination is FDA approved for weight loss and may target brain pathways involved in food addiction.

A systematic review found no significant evidence for psychosocial interventions in food addiction, such as psychoeducation and intuitive eating (Cassin et al. 2020). However, more specific psychotherapeutic interventions, such as cognitive-behavioral therapy (CBT), may play a role in the treatment of food addiction.

Particularly, telephone-based CBT appears to improve symptoms of food addiction in individuals with binge eating disorder and psychiatric symptoms (depression, anxiety, and emotional eating) after bariatric surgery (Cassin et al. 2020; Sockalingam et al. 2019). In addition, many individuals may choose to participate in self-help groups as a potential treatment option. Given the similarities between food addiction and SUDs, some individuals enroll in 12-step programs, which are free and available worldwide. Some examples of support networks, intended to provide access to peers and mentors who overcame food addiction, are Overeaters Anonymous (OA), GreySheeters Anonymous (GSA), Food Addicts Anonymous (FAA), and Food Addicts in Recovery Anonymous (FA). Further research is needed to investigate how self-help groups, individually or in combination with other psychological strategies (i.e., CBT or motivational interviewing), may target food addiction, ameliorate symptoms, and improve medical and mental health outcomes.

12.12 Conclusions

The past decade has witnessed a surge in research on the topic of food addiction. Food addiction shares a similar neurobiological and behavioral framework with drug use. However, the extent to which it is equivalent to SUDs and behavioral addictions remains an open question deserving further exploration.

It has become evident that the presence of food addiction has implications on physical and psychological health outcomes. To better understand the relationship between the core symptoms of food addiction and other health-related outcomes, studies should examine the development and course of food addiction in clinical and nonclinical populations.

Other relevant research avenues should include the influence of comorbid food addiction when addressing other conditions, such as eating disorders, obesity, and mental health disorders. Future research should focus on identifying specific evidence-based therapeutic interventions for food addiction while keeping in mind the need to create an expert multidisciplinary task force to develop concise clinical guidelines for the management of this condition. Notwithstanding that scientific input on this topic exponentially increased in the last years, our understanding of food addiction remains in its infancy and, therefore, further research efforts are needed in the years to come.

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Chapter 13
Nutrition and Anxiety Disorders

Ramli Musa

Contents

Abstract Food and anxiety are interrelated to each other in various relationships. Food may worsen the anxiety symptoms; hence, modification of food intake would certainly help in alleviating some of the anxiety symptoms at a certain degree. Certain foods, particularly organic in nature, are also effective in helping the patients to go through the treatment course and fasten the recovery process. It may not be the only key solution or main treatment, but modification in dietary intake would help the sufferers. In this chapter, we outline how anxiety and types of food are interrelated and different types of food could help or worsen the anxiety symptoms. Also, at the end of this chapter, we outline the effects of microbiome on human guts and anxiety symptoms.

Keywords Anxiety · Depression · Dietary · Panicogenic · Modification

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13.1 Introduction

13.1.1 What Are Anxiety Disorders?

Anxiety disorders are considered to be among common psychiatric disorders in our society that cause significant impact on an individual bearing the disease as well as causing burden on the country as a whole. The prevalence is ranging from 10 to 25%, and this is almost as common as depression. If we list down the common psychiatric disorders in our populations, anxiety and depression are the leading morbidity burden to the health system (Faravelli et al. 1989; Wittchen and Hoyer 2001).

It is reported by the National Health and Morbidity Survey (NHMS) in 2015 that there has been a triple increase of the prevalence of mental health issues in Malaysia from 10.7% in 1996 to 29.2% in 2016. Among the examples, disorders which are categorized under anxiety disorders are panic disorder, post-traumatic stress disorder (PTSD), generalized anxiety disorder (GAD), social phobia, and agoraphobia. It is mentioned that since mental disorders such as depression, dysthymia, and anxiety account for a big proportion of the world's disease problem, they place a large burden on the healthcare system. The global burden of mental disorders was updated by the WHO World Mental Health that poor mental health is very prevalent across the world, with depression and anxiety being the leading common psychiatric disorders (National Health and Morbidity Survey 2019).

Symptoms of anxiety disorders can be divided into emotional symptoms (feeling anxious, worries, fear) and also somatic symptoms such as palpitation, tremor, gastric problem, urinary frequency, loss of appetite, chest tightness, and shortness of breath. Bear in mind that most of the depression cases are also presented with symptoms of anxiety, and these two disorders (anxiety and depression) are closely related. In general, anxiety and depression share many common issues such as similar psychodynamic etiology (lack of serotonin and noradrenaline in the brain) and commonly coexist together. They also share similar treatment modality, that is, antidepressants. Antidepressants are indicated as first-line treatment for both disorders (Clemente-Suárez 2020).

Since anxiety and depression may affect appetite and cause weight loss, these illnesses would have some effects on patient dietary intake, and types of food could influence the symptoms.

13.1.2 How Does Anxiety Could Be Related to Nutrition?

Let us try to figure out the first question. The first question is this: Is there any correlation between food intake and anxiety? It is very clear that the answer is YES. They are interrelated based on various ways.

Firstly, anxiety disorders are commonly presented with gastrointestinal track (GIT) symptoms. Among the common GIT symptoms presented by anxiety are gastric pain, gastroesophageal reflux disease (GERD), and diarrhea. To my observation and as commonly reported, GERD is one of the common symptoms reported by patients with anxiety, and many of my anxiety patients meet gastroenterologists (medical specialists in stomach and gastric problem) but to no improvement although they were given medication. It is not uncommon also for many of them to go through some investigation procedures such as oesophagogastroduodenoscopy (OGDS) to investigate the possibility of having gastritis or ulcer. It does not stop there; they are also prescribed many expensive medicines, particularly the H1 antagonist drugs for gastric pain or complete antibiotic course for *Helicobacter pylori* bacteria. However, the symptoms will not resolve or will just partially resolve (Ünal et al. 2013).

Patients with anxiety disorders are commonly considered as potential for "doctor shopping." The illness itself may exhibit with multiple body or somatic complaints. Among the common physical symptoms are numbness, instability (ataxia), tinnitus, urinary frequency, diarrhea, and body weakness. Based on my observation, I have many patients presented to me who met various specialists before coming to see a psychiatrist. Among other specialists that they had met are cardiologist (for symptoms of palpitation, chest tightness), gastroenterologist (for gastric pain), ENT specialist (for tinnitus and instability), and urologist (for urinary frequency) (Clemente-Suárez 2020).

Second way of correlation is that some of the food may worsen the anxiety; among them are caffeine and spicy food. Food that contains high level of caffeine is considered panicogenic in nature or a panic stimulant (Buhiji et al. 2020).

Growing evidence suggests that there is a link between food and mental health. Recently, the relationship between food intake and mental well-being has been gaining considerable interest. Reports by El-Merabbi et al. from the study done on animals suggest that the food the people consume interacts not only with the enteric nervous system but also with the central nervous system via neural, neuroendocrine, neuroimmune, and humoral links (Sarris et al. 2016; El-Merahbi et al. 2015).

The etiology of anxiety is very complex, be it from the biological, psychological, and social factors involved in inducing the mental illness. Study done by Hjorth et al. (2021) using PET scan proved that serotonin and dopamine play a role in the development of anxiety and its severity. It is proven by the Global Burden of Disease Study, 2010, that 18.9% of all years lived with disability are attributed with mental disorders. It is mentioned that since mental disorders such as depression, dysthymia, and anxiety account for a big proportion of the world's disease problem, they place a large burden on the healthcare system. The global burden of mental disorders was updated by the WHO World Mental Health that poor mental health is very prevalent across the world, with depression and anxiety being the leading common psychiatric disorders (Addolorato et al. 1996).

Anxiety is mainly stimulated by sympathetic nervous system; hence, any food or drug (such as amphetamine) that may stimulate this system, could worsen the anxiety. One of the anxiety symptoms is the feeling of food caught in your throat.

Other anxiety symptoms are gastroesophageal reflux disease (GERD), regurgitation of food from stomach and from esophagus. Anxiety is strongly correlated with digestive system, heartburn, coughing, chest pain, problem swallowing, vomiting, sore throat, and hoarseness of voice (Butwicka et al. 2017).

Some foods can be a protective factor for not just anxiety, but also depression. In a study on the association of food groups with depression and anxiety disorders, Deborah Gibson-Smith found that lower depression and anxiety severity was associated with greater consumption of non-refined grains, fruits, and vegetables. Other types of food which have shown to be negatively associated with anxiety are fish and low-fat dairy. The mechanism is that these foods cause elevations of polyunsaturated fat/saturated fat ratios and have low trans fat.

13.1.3 Food and Brain Functions

It is well known that mood can affect the food choice of a person, using food as a comfort factor during stressful events, but there is also a mechanism that food triggers anxiety. Bad habits, such as poor nutrition, become one of the factors that create a biological basis for different pathologies and psychopathologies. People with nonoptimal nutrition profiles have been implicated with various underlying pathologies of behavioral health disorders due to insufficient nutrients essential in the neuroendocrine system. According to Sarris et al., nutrients which include tryptophan, vitamin B6, vitamin B12, folic acid, phenylalanine, tyrosine, histidine, choline, and glutamic acid are important for the development of neurotransmitters such as serotonin, dopamine, and norepinephrine, which are involved in mood, appetite, cognition, behavior (El-Merahbi et al. 2015), learning (El-Merahbi et al. 2015), and glucose homeostasis (El-Merahbi et al. 2015).

Lee and Choi (2017) also explained how the hypothalamic-pituitary-adrenal axis (HPA) controls the secretion of cortisol and causes changes to the neurological system. It plays an important role in regulating human's emotion and memory since the hippocampus that regulates these functions in the human brain is connected anatomically with the HPA axis.

Hassan et al. (2014) added that anxiety bio-mechanism is being linked to inflammation and oxidative stress. It has been consistently found to modulate the anxiety-related brain region such as in the anterior cingulate cortex, amygdala, and insula, which may have resulted from cytokine effects on the monoamine and glutamate. When there is increased circulating inflammatory cytokines, there is increase in oxidative stress and there will be generation of reactive oxygen species (ROS) as well as reactive nitrogen species. This can be linked with panic disorders. Dietary intake is one of the sources of production of reactive oxygen species.

Hassan et al. (2014) also noted that antioxidant enzymes such as superoxide dismutase (SOD), catalase, and glutathione peroxidase, when in the body, reduce molecules or nonenzymatic antioxidants. It also creates a defense mechanism that avoids the negative effects of ROS. However, in excessive concentration of

antioxidants, the cell reaches the antioxidative capacity and eventually leads to oxidative stress to the cell, damaging the cellular components.

It is stated by Bakhtiyari et al. that food and diet factors may be effective to regulate mental health during a lifetime from the adjustment of the risk of the brain changes. However, the mental disorders itself can affect the mood of the person, and this influences the habits of food intake, appetite, and choices of food that eventually creates an imperfect cycle by influencing the amount of nutrients, so this results in the exacerbation of the psychiatric illness itself.

13.1.4 Can Diet Modification or Healthy Diet Improve the Anxiety?

To answer whether diet modifiation could improve the anxiety, the answer is definitely yes. I strongly believe in the slogan of "we are what we eat." Many studies in the past mainly explored the associations between the effects of nutritious food and depression as compared to anxiety. These are among the modifications that we could adopt to improve the anxiety symptoms:

1. Food content: it is very important for anxiety sufferers to make some adjustment to the types of their diet. The main principle is healthy diet. Among the approaches in this strategy are putting more fiber in your food and including more grains, vegetables, and fruits in the daily dietary plan.
2. Second approach is to make some modifications in the diet habit; the slogan of "eat less but frequent" can be quite helpful in reducing the stomach discomfort among anxiety patients.

The underlying cause of anxiety is diminishing of serotonin and melatonin neurotransmitters in the brain. Hence, any food that could increase serotonin or melatonin would have a positive effect on anxiety. Among foods that were cited to improve mild-to-moderate anxiety were banana, plum, tomato, and pineapple (Feldman and Lee 1985).

The diets that are associated with lower anxiety levels are those with healthy diet patterns, the Mediterranean diet, ketogenic diets, and gluten-free diets (GFD) in specific groups of people. Clemente-Suárez (2020) have proven that people with existing anxiety had improved their anxiety state and anxiety traits after 6 weeks of nutritional recommendation interventions with healthy diet patterns. However, it is stated by Boerema et al. (2016) that they expect relapse of the symptoms after 6 weeks of nutritional intervention, but no relapse of symptoms will be seen only after 8 months of completing the nutritional intervention. It is postulated that good nutrition provides the anti-inflammatory effect to the subject, giving reason why 8 months is needed to observe the effect and also adherence to the intervention.

Food that is considered to improve diet quality and mood resembles food mostly from the Mediterranean diet. These diets focus on lean meats, fish, green leafy

vegetables, legumes, and nuts. Such food groups are rich in B-group vitamins, proving the possibility that there is a relationship between vitamin B intake and benefit to the brain health and mood. Sarris et al. (2016) stated that vitamin B is a cofactor in synthesizing and regulating the dopamine and serotonin neurotransmitters that help in clinical depression and anxiety, which are targeted by antidepressant medication. According to Sarris et al. and Scholey (2017), this has increased the acknowledgement that nutritional deficiency or suboptimal nutritional level heightens the risk for someone to have mood disorders and other psychiatric problems.

According to Ludwig (2020), a ketogenic diet with low amounts of carbohydrate consumption is good for weight mass optimization among people with psychiatric disorders for their possible anxiolytic effects. The diet is described as being low-carb high-fat (LCHF). By doing this, fat comprises >70% and sugar 5–15% of the daily food intake and the rest of the calories are supported with protein. There is my type of LCHF diet such as Atkins diet, modified Atkins, low glycemic index treatment diet, and medium-chain triglyceride ketogenic diet. Forte et al. (2016) in their writing suggested that for people adapting to a diet that induces ketosis, there is inhibition of glycolysis in the brain that reduces the excitation of the neuron by potentiation of GABA transmission via the steroid pathway. Nuss (2015) from their study done on animal subjects stated that there is reduction of anxiety level with infusions of GABA or GABA-A receptor agonists into the amygdala and there are anxiogenic effects upon infusion with GABA antagonists.

Gluten-free diet is also a good medium for people with intestinal disease such as celiac disease and also inflammatory bowel disease in terms of relieving the anxiety level. Since 1996, it has been proven by Addolorato et al. (1996) that people with inflammatory bowel disease and celiac disease are in a higher anxiety state compared to those healthy individuals. Butwicka et al. (2017) also proved that pediatric patients with celiac disease have a 1.4-fold higher anxiety level compared to the normal children. The study also concluded that malabsorption can be linked with brain function. So, there are various studies done across the years worldwide involving participants with IBD and celiac disease in the effects of gluten-free diet (GFD) in their anxiety level. Saadati et al. found that GFD reduces the somatic symptoms such as abdominal pain and bloating in IBD patients, which in turn reduces the anxiety level in Iran participants. The detailed effect of GFD on physiological symptoms remains unclear, but Van Hees et al. (2013) stated that the patients on GFD are linked with better psychological outcomes but only if the participants keep up with the GFD for more than 5 years. This might be due to the restoration of the intestinal lining, which improves the health of the patient as a whole, and this process takes years. The study also assumed that people with continuously untreated malabsorption disturbances can induce depressive symptoms. However, Rostami et al. (2022) reported that GFD, regardless of the duration, does not improve the anxiety level. It postulated that the anxiety symptoms might occur due to the diagnosis of the chronic disease itself, so GFD would not improve the anxiety symptom.

13.2 Food Improving Anxiety

Nguyen et al. (2017), in their study which has excluded people currently treated for anxiety and patients currently taking antidepressants, reported a positive association between consumption of fruits and vegetables, which acts as a protective factor, and anxiety. Same result was reported by Saghafian et al. (2018), Wu et al. (2018), Hodge et al. (2013), and Rienks et al. (2013). Study by Kose et al. (2021) showed that adolescents aged above 45 years old with lower consumption of fruits and vegetables have higher anxiety levels. Lee and Wan Muda on Malaysian adults proved that the intake of fruits and vegetables does not reach the recommendations.

As per Messamor and McNamara, it is suggested by the American Psychiatric Association for mentally ill persons to take at least 1 g of EPA and DHA daily in line with the American Heart Association. Martínez-Cengotitabengoa and González-Pinto mentioned that since 20% of the brain is composed of DHA, DHA constructs the cellular structure of the brain. All the omega-3 formulations give anti-inflammatory mechanisms helping to maintain the brain cells' stability linking to the proper function of neurotransmitters such as serotonin and dopamine.

Hassan et al. (2014) mentioned in their writing that fresh apples and a diet rich in sucrose and honey improve antioxidant status and have anxiolytic effects. Certain antioxidants such as vitamin C, vitamin E, carotenoids, thiol antioxidants for example glutathione, thioredoxin, and lipoic acid, natural flavonoids, melatonin and other compounds are good for improving defense mechanism against ROS.

It is mentioned in the Epidemics by Hippocrates that clean keto version is mostly based on healthy macronutrients such as minimally processed food, for example fat sources such as egg yolk and polyunsaturated fatty acids such as olive, canola, and grapeseed oil, oily fish, and nuts. Fish, meat, cheese, and egg whites are recommended for protein sources. Carbohydrates are limited to mostly unprocessed food and low glycemic index from green vegetables, brown rice, and others.

People adapting to the LCHF diet need a professional dietician's guidance. The previously mentioned divalent ions linked to anxiety can also be supplied in the LCHF menu, such that zinc can be gained through zinc-rich foods such as oysters and other seafood, magnesium can be found mostly in green leafy vegetables, while selenium is found in seafood, poultry, fish, and eggs, which are all favorable choices in LCHF diets.

Young et al. found that there is a significant relationship between vitamin B supplementation and stress level but not with anxiety and depression, so it is suggested that vitamin B supplementation is not worth it for people with anxiety and depression. The same study also exposed that most of the studies done in the previous years used excessive vitamin B supplementation exceeding the recommended daily intakes between 2 and 300 times.

13.3 Dietary Patterns Causing Anxiety

The dietary patterns associated with higher anxiety level include unhealthy diet patterns, diet with recurrent fluctuation of glycemic level, and vegetarian diet. A 1-month study done by Robert et al. during the first lockdown due to COVID-19 in 2019 showed that people stayed at home and adapted with new eating behavior. Some people adapted unhealthy dietary patterns with less fruits and vegetables and more processed meat and snacking, and some people adapted healthy dietary patterns which are more pasta or rice and less snacking. Results showed that people with unhealthy diets are associated with higher anxiety levels compared to those with healthy dietary patterns.

According to Firth et al., repeated fluctuation of blood glucose can increase the risk of developing anxiety. These include high intake of sugar and refined carbohydrates, lower fiber intake, irregular meals, and no caloric restriction. High dietary glycemic load and the resultant compensatory mechanism to reduce the plasma glucose trigger the secretion of autonomic counter-regulatory hormones including cortisol, adrenaline, growth hormone, and glucagon. Towler et al. found that these hormones may cause changes in anxiety, irritability, and hunger. This statement is supported by Lee and Choi (2017); the pathologies occur due to hypothalamic-pituitary-adrenal axis (HPA), which controls the secretion of cortisol and causes changes to the neurological system. The hippocampus, having an anatomical link with the HPA axis, plays a vital function in controlling human's emotion and memory.

In this situation, people with existing diabetes mellitus are vulnerable to develop anxiety due to poor glycemic control. Study done by Hendrieckx et al. suggested that there is a bidirectional relationship between diabetes mellitus and anxiety. In this context, patients with anxiety symptoms have higher risk of developing type 2 diabetes mellitus, and patients with type 2 diabetes mellitus have increased risk to develop anxiety disorders. A study done on Chinese individuals by Kose et al (2021) had shown that high-anxiety individuals aged under 45 years had significantly higher mean consumption of added simple sugars. High suger level has been associated with anxiety. However on other hand low sugar also could be related to anxiety. According to Seaquist et al., repeated low blood sugar levels are also associated with anxiety. In conclusion, moderate and well control of sugar is the best approach in anxiety control.

Woo, Kwok, and Celermajer stated that a vegetarian diet is well known due to the principle to have only vegetables and fruits in their diets, but people with this kind of diet may have insufficient essential nutrients such as vitamin B12, which eventually induces anxiety disorders. Lakin et al. also postulated that vegetarian diets also lack chain omega-3 fatty acids (EPA and DHA) that are a protective factor against anxiety. They concluded that this occurs due to the difference in bioavailability of certain nutrients such as iron, which is higher in animal sources than in plants. Therefore, people adapting vegetarian diets have limited absorption of iron from their diets.

13.4 Food Causing Anxiety

People take energy drinks to enhance alertness, physical ability, and cognitive enhancement. According to Bodenmann et al., in energy drinks, caffeine is the main component that causes GABA inhibition, phosphodiesterase modulation, ryanodine receptor activation, and A2 adenosine receptor antagonist. Caffeine presents naturally with different concentrations in many foods such as coffee, tea, and cocoa. Jin et al. stated that energy drinks have more caffeine than coffee and Coca-Cola and can cause attention problems, headache, anxiety, insomnia, overexcitement, and hyperactivity to the extent of causing death when taken excessively or being drunk with alcohol. Willson stated that it had also been used legally and safely as a mild stimulant before. However, caffeine consumption exceeding more than 1–1.5 g/day can cause caffeinism or caffeine poisoning. When this occurs, people consuming caffeine will experience anxiety, agitation, insomnia, gastrointestinal disorder, tremors, and mental disorders.

Richards and Smith also added that caffeine consumption can cause anxiety and increase the risk of relapse in secondary school children. Observational study done by Jahrami et al. on university students in Bahrain shows that students with higher caffeine intake have more anxiety-related symptoms such as headache, panic, feeling trapped or caught, worrying too much about things, anxiety, and psychological distress. Study done by Jin et al. on Korean adolescents stated that groups with higher caffeine intake are associated with higher anxiety levels.

Preservatives, flavoring agents, sweeteners, and coloring agents are commonly used as food additives in food manufacturing. Iwasaki et al. mentioned that antioxidants were added to food to avoid the degradation of food and fading of food's color. These antioxidants accumulate the reactive oxygen species (ROS) and stop ROS-induced oxidative DNA damage. However, mineral and trace elements are also found in many food and diet supplements such as iron and copper. When this ion interacts with antioxidants, the process produces ROS and causes DNA degradation in vitro. Study done by Bakhtiyari et al. (2013) proved that the level of anxiety level was obvious in people taking more processed food even after adjusting for the total calorie intake.

13.4.1 Relationships Between Caffeine and Anxiety

Based on the available evidence, the effects of caffeine to mental health are contradicting. Caffeine is said to be a mental stimulant. For this reason, it is considered as mental energy, whereby it causes increase in the level of arousal and better concentration to the extent of elevating the mood (Ferre 2008; Fredholm et al. 1999).

However, at a higher dose of caffeine, it could make the anxiety even worse. At this level, individuals would exhibit symptoms of restlessness, nervousness, panic,

insomnia, and agitation. In general, caffeine sounds good for depression as it is stimulating but not for anxiety. Based on one systematic review on the effects of caffeine on panic disorder patients, about half of the patients would experience the panic attack after consumption of caffeine. This clearly shows that caffeine could trigger the panic attack among these vulnerable individuals (Buhiji et al. 2020). Caffeine can be found naturally in beans of coffee, some fruits, and leaves. The consumers should be aware that many energy drinks and soda contain caffeine as it was added by the drink manufacturers.

13.4.2 Other Types of Food Related to Anxiety

Many studies have proven that high fiber intake such as vegetables and fruits could lower the anxiety symptoms. A study done by Deborah Gibson showed that the magnitude of ability in reducing anxiety is 0.7, which is considered a modest effect (Khan and Khan 2016).

13.5 New Food Dimension

In the recent studies on a new dimension, probiotics have been shown to have positive effects on anxiety. The effects are more apparent to be seen among healthy adults with minor A allele of rs16944. This led the scientists to further this new area of "psychobiotics" (Gualtieri et al. 2020).

Tea contains antioxidants but also contains a small amount of caffeine, which is a stimulant.

13.6 Anxiety, Stress, and Inflammation

In the recent studies, depression and anxiety happen due to abnormal response toward stress and inflammation. The fact that there was an increase in the number of people with depression and anxiety may be in part due to current lifestyle including dietary intake and social demand, which could lead to abnormal stress response. Anxious patients have been studied to have increased levels of proinflammatory cytokines compared to healthy individuals (O'Donovan et al. 2010). This inflammatory state is particularly of our concern as it may ultimately cause neuroinflammation, possibly affecting mental health. Moreover, anxiety patients may be associated with stress-induced interleukin (IL)-6 activity, which results in alteration in gene expression in monocytes as can be seen in anxiety-like behavior in mice according to the study made by Niraula et al. (2019). Plus, this population also has reduced level of microbiome-derived short-chain fatty acid

(SCFA), which is essential to prevent proinflammatory state ((Fukuda et al. 2011; Singh et al. 2010). Reduced SCFAs will also result in compromised intestinal barrier, thereby promoting microbial endotoxins to enter circulation and initiating an inappropriate immune response (Singh et al. 2010; Kelly et al. 2015).

Besides, stress often acts as a precipitator, which indirectly increases proinflammatory cytokine by dysregulating immune function as well as altering intestinal barrier permeability. The former acts as a preparation for human body to fight pathogen and helps in wound healing, while the latter is essential to increase water and sodium availability in the circulation. However, the diffusion of water and sodium into the circulation would also be accompanied by endotoxin and cause endotoxemia. This peripheral inflammation can actually induce central inflammation or neuroinflammation through the migration of activated immune cell into the brain as a result of endotoxemia. In short, stress-induced endotoxemia and increase in proinflammatory cytokine may cause neuroinflammation in brain, eventually affecting mental health.

13.7 Microbiome and Mental Health

Many points suggest that microbiome does influence mental health. First, patients with generalized anxiety disorder (GAD) have shown to have a different microbiome composition compared to healthy population. They have reduced amount of five genera, which include Faecalibacterium, *Eubacterium rectale*, Lachnospira, Butyricicoccus, and Sutterella, as compared to normal population in which 70% of them come from the two most prominent phyla Firmicutes and Bacteroides, while Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia are present in reduced numbers (Jiang et al. 2018; Peirce and Alviña 2019). This change in composition of microbiome will lead to reduced short-chain fatty acid (SCFA) compounds and indirectly disrupt appropriate immune response because of impaired intestinal permeability, ultimately affecting normal brain function.

In view of recent studies that suggest that microbes play a significant role in stress response, intestinal barrier, and immune system, use of probiotics and prebiotic in an effort to improve microbiome has been done (de Vrese and Schrezenmeir 2008). Probiotics are live microorganisms to provide health benefit by altering gut microbiome, while prebiotics are dietary fiber ingested to feed and promote balanced gut microflora (de Vrese and Schrezenmeir 2008). Sudo et al. proved in their study that colonizing *Bifidobacterium infantis* strain in germ-free mice could reduce previously exaggerated response of HPA axis to normal level similar to what is seen in normal control. However, they concluded that more research still needs to be done to validate the result in humans (Sudo et al. 2004). Besides, Ait-Belgnaoui et al. stated that *Lactobacillus farciminis* administration could enhance intestinal barrier, thus preventing endotoxemia from occurring and causing neuroinflammation in the brain (Ait-Belgnaoui et al. 2014). Plus, those given *B. infantis* have more proper immune response compared to control by giving anti-inflammatory signals to

immune cells. To sum it up, prebiotic and probiotic may potentially be used to treat anxiety by improving the response to stress, intestinal barrier, and immune response.

To date, it has been recognized that physiological pathways involving inflammatory and stress responses likely play a significant role in the occurrence of anxiety and depression (Benatti et al. 2016; Bekhbat and Neigh 2018; Dantzer et al. 2011). Much research had found that microbiome does affect mental health through various mechanisms that alter the normal inflammatory and stress response, which ultimately causes increase in the level of proinflammatory cytokine compared to normal population. However, the evidence that stress-induced inflammatory response causes anxiety alone is still inconclusive as the analysis may be confounded with depression, which is a common comorbidity associated with anxiety, and due to the fact that HPA axis alteration occurs in temporary state (Peirce and Alviña 2019). Our culture and upbringing in this current era can lead to underdeveloped immune system later in life, eventually posing risk to mental health. One of them is wide consumption of fast food, which may contribute to poor microbiome health. Further research should be made on the role of probiotic, prebiotic, and other possible approaches that can improve microbiome health so that a more effective targeted treatment can be achieved.

13.8 Conclusion

There are close relationships between anxiety symptoms and food that we are taking. Some types of food may give good effects to anxiety, and in contrast some are detrimental. It depends on the ingredient of food. Anxiety patients are advisable to do some modifications in their diet, particularly to avoid food containing panicogenic ingredients such as caffeine.

However, those who exhibit severe symptoms of anxiety and depression which affect their daily function are advisable to seek a proper medical treatment, particularly treatment with antidepressants. With dietary modification alone, it is very unlikely that the person could easily be cured from the illness.

Nutritional psychiatry is the new emerging field focusing on diet intervention as adjunct to pharmacological therapy and psychotherapy in treating people with anxiety. This includes diet counseling, education, and food as intervention to anxiety disorders. The proposed mechanism of relationship between food and anxiety includes the development of neurotransmitters that are involved in emotion regulation such as serotonin and dopamine which are lower in people with anxiety. Other mechanisms are HPA axis regulation that produces cortisol which is the stress hormone, inflammation and oxidative stress that trigger anxiety, and also production of ROS.

Lifestyle changes need to be promoted to the community so that people can eat healthily together, avoiding the development of noncommunicable diseases that are now existing, becoming a big burden to Malaysian health care. The dietary pattern that should need to be promoted to reduce the exacerbation and induction of anxiety

includes healthy diet patterns, the Mediterranean diet, ketogenic diets, and gluten-free diets (GFD) in specific groups of people. They also need to avoid unhealthy diet patterns, diet with recurrent fluctuation of glycemic level, and vegetarian diet.

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Chapter 14
Nutrition and Substance-Use Disorder

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Abstract Substance-use disorder (SUD) has become a global cause of morbidity and mortality and has an impact on general mental health. Substance users are mostly considered at high risk of nutritional deficiency, but most of the treatment centers do not provide any nutritional guide. The nutritional status of individuals in SUD needs to be properly addressed as it is responsible to cause malnutrition and making recovery more difficult. Hormonal alteration in SUD is the cause of low appetite and change in eating patterns, which leads to malnutrition. Furthermore, alterations in the absorption, utilization, metabolism, storage, distribution, and excretion of nutrients are responsible for nutritional deficiency. Micronutrient deficiency is reported in many of SUDs. Amino acid deficiency compromises the synthesis of neurotransmitters, which further exacerbates drug-seeking behavior. Moreover, craving for substances is altered by nutritional requirements, and the deprivation of food has shown to reduce the threshold for activation of reward pathways, which impedes recovery from SUD. During recovery, addiction transfer is a challenge in which patients start to crave for sweet food, which is also a cause of undernutrition and obesity. Hence, biopsychology of appetite and SUD can help to understand the causes of malnutrition. Therefore, in the recovery programs, planned nutrition can aid faster recovery and reduce the chances of food addiction and SUD relapse. Furthermore, alteration in dopaminergic and other brain pathways can also be considered via dietary intervention. It will not only be helpful in controlling the SUD, but also be beneficial for patient's health.

Keywords Substance-use disorder · Nutrition · Malnutrition · Reward pathway · Hormones · Dietary intervention

14.1 Introduction

The disorder in which there is a use of a substance in a manner that can cause social, academic, and/or occupational impairment is called substance-use disorder (SUD). The major risk factor of SUD is the persistent use of psychoactive drugs. SUD usually leads to dependence on the drug, which can be defined as a collection of cognitive, physiological, and behavioral changes that occur after recurrent substance use. These changes usually entail a strong craving for the drug, facing difficulty in controlling the use of the substance, perseverance in using it despite negative effects, precedence given to drug usage over responsibilities and other activities, higher drug tolerance, and/or a physical withdrawal state. SUD has become a global cause of morbidity and mortality, which is also inducing social and financial burden. According to the World Drug Report published by the United Nations Office on Drugs and Crime, approximately 35 million people suffered from SUD globally in 2018 while 0.585 million died in 2017 due to drug use. The report also mentioned that the SUD sufferers require treatment services, but only 14% of them receive the treatment (UNODC 2018). The comorbidity of SUD with other mental disorders

usually occurs such as anxiety, post-traumatic stress disorder, depression, and personality disorder. Consequently, familial violence, intimate partner violence, suicide due to overdose, and other accidental fatalities are also linked to SUD. Therefore, SUD has a profound detrimental impact on general mental health, and it increases the likelihood of co-occurring mental health problems and makes recovery more difficult (Connery et al. 2020).

14.2 Types and Mechanisms of SUDs

There are different types of SUDs depending upon the type of substance misused by the patient. Stimulant-use disorder includes the misuse of cocaine, nicotine, and methamphetamine. Opioid-use disorder involves the misuse of morphine, heroin, fentanyl, and prescribed pain killers acting on opioid receptors. Abuse of beer, wine, and spirits is included in alcohol-use disorder. Misuse of benzodiazepines and gamma-hydroxybutyrate (GHB) is involved in sedative-use disorder. Cannabis-use disorder includes the abuse of cannabinoids. Moreover, some patients are diagnosed with polysubstance-use disorder due to misusing of more than one type of substances. All the aforementioned substances have a unique mechanism of action that leads to SUD and ultimately addiction (Fig. 14.1). Understanding of neurobiological pathway of SUD helps to understand pharmacotherapy and its possible association with other factors such as the nutritional status of the individual.

14.2.1 Stimulant-Use Disorder

Stimulants such as cocaine and amphetamine act by stimulating the reward pathway of brain involving dopamine (DA) neurons. The dopaminergic neurons are projected from the ventral tegmental area (VTA), and their axons are extended into the nucleus accumbens (NAc) and prefrontal cortex (Gupta and Kulhara 2007). Cocaine and amphetamine, respectively, activate the dopaminergic pathway by inhibiting the DA reuptake mechanism and stimulating the release of DA into the synapse. In both cases, DA levels are increased in the synapse, which is responsible for the activation of the reward pathway and results in euphoric effects (Volkow et al. 2009). The activation of brain reward pathway is a normal phenomenon associated with the motivation and incentive drive. Activation of this pathway makes the individual to take the stimulants repeatedly. Besides DA, other monoamine levels such as serotonin and norepinephrine are also increased by the use of cocaine and amphetamine. This increase also contributes to the rewarding behavior of stimulant use. The upregulation of glutamate is also involved in drug-seeking behavior and relapse of stimulant-use disorder (Ciccarone 2011).

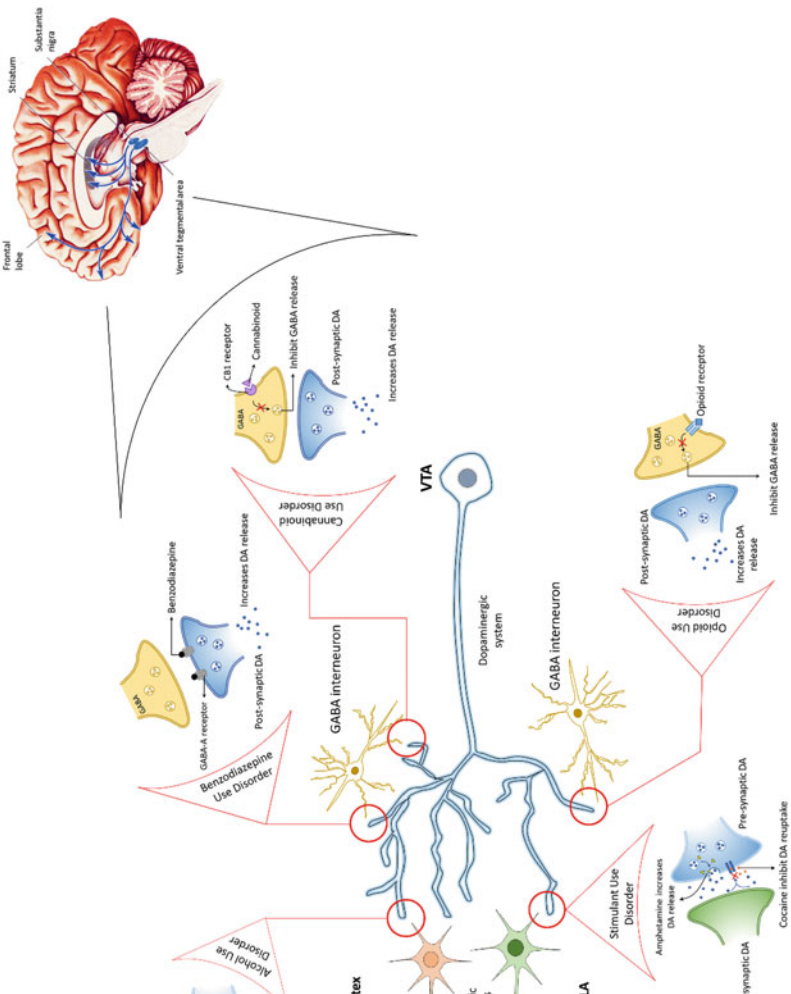

Fig. 14.1 Mechanism of different types of substance-use disorders. Refer to the text for details. *VTA* ventral tegmental area; *BLA* basal lateral amygdala; *NAc* nucleus accumbens

14.2.2 Opioid-Use Disorder

Opioids (e.g., morphine and heroin) use the same dopaminergic reward pathway, but these substances act through specific opioid receptors including m (mu) receptor, d receptor, k receptor, and recently discovered nociceptin opioid receptors (Toll et al. 2016; Cao et al. 2021). Endogenous opioids such as endorphins and enkephalins also induce reward activation through these receptors. m-receptors are particularly involved in mediating hedonic behavior of opioids. It is suggested that the presence of m-receptors on GABAergic interneurons in VTA releases the inhibition from dopaminergic neurons resulting in increased DA to mediate drug reward and leading to drug-seeking and repeated drug-taking behaviors (Gardner 2011; Darcq and Kieffer 2018). However, k receptors arbitrate the anti-hedonic effects to compensate the reward behavior of opioids by impeding the dopaminergic release in the NAc (Banks 2020). It is suggested that exposure to stress upregulates the functioning of k receptors and thus increases the dysphoric effect (Wee and Koob 2010). It has been linked with the long-term misuse of opioids and enhanced functioning of HPA axis leading to increased k receptor signaling, which ultimately induces obsessive use of drug and SUD relapse. Here, k receptor antagonists are recommended to reduce negative reinforcement and ameliorate withdrawal as well as relapse of opioid-use disorder (Banks 2020). The nociceptin opioid receptors also regulate the opioid system by producing anti-opioid action (Caputi et al. 2019). These receptors have been reported to inhibit conditioned place preference mediated by morphine (Ciccocioppo et al. 2000). In addition, some non-opioid receptors are also involved in opioid-use disorder especially dopaminergic and glutamatergic systems present in mesocorticolimbic reward pathway (Thompson et al. 2021). The acute and/or chronic use of opioids has a tremendous ability to alter DA and glutamate release in NAc leading to substance use and addiction. Therefore, it is recommended that targeting these non-opioid receptors may provide a better strategy to treat opioid-use disorder (Cao et al. 2021).

14.2.3 Alcohol-Use Disorder

Alcohol-use disorder is the most prevalent SUD, particularly in high-income and upper-middle-income countries, which is associated with comorbidities and high mortality rates because of serious medical consequences like liver cirrhosis and hepatic failure (Rehm and Shield 2019). Use of alcohol is also associated with the increased release of DA in reward pathway (You et al. 2018). The increased DA in NAc and prefrontal cortex is responsible for the reinforce alcohol drinking behavior (Deehan Jr et al. 2013). Alcohol does not particularly bind with the DA receptor; however, the action on DA release is mediated by interacting with other neuromodulatory systems such as glutamate, GABA, 5-HT, endorphins, and enkephalins (Sirohi et al. 2012). Acute and chronic alcohol use has different

physiological actions. Inhibition of N-methyl D-aspartate (NMDA)-type glutamate receptors and activation of GABA receptors occur following acute administration of alcohol resulting in inhibitory influence on neurons (Davies 2003; Nagy 2008). However, chronic use of alcohol causes neuronal excitability due to the upregulation of NMDA receptors. This upregulation alters the glutamatergic signaling pathways, which may lead to the conditioning of alcohol drinking behavior (Hade et al. 2021). The imbalance between GABA and glutamate develops a hyper-excitable state, which contributes to alcohol withdrawal symptoms (Banerjee 2014). This imbalance is also responsible for the induction of anxiety and aversive response in the individuals, which leads to repetitive and compulsive alcohol intake to reduce the anxiogenic withdrawal effects and thus develops alcohol dependence (Agostini et al. 2020). In an attempt to reduce the alcohol-use disorder, it is suggested to apply pharmacological strategies that can correct the GABA-glutamate imbalance.

14.2.4 Sedative-Use Disorder

Sedatives such as benzodiazepines are highly prescribed medicines for the treatment of anxiety, muscle relaxation, insomnia, CNS-mediated spasms, and epilepsy. Benzodiazepines have binding site on GABA-A receptor and act as GABAergic agonists (Elgarf et al. 2018). The inhibitory action of GABA is potentiated following the binding of benzodiazepines, which results in the reduction of excitable state and thus produces brain-calming effects (Gravielle 2016). The sedative-use disorder is also associated with the activation of dopaminergic pathways of VTA. The allosteric binding site of benzodiazepines exists between α and γ subunits of GABA-A receptor (Hanson and Czajkowski 2008). There are different subtypes of α subunits including α1, α2, α3, and α5, which are responsible for the action of benzodiazepines (Rudolph and Knoflach 2011). The α1 subunit is present on around 50% of GABA-A receptors and mediates sedative action, whereas α2 and α3 subunits, constituent of 10–20% GABA-A receptors, exert anxiolytic action of benzodiazepines (D'Hulst et al. 2009). The GABA receptors with α1 subunits, particularly which are present on interneurons in VTA, are thought to produce benzodiazepine-mediated dependence. Normally, these receptors control the activity of GABA interneurons, which make synapse with dopaminergic neurons in NAc (Hood et al. 2014). In benzodiazepine dependence, there is a disinhibitory effect of GABA interneurons on dopaminergic neurons due to the binding of the drug with GABA-α1 receptors, which results in a DA surge in NAc (Haider et al. 2019). The dependence produced by benzodiazepines is similar to that produced by opiates and cannabinoids (Stewart and Fong 2021).

14.2.5 Cannabis-Use Disorder

Cannabis-use disorder is the second most prevalent SUD after alcohol (Carliner et al. 2017). Cannabis has binding affinity with cannabinoid receptors CB1 and CB2, which have specificity for endocannabinoids such as anandamide and 2-arachidonoylglycerol. CB1 receptors are most abundantly present in the CNS, whereas CB2 receptors are present in the periphery (Ligresti et al. 2005). Centrally, CB1 receptors are present in cortex, hippocampus, striatum, hypothalamus, substantia nigra pars reticulata, thalamus, and cerebellum (Galaj and Xi 2019). The functional involvement of these receptors in cognition, memory, emotions, hunger, and reward is accounted for by these distinct distributions (Freund et al. 2003; Mátyás et al. 2006; Han et al. 2017). In VTA and striatum, their high expression is found on glutamatergic or GABAergic neurons, which are particularly involved in the induction of drug reward and relapse (Han et al. 2017). Cannabis binds with the presynaptic CB1 receptors, which are Gi/o protein-coupled receptors. Their activation leads to inhibition of the release of neurotransmitter, such as inhibition of release of GABA at the inhibitory synapse as well as inhibition of glutamate at the excitatory synapse (Freund et al. 2003). The former action is responsible for the development of dependence due to disinhibition of GABA on DA neurons, which leads to the increased surge of DA in NAc, whereas the latter action is accounted for the aversive response of cannabis (Galaj and Xi 2019).

14.3 Nutrition and SUD

The development of any kind of SUD and its relation with the nutritional status of an individual are strongly correlated. It has been suggested that monitoring the nutritional status of the affected person can help in the treatment and management of SUD. In the following sections, we are discussing the relationship between the nutritional status and SUD, importance of nutritional components in SUD, and finally some nutritional supplements that have been suggested for the treatment and management of SUD.

14.3.1 Malnutrition and Substance-Use Disorders

Nutrition is a critical component in the maintenance of healthy life (Jeynes and Gibson 2017). A healthy diet and nutrition influence the body at the gut level, regulating metabolic functions, reducing inflammation, and stimulating brain growth (Mörkl et al. 2018). The nutritional status of individuals with a substance-abuse disorder needs to be properly addressed. Studies report that SUD is responsible to cause malnutrition, compromises the health condition, and may lead to serious health

complications (Jeynes and Gibson 2017; Kaiser et al. 2008). Approximately, 3.3 million people die due to alcohol consumption, and 15.3 million people have poisonous effects of drugs every year worldwide (World Health Organization 2017). Malnutrition is a condition that arises from the inappropriate intake of nutrients, such as protein, iron, and vitamins (Kaiser et al. 2008). The observed symptoms of malnutrition are muscle weakness, fatigue, low mood, illness, or a high rate of infection (BAPEN 2016).

14.3.2 Etiology of Malnutrition in SUD

Primary malnutrition is commonly observed in SUDs due to an increased intake of abused substances, a low appetite, and alteration in eating patterns (Ross et al. 2012). SUDs have been shown to reduce taste for food besides appetite (Neale et al. 2012) and reduce the body's physical ability to access nutrients (Egerer et al. 2005; Jeynes and Gibson 2017). It was also observed that poor micronutrient status increased the likelihood of SUDs (Schroeder and Higgins 2017). Moreover, secondary malnutrition may also occur with SUD when these people experience an alteration in the absorption, utilization, metabolism, storage, distribution, and excretion of nutrients (Wiss and Waterhous 2014; Kaiser et al. 2008).

Alcohol severely affects gastrointestinal tract activity and inhibits the absorption of various nutrients directly or indirectly. Damage to the mucosal membrane in the mouth, esophagus, and stomach; increased intestinal permeability; delayed gastric emptying; bacterial overgrowth; and cancer are the possible dysfunctions that have been linked to the long-term intake of alcohol (Egerer et al. 2005). High consumption of alcohol may increase the secretion of gastric acid resulting in hyperchlorhydria and atrophic gastritis that impairs the absorption of micronutrients including vitamin B12 and thiamine (Kaiser et al. 2008). Alcohol also increases the excretion of minerals such as zinc, which induces a deficiency of that nutrient (Jeynes and Gibson 2017). Moreover, alcohol also blocks thiamine uptake by decreasing the transcription of two transporters that play a role in thiamine absorption in the brush border cells (Kiela 2010). In addition, the use of alcohol reduces thiamine pyrophosphokinase synthesis, an enzyme involved in the conversion of thiamine into thiamine pyrophosphate (TPP). TPP is an important coenzyme for various metabolic activities (Kiela 2010).

On the other hand, drugs of abuse unlike alcohol do not particularly affect the gastrointestinal structures; however, people with SUD do have difficulties in digestion and absorption processes (Neale et al. 2012). Eating disorders are also prevalent in individuals with SUD (Wilson 2010) Jeynes and Gibson 2017). Opioids decrease gastrointestinal tract motility (White 2010). On the other hand, heroin works as an appetite suppressant and impairs gastrin release, which delays gastric emptying (White 2010). Cocaine also reduces appetite (Wiss and Waterhous 2014). Drugs of abuse slow down gastric motility (Mysels and Sullivan 2010), alter the

metabolism, and also affect hepatic storage (Tang et al. 2010), resulting in nutritional deficiencies' prevalence in SUD.

14.3.3 Nutritional Deficiencies and SUD

Deficiency of a number of micronutrients was reported in cases of alcohol-use disorder including thiamine, pyridoxine, folic acid (de la Monte and Kril 2014; Ströhle et al. 2012), riboflavin, niacin (Chopra and Tiwari 2012), vitamin B5 (Nabipour et al. 2014), vitamin A (Ross et al. 2012), vitamin D (Quintero-Platt et al. 2015; Wilkens Knudsen et al. 2014), vitamin E (Chopra and Tiwari 2012), vitamin C, vitamin K, selenium, magnesium (Jeynes and Gibson 2017; Dingwall et al. 2015; Wilkens Knudsen et al. 2014), and zinc (de la Monte and Kril 2014; Ströhle et al. 2012; Wilkens Knudsen et al. 2014). In nonalcoholic drug users, deficiency of thiamine, riboflavin, niacin, vitamin C, vitamin D, magnesium, calcium, copper, and iron (Hossain et al. 2007; Saeland et al. 2011) has been reported. Depleted levels of riboflavin, folate, thiamine, vitamin B6, vitamin E, and protein have been reported in particularly heroin-dependent individuals (Jeynes and Gibson 2017). However, copper and zinc levels were found to be higher in a few studies that could be linked to stress, infection, and inflammatory reaction in the body (Hossain et al. 2007; Saeland et al. 2011). Studies on opioid addicts reported low levels of vitamins A and E, folic acid, potassium, and selenium (Estevez et al. 2004; Hossain et al. 2007).

14.3.4 The Psychology Behind Malnutrition and Appetite Alteration in SUD

The biopsychological mechanisms behind substance abuse and eating patterns share the same reward mediating brain circuitry. Scientists highlighted that the substances of abuse strip the essential fats from the brain as well as alter the absorption and metabolism of amino acids that compromise the synthesis of important neurotransmitters. Low levels of brain DA due to reduced levels of amino acids exacerbate substance-seeking behavior (Wiss and Waterhous 2014). Preference of drug over food is the main cause of poor nutrition in SUD such as opioid-use disorder. Due to irregular sleep and dietary patterns, substance users usually neglect their basic necessities of life (Nabipour et al. 2014). Furthermore, subjects with SUD exhibit decreased appetite and have no taste for food and hence prefer cheap, convenient, and palatable food (sweet and fatty food). These can be the possible reasons for altered body composition and nutritional deficiency in SUD (Neale et al. 2012). It has been reported that opioid users have drastically reduced food intake because of a different taste for food due to changes in gastrointestinal function (Ruiz 2021). So,

here it can be said that SUD is the cause of malnutrition, and this malnutrition further increases the craving for the drugs, which leads to severe adverse effects in the SUD patients.

SUD and eating disorders share a common neurobiological pathway, which includes serotonin, DA, GABA, and endogenous opiates (Gregorowski et al. 2013). DA is associated with rewarding pathway. Sweet- and fat-containing foods increase DA levels, which is attributed to the increase in addiction potential. Consumption of carbohydrate-rich food is associated with low levels of tryptophan, which reduce serotonin level in the brain. It was described that low level of serotonin reduces inhibitory control on eating and drug-seeking behavior. Reduced level of serotonin is associated with greater intake of alcohol and craving, while increased serotonin availability reduces withdrawal symptoms of smoking (Schreiber et al. 2013). Furthermore, substance use and food consumption are controlled by glutamate, but increased eating behavior blocks glutamatergic receptors in the NAc, which results in loss of inhibitory control (Schreiber et al. 2013). In animal models, cocaine- and heroin-seeking behavior reduced via restoring glutamate neurotransmission to normal levels (Schreiber et al. 2013). It has been described that childhood trauma increased the chances of eating disorder and SUD as both share the same neurobiological, genetic, and addiction pathways. People suffering from bulimia nervosa start to drink more alcohol just to distract themselves from eating behavior to cope with their hunger. So, SUD control program should also carefully manage comorbid eating disorder especially in alcohol users. It will increase the efficacy of addiction treatment regimens. Future research on genetic basis is needed for better understanding of the eating disorder and SUD (Eskander et al. 2020).

14.3.5 Nutrition and Recovery of SUD

Substance users are mostly considered at high risk of nutritional deficiency, but most of the treatment centers do not provide any nutritional guide or support for these individuals (Coulbault et al. 2021; Richardson and Wiest 2015; Wiss et al. 2019). Drug-seeking behavior can be promoted by nutritional deficiencies, which impedes recovery from substance use. Literature shows a relationship between malnutrition, substance use, and appetite regulation. The role of nutrition in SUD can be understood by considering its association with the biopsychology of appetite and addiction. Nutritional deficiencies in alcoholic use disorders are associated with myopathy, mood disorders, and osteoporosis. Nutritional imbalance in SUD leads to altered body composition and hormonal disbalance. SUD patients often suffer from mental illness and metabolic disorders due to a lack of proper nutrition (Nabipour et al. 2014). Hence, balanced nutrition should be an important part of SUD recovery program to support healthy and faster recovery (Grant et al. 2004). Fundamental brain processes are activated by certain foods, especially by sweet food and also by substance use. When a person recovers from SUD, he/she gets confused (addiction transfer) between the craving of food and substance use (Jeynes and

Gibson 2017). Hence, biopsychology of appetite and SUD can help to understand the causes of malnutrition in SUD and is also useful for the intervention of nutritional therapy in the recovery of SUD. Addictive individuals mostly suffer from malnutrition, and when they experience craving, they are unable to distinguish between urge to use addictive drug or food. Therefore, people who stop substance use, such as alcohol use, are associated with food addiction and obesity (Brunault et al. 2015). Hence, more efficient treatment for alcohol-use disorder can be developed by finding the link between alcohol use and food addiction.

A basic survival behavior under the reward pathway is called craving (Carr 2007; Volkow et al. 2012), and this pathway is altered by nutritional requirement (Hetherington et al. 2013), but the threshold for activation of reward pathway is reduced via deprivation of food. Hence, sensitivity to substance use and food consumption is increased (Aitken et al. 2016; Carr 2007; Volkow et al. 2012). It was described that drug-seeking behavior is increased by nutritional deficiency (Gibson 2001). Animal studies have shown that nutrient depletion enhanced the seeking of novel reinforcing experiences, which is mediated via activation of dopaminergic pathway in the brain (Keller et al. 2014; Costa et al. 2014). The intake of alcohol was increased in these experimental animals, and they also showed a preference for alcohol-related flavors (Jeynes and Gibson 2017). Therefore, it can be concluded that for the recovery process, balanced dietary plan is a prerequisite to ensure the proper nutrition of the patient. Furthermore, it should also be considered that the patient is not going towards addiction transfer, which could also lead to obesity and impediment to the recovery process.

There are many types of treatments available for the recovery of SUD including detoxification and opioid substitution treatment (OST). It has been observed that during detoxification, dietary habits of the patient change. In the early phase of recovery, they consume very less food because of having gastrointestinal problems and nausea. Their preference is food having high sugar such as cakes, and they also have a craving for table sugar with a very little desire for fruits and vegetables (Mahboub et al. 2021). Offering nutritional knowledge in OST program reduces the craving for sugary foods and replaces it with healthier foods. Although these patients still experience craving, they adopt a healthy eating style (Nolan and Scagnelli 2007).

Physiology and psychology of eating behavior and SUD overlap each other, and both share the same brain circuitry, which mediates motivation and reward (Volkow et al. 2012). Emotions and stress are the influencers of both behaviors (Gibson 2012; Vögele et al. 2017; Martin et al. 2016). Drugs of abuse potentially activate pleasure and reward pathways in brain including dopaminergic, opioidergic, cannabinoid, serotoninergic, and noradrenergic (Richard et al. 2013; Higgins et al. 2013). Interestingly, these pathways are activated by food (Hill et al. 2014; Morganstern et al. 2011), particularly while having palatable food items and by the consumption of food in a hungry state (Goldstone et al. 2009). Primary reinforcement behind food consumption is energy, and brain requires a continuous supply of energy (Gearhardt et al. 2016; Peters et al. 2007; Hetherington et al. 2013). It has been described that stress and hunger contribute to the binging act of animals for sweet palatable food.

These animals show addiction-like behavior, which is mediated via DA and opioid neurotransmitters (Boggiano et al. 2005; Gibson 2012; Avena et al. 2011).

14.3.6 Role of Hormones in Appetite Regulation and SUD

It has been described that the expression of appetite and cravings both are controlled via some anorexigenic and orexigenic hormones. Overlap between eating behavior and SUD has already been described above. So, here it is expected that SUD can interact with appetite hormone and SUD can also be affected via hormonal actions (Gonçalves et al. 2016; Hillemacher 2011; Mysels and Sullivan 2010). Appetite hormones including ghrelin and leptin are involved in these interactions (Leggio et al. 2010).

14.3.6.1 Ghrelin

Gastric mucosal cells secrete ghrelin, which is a peptide hormone, and it has an association with the feeling of hunger preceding a meal. Blood level of ghrelin falls after having meal (Al Massadi et al. 2017). It increases the alcohol consumption, and ghrelin antagonism can reduce alcohol intake (Gomez et al. 2015), but conversely, intake of alcohol reduces the production of this hormone (Badaoui et al. 2008; Leggio et al. 2011). A plethora of researches have shown that in alcohol-use disorder, ghrelin levels are reduced (Badaoui et al. 2008; Addolorato et al. 2006; de Timary et al. 2012; Gomez et al. 2015; Leggio et al. 2011), except few which reported a weak correlation between alcohol consumption and ghrelin levels (Kraus et al. 2005; Badaoui et al. 2008). Moreover, it was also described that ghrelin levels increased in abstinence and have a positive association with alcohol craving (Addolorato et al. 2006; Leggio et al. 2012; Koopmann et al. 2012). Animal studies have shown that during abstinence ghrelin levels rebound after 30 days (Gomez et al. 2015). However, the effect of nutritional status in these researches was ambiguous, may be the decreased levels of ghrelin increase the risk of undernutrition or increased ghrelin can be a cause of relapse during abstinence. Ghrelin antagonism can be used to treat alcohol-use disorder (Addolorato et al. 2006; Egecioglu et al. 2011; Leggio et al. 2012; Koopmann et al. 2012) as well as SUD (Jerlhag et al. 2010). It can be concluded that the role of ghrelin in appetite, maintaining nutritional status, and craving in SUD and alcohol-use disorder remains conclusive. By improving this knowledge, we can better suggest a nutritional therapy to circumvent SUD. A recent study described strong evidence of involvement of ghrelin in alcohol-use disorder, but for other addictive drugs, it has not been extensively studied. However, future studies will warrant to develop a relationship between ghrelin and alcohol-use disorder. Maybe in future, the implication of ghrelin in SUD will go beyond the treatment but also facilitate to find some biomarkers (Shevchouk et al. 2021).

14.3.6.2 Leptin

Leptin is a hormone that suppresses hunger and reduces fat deposition in body. Individuals who take low-to-moderate levels of alcohol show increased levels of leptin (de Timary et al. 2012). High alcohol consumption reduces leptin levels because of increased lipolysis. In cocaine and heroin users, leptin levels are also reduced due to increased glucocorticoid levels (Billing and Ersche 2015; Housová et al. 2005). Central administration of leptin reduces food consumption, and drugs of abuse sensitivity also increases (Carr 2007). One other study has shown that increased levels of leptin reduce heroine relapse (Mysels and Sullivan 2010). It has been shown in rats that food deprivation stress increases relapse of heroine-seeking behavior via leptin-dependent pathway, but in foot-shock stress, relapsing was not a leptin-dependent mechanism (Shalev et al. 2001). It has been described that leptin modifies reward-based behavior via alteration in dopaminergic pathway (DiLeone 2009). All these discussions provide link among food consumption, drug seeking, and reward pathway via neuroendocrine pathway (Jeynes and Gibson 2017). So, here it is suggested that SUD can be treated via modulation of leptin levels, but careful dietary plan should be followed as increased levels of leptin also reduce appetite. So, there is a chance of undernutrition in SUD patients as these individuals are already suspected to malnutrition and it can also increase the chances of relapse.

14.3.7 Dietary Intervention to Regulate Mood Disorders in SUD

Patients with SUD mostly suffer from anxiety, depression, and mental illness, which is the cause of slower recovery or resistance to recovery (Tolliver and Anton 2015). Mood disorders can be regulated via nutritional intervention (Du et al. 2016). Nutritional deficiency in SUD contributes to mood disorders. Tyrosine, tryptophan, and phenylalanine are essential amino acids for synthesis of neurotransmitters including DA, serotonin, and noradrenaline, respectively (Jongkees et al. 2015; O'Hara et al. 2016; Ormstad et al. 2016). Mood disorders can be treated by amino acid supplementation (Markus and De Raedt 2011; Ormstad et al. 2016; Parker and Brotchie 2011). It has been described that depression is reduced by higher consumption of dietary tryptophan (Lieberman et al. 2016). Studies have shown that intake of tryptophan-rich foods has beneficial effects on mood (Gibson et al. 2014; Capello and Markus 2014; Mohajeri et al. 2015). It indicates the notion that sufficient levels of nutrient have a positive effect on mood along with cofactors such as zinc, chromium, and pyridoxine, which is necessary for serotonin production (Muss et al. 2016). It was described that micronutrient deficiency could be linked to depression including magnesium (Młyniec et al. 2014), zinc (Tyszka-Czochara et al. 2014), chromium (Młyniec et al. 2014), vitamin B12, folate (Almeida et al.

2015), and selenium (Pasco et al. 2012). Furthermore, anxiety can be linked to magnesium, zinc, and lithium deficiency (Młyniec et al. 2014). It has been described that magnesium deficiency leads to neuropathy in alcohol-use disorder. Therefore, magnesium can be used prophylactically to reduce alcohol withdrawal symptoms (Sachdeva et al. 2015). Low levels of polyunsaturated fatty acids in SUD individuals have a negative effect on mood, and chances of relapse increased via this scarcity (Barbadoro et al. 2013; Buydens-Branchey et al. 2009). It was thought that the improvement in nutritional status could aid the chances of early recovery and help in mental health stability. As it has been described that polyunsaturated fatty acids including omega-3 and -6 have a key contribution in the proper functioning of membranes in the biological system, any physical change in the membranes will lead to alteration in the neurotransmission (Borsonelo and Galduróz 2008). Furthermore, it was documented that neuroinflammation due to deficiency of polyunsaturated fatty acids is implicated in the pathophysiology of addiction and mental illness. Findings from literature suggest that supplementation of polyunsaturated fatty acids has a potential to reduce neuroinflammation and is helpful in the treatment of addiction and mental illness (Peng et al. 2021). So, there is a need of nutritional intervention for SUD patients to overcome the nutritional barriers in the treatment of SUD (Wiss et al. 2019; Wiss et al. 2021).

Use of probiotics in SUD is also linked to reduce depression and anxiety in patients (Smith et al. 2021). Furthermore, probiotics are useful to treat alcoholic liver disease (Hong et al. 2019). Detoxification programs in hospitals commonly use multivitamins in the treatment of SUD. During detoxification of alcohol, hypoglycemia and electrolyte imbalance are common withdrawal symptoms. Chronic alcohol intake is also associated with thiamine, magnesium, and niacin deficiency. Thiamine deficiency is associated with Wernicke's encephalopathy (WE). Confusion, ataxia, and ophthalmoplegia are common symptoms of WE, which is caused by neuronal loss in hippocampus, mammillary body, and thalamus. Patients suspected of WE should be given intravenous thiamine before glucose administration as thiamine deficiency could lead to glucose precipitation. Oral administration of glucose is suggested in patients without WE. Furthermore, patients with severe withdrawal symptoms and suspected of poor diet should be given intramuscular thiamine (Sachdeva et al. 2015). Fish oil has also been found effective against aggression and impulsive behavior (Bozzatello et al. 2016).

14.3.8 Dietary Intervention to Reduce SUD Relapse

Patients who are under treatment for the SUD often have higher desire of sweet foods, which leads to micronutrient deficiency (Schroeder and Higgins 2017). This affects mood and results in poor mental health and depression (Oddy et al. 2009; Alaimo et al. 2002). All these factors contribute to slower recovery and increase the chances of relapse (Jeynes and Gibson 2017; Tolliver and Anton 2015). Amino acid supplementation in heroin and opioid users who are undergoing detoxification

shows reduced cravings (Chen et al. 2004). Food supplements positively affect the psychological behavior that decreases the chances of relapse (Mahboub et al. 2021). Therefore, nutritional therapy has beneficial effects in SUD treatment, but for this purpose, further studies should be conducted to enhance the knowledge about this subject and increase the efficacy of micronutrients to treat the underlying disorder.

The role of ketogenic diet is also described in SUD treatment. Ketosis is a condition in which brain and plasma levels of ketone bodies are increased. Prolonged fasting, ketogenic diet, and ketogenic food supplements can induce ketosis in body (Mahajan et al. 2021). Diet comprising low carbohydrate content and higher fats is termed as a ketogenic diet (KD). It has been described that KD is used in many neurological disorders, and it has promising effects. Traditionally, KD formulations have been used to treat epilepsy. As SUDs induce neurobiological changes including reduced neurotransmission, neuroinflammation, and reduced metabolism, in this scenario, KD can be used as a therapy in SUD. It has been reported that rats fed on KD showed decreased cocaine-induced behaviors as compared to control. KD has an impact on behavioral responses, which are mediated by dopaminergic pathway (Martinez et al. 2019). Furthermore, evidence has shown that withdrawal symptoms of alcohol including rigidity and irritability were also decreased by KD (Dencker et al. 2018). Alcoholic relapse is very common due to withdrawal symptoms including restlessness, negative emotions, and seizures. Available treatments for these withdrawal symptoms such as benzodiazepines and anticonvulsants are helpful to minimize these symptoms but can cause dependence and have side effects. Hence, there is a need for intervention to reduce the withdrawal symptoms and chances of relapse (Mahajan et al. 2021). Dietary supplementation of (R)-3-hydroxybutyl (R)-3-hydroxybutyrate (ketone ester (KE)) can be used for inducing ketosis as it is safe and most effective rather than traditionally available methods (Clarke et al. 2012; Soto-Mota et al. 2019; Mujica-Parodi et al. 2020). It has been described that KEs induce increase in ketone bodies and circumvent alcohol-induced suppression of AMP-activated protein kinase (AMPK). Alcohol use reduces AMPK protein levels and also inhibits its activity via producing reactive oxygen species (You et al. 2004; Liangpunsakul et al. 2008). AMPK system is a mediator of lipolysis (Viollet et al. 2006); therefore, lipolysis is reduced in alcohol-use disorder. KE is found to be effective in alcohol-use disorder as it shifts energy metabolism towards beta-oxidation of fatty acids. KE has been suggested as an intervention to treat psychiatric illness and to mitigate the withdrawal symptoms of alcohol and reduce alcohol craving. In rodent model of alcoholism, KD reduced muscular rigidity during detoxification as compared to controls (Mahajan et al. 2021). Another potential mechanism of ketosis in alcohol-use disorder is that it shifts energy metabolism towards ketone bodies (KB). During carbohydrate fasting, KB crosses blood-brain barrier and provides energy via tricarboxylic acid cycle. Potential benefit of the using of KB by the brain is the elevation of levels of reduced nicotinamide adenine dinucleotide (NAD) (Marosi et al. 2016; Pawlosky et al. 2017), which increases mitochondrial functions and produces more energy for neuronal functions (Marosi et al. 2016; Mahajan et al. 2021). It was suggested that body weight should be considered while giving the KD intervention in alcohol-use disorder and proper

nutrition should be given to the patient to avoid nutritional deficiency (Dencker et al. 2018). It has been shown that KD-induced nutritional intervention reduced benzodiazepine use in patients during the first week of alcohol detoxification; furthermore, alcohol consumption is reduced in patients with a previous history of KD (Wiers et al. 2021). A hypothesis has shown that the interaction of KD with alcohol dehydrogenase or aldehyde dehydrogenase enzymes affects alcohol metabolism in the liver, but further research is needed to validate this hypothesis (Blanco-Gandía et al. 2021). It is not sure whether KD will have effects on alcohol consumption, tolerance, and metabolism, but inpatient trials have showed the reduction of withdrawal symptoms during detoxification by the use of KD (Wiers et al. 2021). In short, we can conclude that KD can be an intervention for the alcohol-use disorder and other SUDs. It can be used as an adjunct therapy, but further clinical research is needed to explain the criteria for the patients with a previous history of ketoacidosis. Furthermore, age and sex differences should also be considered while studying the effects of KD in SUD.

14.4 Concluding Remarks

It can be concluded from the above discussion that a bidirectional relationship occurs between SUD and nutrition status of an individual. There are evidences that malnutrition can lead to delay in the SUD treatment or may also lead to drug relapse. Therefore, malnutrition is an important factor to be considered while dealing with the SUD patients. During the treatment of SUD, nutritional supplementation would help to recover the malnutrition and hence provide fast recovery and may also reduce the chance of drug relapse. Moreover, identification of the type of nutrient deficiency may suggest specific type of nutritional supplementation. Nonetheless, future preclinical and clinical studies are required to identify more effective nutritional supplementations that would help in the treatment of SUD.

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Chapter 15
Nutrition and Psychiatric Disorders: Focus on Schizophrenia

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"Let your food be your medicine, and your medicine be your food"
Hippocrates

Contents

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Abstract Nutrition is vital for normal brain functions. Psychiatric disorders constitute a major percentage of disability worldwide and impose economic, social, and health burdens. Current treatments are focused on pharmacotherapy and psychotherapy. Nevertheless, such therapies prevent only about 50% of the disease's impact, revealing that new approaches are required to prohibit and cure psychiatric diseases. Appropriate dietary nutrition helps in the prevention and treatment of psychiatric disorders. This chapter aims to discuss the effects of dietary nutrients on oxidative stress, neuroinflammation, mitochondrial dysfunction, and kynurenine pathway, which are significant mechanisms relevant to nutrients' effects on brain health and disease. Furthermore, this chapter emphasizes the relevance of multiple possible pathways such as metabolic regulation, nutrigenomics, and gut-brain axis of nutrition to psychiatric diseases and therapeutic potential. Also, it provides insights into the effects of macronutrients such as AAs and fatty acids, and micronutrients, including vitamins and minerals, on psychiatric disorders like autism spectrum disorder, anxiety, attention deficit hyperactivity disorder, obsessive-compulsive disorder, depression, and bipolar depression. Particular attention will be given to the nexus between nutrients and schizophrenia. Taken together, dietary interventions may be repositioned as burgeoning, cost-effective therapeutic approaches in psychiatric disorders.

Keywords Nutrition · Vitamins · Gut-brain axis · Nutrigenomics · Autism · Depression · Schizophrenia · Attention deficit hyperactivity disorder · Obsessive-compulsive disorder

Abbreviations

AAs	AAs
ADHD	Attention deficit hyperactivity disorder
ASD	Autism spectrum disorder
BCL-2	B-cell lymphoma 2
BDNFs	Brain-derived neurotrophic factors
BPD	Bipolar depression
CNS	Central nervous system
DHA	Docosahexaenoic acid
FAs	Fatty acids
GABA	Gamma-aminobutyric acid
HPA axis	Hypothalamic-pituitary-adrenal axis
IL	Interleukin
KYN	Kynurenine
KynA	Kynurenic acid
MDD	Major depressive disorder
NGFs	Nerve growth factors
NMDA	N-methyl-D-aspartate
OCD	Obsessive-compulsive disorder
PUFAs	Polyunsaturated fatty acids
QA	Quinolinic acid
SCFAs	Short-chain fatty acids
SCZ	Schizophrenia
TLR	Toll-like receptor
TNF-α	Tumor necrosis factor-alpha

15.1 Introduction

Psychiatric diseases are reported to affect almost one billion people globally (Rehm and Shield 2019). According to the latest statistics, the global burden of psychiatric diseases accounts for at least 32% of disability-adjusted life years (Vigo et al. 2016). The global economic costs of psychiatric disorders are predicted to surpass 2.5 trillion USD, implying a large economic cost (Rehm and Shield 2019). The economic expenses of schizophrenia are huge, accounting for 2.5% of global healthcare expenditures (Baruth et al. 2021). Patients with schizophrenia spectrum disorders (SCZ) account for the vast majority of criminal hospitalized patients globally, as schizophrenia is linked with elevated statistics of violent crime (Fazel et al. 2009). Treatments available for psychiatric diseases have been gradually increasing the number of pharmacologic and non-pharmacologic interventions being accessible in the latest years (Cipriani et al. 2018). Despite the fact that recent thorough meta-analyses have shown that the majority of medications now used to treat the most

prevalent psychiatric disorders are effective, the majority of psychiatric drugs must be taken for years (or perhaps for life), resulting in serious undesirable side effects. Moreover, the cost of psychiatric prescription drugs has risen dramatically over the previous decade (Wang et al. 2018). Most psychiatric diseases share many pathogenic mechanisms like neuroinflammation, mitochondrial dysfunction, oxidative stress, gut dysbiosis, and disrupted kynurenine pathway (Czarny et al. 2018; Naveed et al. 2021; Więdłocha et al. 2021). For instance, the higher use of oxygen (almost 20% of oxygen) and the brain's inadequate antioxidant defense mechanisms receive more attention when it comes to oxidative stress. Neurons are particularly vulnerable to oxidative stress. Following neurological damage is begun by elevated glutamate levels, which can also result in Ca2+ buildup and subsequent increased reactive oxygen species (ROS) generation, leading to oxidative stress (Cobley et al. 2018). Functional alterations in microglia and astrocyte are underlying causes of psychiatric diseases through disruption of neuronal nutrient availability, neurogenesis, recycling of neurotransmitters, and immunoregulation (Greenhalgh et al. 2020). The role of diet in controlling the microbiota has received much interest in the field of psychiatric disorders. Recently, the microbiota has been considered as one of the main culprits in many psychiatric disorders. For instance, there is a change in the gut microbiota in patients with SCZ, major depressive disorder (MDD), attention deficit hyperactivity disorder (ADHD), and autism spectrum disorder (ASD) (Cussotto et al. 2021).

There is an urgent need for promising therapeutic choices that are safe, effective, and cost effective for patients (Botturi et al. 2020). Extensive epidemiologic studies have revealed the nexus between healthy diets and a decreased incidence of psychiatric diseases, making diet interventions a research area. It has been demonstrated that oral nutritional supplements enhance clinical outcomes in hospitalized patients, as well as being a cost-effective approach (Philipson et al. 2013). There has been an upsurge in the quantity of research done in the discipline of nutritional psychiatry (Sarris 2019), in which research has focused not only on the effects of dietary patterns on various psychiatric disorders but also on the potential role of micronutrient supplementation in these diseases (Firth et al. 2019). Modern life has increased chronic diseases because of alterations in lifestyle factors such as unhealthy dietary habits (Branca et al. 2019). Dietary aspects have been estimated to be implicated in 255 million disability-adjusted life years and 10.9 million deaths. Modern life is marked by nutritional transformation, which includes a global trend away from conventional dietary habits towards Westernized diets high in refined sugars, fast foods, saturated fatty acids, too much sodium, and a lack of intake of plant-derived foods, as well as an imbalance between calorie consumption and expenditure via regular exercise (Logan and Jacka 2014). Many studies consider the nexus between diet and psychiatric disorders. Because of all of these factors, there is an emerging interest in "nutritional psychiatry" that seeks to characterize and elucidate the correlation between dietary components and psychiatric diseases (Lakhan and Vieira 2008). For instance, a systematic review investigating the nexus between nutrition and common psychiatric diseases has demonstrated that a healthy diet is negatively associated with the probability of depression and anxiety (Opie et al. 2015). Similar

research exists in prenatal and postnatal stages when inadequate prenatal nutrition intake and early-life nutrition are related to childhood behavioral and emotional dysfunction (Steenweg-de Graaff et al. 2014).

Neuroinflammation, mitochondrial dysfunction, oxidative stress, and kynurenine pathway have all been implicated in research into the probable biological processes involved in the nutrition and psychiatric disorder association, with the gut microbiota serving as a major underpinning factor of previous pathogenic mechanisms (Marx et al. 2017). Considering these strategies has encouraged research into the adjunct consumption of dietary interventions that modify these pathways in psychiatric diseases, such as n-3 omega FAs in MDD (Sarris et al. 2016) and N-acetyl cysteine in SCZ (Berk et al. 2013).

Early nutritional status, such as appropriate nutrition or malnourishment, may influence our reaction to stressors later in life through epigenetic pathways. Accumulating data postulates that diet interacts with genes. There is a strong correlation between proper nutrition and mental health over a lifetime. Environmental variables like prenatal and postnatal malnutrition have been demonstrated to cause epigenetic alterations such as histone methylation, DNA modification, and gene expression modulation, especially sensitive periods of development (Bekdash 2021).

In healthy individuals, the diversity of gut microbiota is usually stable. Alterations in this composition have been implicated in various psychiatric disorders. Dietary factors have a significant impact on shaping the gut microbiome. For example, higher consumption of carbohydrates was positively correlated with reduced microbiota diversity; bifidobacteria increased, whereas Streptococcus, Lactobacillus, and Roseburia species decreased. Microbiota diversity, on the other hand, increased with the consumption of fruits, vegetables, and coffee. Recently, it has been revealed that the enteric and central nervous systems (CNS) are interrelated via a bidirectional network called the gut-brain axis, which is disrupted in psychiatric disorders (Hills et al. 2019). Gut microbiota affects brain functions through modulation of the HPA axis, alteration of neurotransmitter metabolism, and production of SCFAs, neuropeptide Y, folate, bile acids, and tryptophan metabolites (O'Mahony et al. 2015). SCFAs, released by gut microbiota, are anti-inflammatory components that inhibit a neuroinflammatory process in microglia. Moreover, gut neurotransmitters, including serotonin, have been revealed to have anti-inflammatory and proinflammatory effects, hence modulating inflammatory and immune responses (Sherwin et al. 2016).

Macronutrients such as AAs and fatty acids (FAs) affect psychiatric disorders. For instance, L-histidine is the major source of histamine. The disturbance of histamine is involved in many psychiatric disorders including eating disorders and MDD (Haas et al. 2008). Histamine H3 receptor antagonists were investigated in clinical studies of the treatment of MDD, SCZ, ADHD, and excessive daytime sleepiness (Schwartz 2011). A reduction in sympathetic activity and anxiety was reported in rats that consumed a diet rich in L-lysine, suggesting the anxiolytic effect of L-lysine. In a parallel clinical study, anxiolytic effect and reduction in emotional stress have been found after the addition of L-lysine and L-arginine in food (Severyanova et al. 2019). L-lysine also has an antidepressant effect due to a

reduction of noradrenaline in the hypothalamus and affinity of L-lysine in GABA-benzodiazepine receptor (Chang and Gao 1995). Tyrosine is beneficial in the treatment of MDD through increasing catecholamine levels (Gelenberg et al. 1990). Also, previous research shows the beneficial role of L-arginine in the pathophysiology of SCZ (Liu et al. 2016). Omega-3 FAs are vital for neuronal cell membranes; control multiple mechanisms in the brain, such as gene expression, neurogenesis, neurotransmission, and neuronal survival; and have anti-inflammatory and antioxidant properties. Omega-3 FAs have neuroprotective effects in ADHD, MDD, SCZ, and bipolar depression (BPD) (Goh et al. 2021).

Furthermore, micronutrients such as vitamins and minerals have various effects in many psychiatric disorders. Vitamin C has an anxiolytic effect. Stress-related diseases such as anxiety have been associated with vitamin C deficiency. Many studies have demonstrated that the administration of vitamin C improves mood and produces an antidepressant effect through modulation of glutamatergic neurotransmitters and monoaminergic system (Moritz et al. 2020). Recent research has displayed that vitamin A is negatively correlated with ASD, SCZ, and ADHD (Kaplan et al. 2007; Reay and Cairns 2019; Li et al. 2020a). Vitamin D has different functions in the inflammatory response, neurotransmission, neuroprotection, immunity modulation, antioxidant processes, and brain development and function. Vitamin D inadequacy has been linked to various psychiatric diseases, including ASD, major depressive disorder (MDD), SCZ, and obsessive-compulsive disorder (OCD) (Saad et al. 2016; Kuygun Karcl and Gül Celik 2020). Vitamin E has antidepressant, anti-inflammatory, and antioxidant effects on MDD (Manosso et al. 2020). Low vitamin B12 intake causes depression, poor memory, mania, fatigue, and psychosis, whereas vitamin B1 deficiency causes CNS symptoms, and vitamin B9 deficiency results in neurodevelopmental defects and is associated with depression (Calderón-Ospina and Nava-Mesa 2020). Disturbance of minerals like zinc, copper, calcium, magnesium, iron, and other minerals has been reported in different psychiatric disorders such as ASD, MDD, and SCZ (Yamamori et al. 2014; Hagmeyer et al. 2018; Skalny et al. 2020; Botturi et al. 2020).

Herein, we discuss the effects of macronutrients, including AAs and fatty acids, as well as micronutrients, including minerals and vitamins, on psychiatric disorders like ASD, ADHD, anxiety, OCD, MDD, and BPD. A focus is given on SCZ. Furthermore, this chapter explores the possible pathways behind nutrition's therapeutic effects, including neuroinflammation, oxidative stress, mitochondrial dysfunction, and kynurenine pathway. It is particularly proposed that dietary intervention reconfigures the metabolism, epigenetics, and gut-brain axis to have a positive effect on the brain's health.

15.2 Common Culprits of Psychiatric Diseases

15.2.1 Neuroinflammation

Neuroinflammation is defined as a fundamental host defense by microglial activation and presence of infiltrating leukocytes. Microglia are present in the CNS. Microglia are triggered to remove debris or infections through phagocytosis. However, when microglia remain activated persistently, they may induce neuroinflammation by producing cytokines such as tumor necrosis factor-alpha, interferon-gamma, interleukin (IL-6), IL-8, and free radicals (Mansour et al. 2021a). Neuroinflammation is common in psychiatric diseases like ASD, ADHD, MDD, BPD, and SCZ (Sandhu et al. 2017; Leffa et al. 2018). Also, the role of neuroinflammation in the pathogenesis of anxiety has been reported (Casseb et al. 2019).

There is strong proof that dietary nutrients such as flavonoids and omega-3 fatty acids reduce neuroinflammation and have neuroprotective effects in many psychiatric disorders. These neuroprotective effects are attributed to suppression of cytokines, microglial activation, and HPA axis, along with improvement in synaptic plasticity and brain-derived neurotrophic factors (Fourrier et al. 2019). Furthermore, omega-3 and omega-6 FAs disrupt neuroinflammation through competition with arachidonic acid, inhibiting production of cyclooxygenase and lipoxygenase (Shibata et al. 2017). In addition, quercetin, a flavonoid present in apples, onions, asparagus, shallots, nuts, tomatoes, grapes, and berries, inhibits cytokines such as TNF-α and IL-1 by glial cells and macrophages, as well as suppresses lipoxygenase and cyclooxygenase (Estrada and Contreras 2019). Vitamins play a role in suppressing neuroinflammation. For instance, vitamin D may inhibit differentiation of Th17 cells, increasing the production of TGF-β (Ooi et al. 2012).

Neuroinflammation has been reported in the CNS of ASD patients. In brain tissues from ASD patients, an increase in biomarkers of inflammation like cytokines, microglial cell activation, expression of immune-related genes, and others have also been noticed (Rossignol and Frye 2014). Many studies indicated that ASD patients reported microgliosis and astrogliosis in the cerebellum, anterior cingulate gyrus, brainstem, anterior cingulate, fusiform gyri, orbitofrontal cortex, corpus callosum, parietal lobes, and middle frontal gyrus relative to controls (Vargas et al. 2005; Suzuki et al. 2013). ADHD has been proved to be the result of an exacerbated CNS inflammation in a fetus linked with a maternal inflammatory response (Leffa et al. 2018). Infections that cause inflammatory responses in the first postpartum month have been related to a higher risk of ADHD by the age of 10 (Allred et al. 2017). ADHD has been linked to exaggerated immunoreactivity and increasing concentrations of cytokines like IL-6 and C-reactive protein (Chang et al. 2020b).

Neuroinflammation contributes to the pathogenesis of MDD. Activated microglia have been reported in the brain of postmortem patients of MDD (Tiemeier et al. 2003) During the depression, toll-like receptors (TLR) represent innate immune receptors, activating microglia-induced inflammation. They mediate inflammatory responses. TLR2/4-deficient mice did not display social defeat stress-induced

behavior, proving that immunity has a role in MDD and suggesting the importance of anti-inflammatory drugs in mitigating depression (Nie et al. 2018). Furthermore, the blood-brain barrier of patients with MDD is weaker, resulting in increased permeability of monocytes, neutrophils, and macrophages from the blood into the brain (Yarlagadda et al. 2009). Depressed patients also have elevated levels of IL-6 and C-reactive protein (Raison et al. 2006) along with a reduction of BDNF. In depression, inflammation may be induced, influencing numerous inflammatory pathways such as JNK, ERK, MAPK, and JAK/STAT (Malemud and Miller 2008).

There are various theories for the pathogenesis of SCZ linked to inflammation. "Inflammation and two-hit theory" for SCZ suggests genetic vulnerability and inflammatory stimulus during the prenatal period (Feigenson et al. 2014). Elevated microglial activation was found in postmortem analysis of brains from SCZ patients (van Berckel et al. 2008). IL-6, IL-2, IL-1β, IL-12, IL-18, IL-6, and interferon γ were found to be elevated in patients with SCZ (Cha and Yang 2020).

15.2.2 Oxidative Stress

The brain needs a large amount of oxygen for aerobic demands. Nevertheless, oxygen is implicated in psychiatric disorders because of the production of free radicals (Tardy et al. 2020). Oxidative stress is defined as an imbalance between the oxidation and antioxidant processes that results in an excess accumulation of oxidative molecules such as reactive nitrogen species like peroxynitrite, nitrogen oxide, and nitric oxide, and reactive oxygen species like hydroxyl radicals and hydrogen peroxide (Mansour et al. 2021a). The antioxidants include superoxide dismutase, glutathione peroxidase and catalase, vitamin E, vitamin C, glutathione, alpha-lipoic acid, melatonin, carotenoids, zinc, copper, and selenium (Sies et al. 2017). Oxidative stress has a significant physiological effect on health. Phagocytic cells, for example, destroy pathogenic organisms, engage in detoxification and enzymatic processes, and synthesize some physiologically useful compounds. Nevertheless, it can harm the body by causing cell membrane damage, denaturation of proteins, neuronal loss, and nucleic acid mutations (Mansour et al. 2021c).

The CNS is susceptible to oxidative stress because of its high energy demands, presence of unsaturated FAs in the cell membrane, excitotoxic nature of some neurotransmitters, iron production, low antioxidant mechanism, reactive oxygen species produced from activated microglia, as well as non-neuroreplicating nature of neurons (Mansour et al. 2021b). Many pieces of research have proved the implication of oxidative stress in patients with ASD (Rossignol and Frye 2014). A meta-analysis showed that ASD has been linked to genetic changes in glutathione-related pathways and reduction in the levels of glutathione, cysteine, methionine, and glutathione peroxidase relative to controls (Frustaci et al. 2012). Many studies have established evidence of oxidative stress markers along with reductions of superoxide dismutase levels in the postmortem brains of patients with ASD (Tang et al. 2013). Depression and SCZ are correlated to defective antioxidant mechanisms

and elevated levels of superoxide dismutase malondialdehyde and lowered levels of vitamin E and vitamin C (Maes et al. 2000; Uddin et al. 2021). The deficiency of magnesium leads to oxidative stress (Mazur et al. 2007). Furthermore, magnesium suppresses the antioxidant defense mechanism because magnesium is essential for the production of gamma-glutamyl transpeptidase, which is vital for glutathione synthesis (Tohidi et al. 2011). Magnesium levels are inversely proportional to levels of some oxidative stress markers such as malondialdehyde and superoxide anion (Barbagallo et al. 2021).

15.2.3 Mitochondrial Dysfunction

Mitochondria are essential for cellular energy metabolism, as well as AA, FA, and steroid metabolism, apoptosis regulation, and cellular calcium modulation. As a result, mitochondrial malfunction impacts their potential to not only provide energy, but also perform other vital cellular functions, including neural plasticity, neurotransmission, and cellular resilience. Mitochondria have a role in apoptotic pathways. Also, mitochondria are the main source of reactive oxygen species. Hence, it is not surprising that mitochondrial dysfunction has been implicated in normal aging and neuropsychiatric diseases like depression, BPD, and SCZ (Manji et al. 2012). The brains from postmortem BPD patients revealed mitochondrial dysfunction and mutation relative to controls (Manji et al. 2012). The B-cell lymphoma 2 (BCL2) family includes pro- and anti-apoptotic proteins that are important effectors of mitochondrial functions. Administration of lithium and valproate in mood disorders upregulated BCL2 in the striatum, hippocampus, and cortex, exerting anti-apoptotic effects (Chen et al. 1999). Electroconvulsive therapy and some antipsychotic and antidepressant drugs upregulate BCL2 in rats' brains (Chen and Henter 2010). In a nutshell, the level of anti-apoptotic BCL2 is downregulated in patients with BPD, while the expression of pro-apoptotic proteins is upregulated (Manji et al. 2012).

High-fat and carbohydrate diets are associated with disrupted mitochondrial biogenesis, which is linked with increased ROS production, insulin resistance, and neuroinflammation (Sihali-Beloui et al. 2019; Kuipers et al. 2019). Bioactive compounds including curcumin, resveratrol, and hydroxytyrosol exert neuroprotective effects by promoting mitophagy, destruction of damaged mitochondria, while increasing mitophagy mediators, along with production of new mitochondria (Varghese et al. 2020). Certain vitamins, including vitamin E, vitamin C, and vitamin A, act as antioxidants, while minerals, including zinc, copper, and selenium, act as enzyme cofactors in the mechanisms of antioxidant defense (Wesselink et al. 2019). Alpha-lipoic acid, which is present in potatoes, spinach, carrot, red meat, and broccoli, protects mitochondria from oxidative stress (Liu 2008). Collectively, greater knowledge of the mechanisms of different dietary nutrients through mitochondrial pathways may lead to new approaches in targeting psychiatric disorders.

A meta-analysis shows that biomarkers of mitochondrial damage have been found in ASD patients. Postmortem brain analyses and neuroimaging results were consistent with the mitochondrial dysfunction and alterations in mitochondrial gene expression (Rossignol and Frye 2012). A previous study looked at how proteins that modify mitochondrial dynamics changed in 20 ASD patients. In brain samples, there was an increase in mitochondrial fission molecules and a reduction in mitochondrial protein. Furthermore, changes in genes that control mitochondrial dynamics have been found in the temporal lobe (Tang et al. 2013). In SCZ, the proof for mitochondrial dysfunction is contradictory and limited. Genetic studies and in vitro studies of SCZ show downregulation of BCL2 and an increase of pro-apoptotic proteins. Also, brains from postmortem patients with SCZ revealed mitochondrial dysfunction in the cerebral cortex relative to controls (Jarskog et al. 2004). Together, the capability to modify mitochondrial function may play a key role in modulating cellular resilience and synaptic strength in neuronal networks that underlie sophisticated brain functions including cognition, emotion, perception, as well as behavior. Regrettably, there has been minimal progress in the field of really innovative medications for these severely incapacitating diseases. Improving mitochondrial function might be a key component of developing such therapies for at least certain aspects of these complicated diseases.

15.2.4 Kynurenine Pathway

Tryptophan is transformed into numerous bioactive compounds such as serotonin. Nevertheless, just a little amount of tryptophan is converted to serotonin. Most tryptophan is converted by indoleamine 2,3-dioxygenase into kynurenine (KYN), generating nicotinamide adenine dinucleotide which is a vital cellular energy source. KYN is metabolized into kynurenic acid (KynA), 3-hydroxyanthranilic acid, quinolinic acid (QA), and 3-hydroxykynurenine (Savitz 2019).

In the microglia, KYN is metabolized by kynurenine monooxygenase into a 3-hydroxykynurenine, which is metabolized by kynureninase into 3-hydroxyanthranilic acid to QA (Więdłocha et al. 2021). QA is an NMDA receptor agonist. It also inhibits glutamate reuptake by astrocytes, resulting in excitotoxicity (Stone and Perkins 1981). QA exerts neurotoxic effects via various mechanisms such as oxidative stress, excitotoxicity, neuroinflammation, disruption of autophagy, impairment of blood-brain barrier, destabilization of the neuronal axon, and neuronal death (Guillemin 2012). In astrocytes, KYN is transformed into KynA by the kynurenine aminotransferase (Więdłocha et al. 2021). KynA is neuroprotective. It inhibits NMDA receptors. Administration of kynurenic acid can decrease glutamate levels (Carpenedo et al. 2001). Kynurenic acid is a G protein-coupled receptor agonist and a negative modulator of α7-nicotinic acid, and also inhibits Ca^{2+} channels, suppressing inflammation (Wirthgen et al. 2018).

Homeostasis between the QA and KynA is important for brain functions (Savitz 2019). The dopaminergic hypothesis of SCZ stated that increased striatal

dopaminergic neurotransmission is the underlying cause of SCZ (Olney and Farber 1995). This theory was modified to include the hypofunction of GABAergic neurons. KynA is an endogenous NMDA receptor antagonist. So, SCZ was hypothesized to be triggered by the effect of increased KynA on NMDA receptors and the consequent effect on dopaminergic neurotransmission (Lavebratt et al. 2014). In consistent with this modified hypothesis, high levels of KynA have been observed in brains and cerebrospinal fluid of postmortem patients with SCZ (Schwarcz et al. 2001). Reductions in the level of KynA and an increase in QA were found in patients with depression compared to controls (Savitz et al. 2015). Decreased levels of tryptophan, KynA, KYN, and KynA/QA ratio were detected in patients with bipolar depression (BP) (Poletti et al. 2018). Disrupted KP with a high KYN/tryptophan ratio has been found in ASD patients (Foster et al. 2017) (Fig. 15.1).

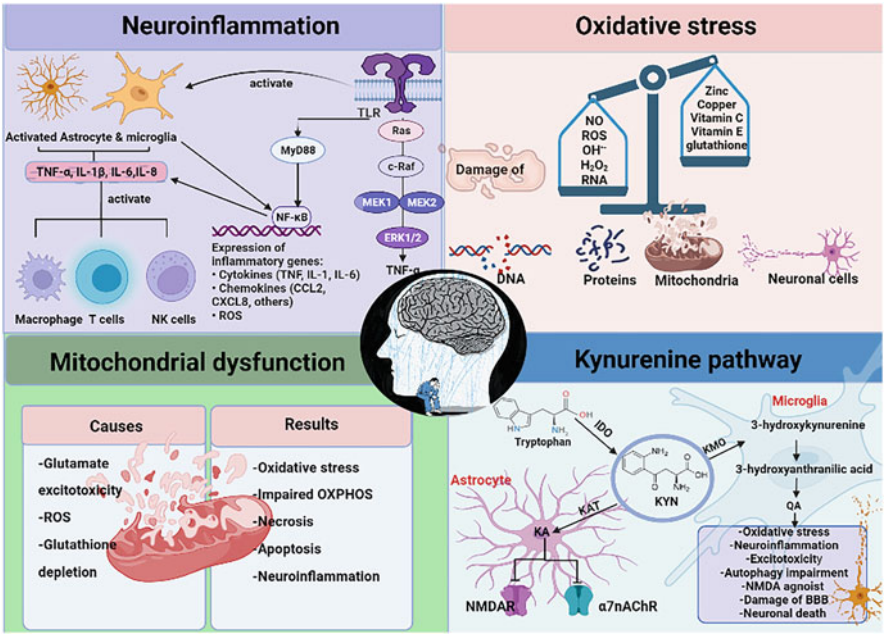

Fig. 15.1 Common culprits of psychiatric diseases. *TNF-α* tumor necrosis factor-alpha; *IL* interleukin; *CCL2* the chemokine ligand 2; *CXCL8* chemokine (C-X-C motif) ligand 8; *ROS* reactive oxygen species; *TLR* toll-like receptor; *ERK* extracellular signal-regulated kinase; *MyD88* myeloid differentiation primary response 88; *NF-κB* nuclear factor-kappa B; *NK cells* natural killer cells; *NO* nitric oxide; *OXPHOS* oxidative phosphorylation; *IDO* indoleamine 2,3-dioxygenase; *KYN* kynurenine; *QA* quinolinic acid; *KAT* kynurenine aminotransferase; *KA* kynurenic acid; *NMDAR* N-methyl-D-aspartate receptor; *α7nAChR* alpha-7 nicotinic acetylcholine receptor; *BBB* the blood-brain barrier

15.3 Mechanisms Linking Nutrition and Psychiatric Diseases

Many recent epidemiological studies have revealed the nexus between nutrition and a healthy lifestyle and a decreased incidence of psychiatric diseases, making diet strategies and lifestyle intervention studies targets (Provensi et al. 2019). The mechanisms behind the nexus between nutrition and psychiatric disorders are not completely understood. Several theories have been postulated to emphasize the importance of metabolic control, epigenetic programming, inflammatory processes, and gut-brain axis (Mao et al. 2021).

15.3.1 Metabolic Regulation and Psychiatric Diseases

Despite representing only 2% of body weight, the brain seems to be very metabolically active, requiring around 25% of the glucose and 20% of the oxygen used by the body. Neurons in the brain use glucose as a source of energy, whereas lactate and ketone bodies are used throughout brain development, respectively. Metabolic alterations in the brain affect adult neurogenesis and are known as key factors of psychiatric diseases. For instance, ASD in children has been supposed to be developed from maternal metabolic disturbance such as obesity and diabetes (Krakowiak et al. 2012). A previous study has established that postnatal administration of pioglitazone enhanced ASD-like symptoms in rats. Following brain insult, brain energy declines, promoting insulin resistance and mitochondrial dysfunction. Targeting metabolic alterations may offer up new possibilities for treating psychiatric disorders. Dietary interventions have therapeutic effects on brain disorders via metabolic regulation. Surprisingly, many drugs used for metabolic diseases have been demonstrated to improve neurogenesis, offering a unique insight into the therapeutic principles of those treatments and leading to the development of new approaches for psychiatric and neurological diseases (Mao et al. 2021). For example, metformin decreased insulin resistance and ameliorated Alzheimer's disease molecular characteristics in mouse Neuro-2a neuroblastoma cells (Gupta et al. 2011). Metformin could inhibit brain atrophy and prompt the generation of new neurons in the middle cerebral artery occlusion model of stroke (Jin et al. 2014). Moreover, a clinical study shows that metformin enhances memory and has an antidepressant effect in diabetic patients with depression (Guo et al. 2014). Patients with SCZ have disturbed glucose metabolism, as observed by impaired concentrations of glucose in their cerebrospinal fluid. Glucose and its metabolites have various effects on signaling molecules, regulate transcription factors, and modulate the secretion of cytokines and hormones (Roosterman and Cottrell 2021). In summary, further research should shed light on the underlying processes of cellular metabolic factors in influencing brain functions in health and disease.

15.3.2 Nutrigenomics and Psychiatric Disorders

Prenatal and postnatal nutrients can influence epigenetic alterations like histone modification, noncoding RNA, and DNA methylation. These epigenetic changes have been implicated in the impaired synaptic plasticity and transmission in ASD. These alterations can be involved in signaling pathways or code for scaffolding proteins, cell adhesion molecules, and ion channels (Bhandari et al. 2020). Recently, the studies of nutrigenomics, diet-genome interactions, have gained huge attention. Histone deacetylation and acetylation are controlled by histone deacetylases and histone acetyltransferases, respectively. Histone modifications of vitamin D receptors have been implicated in the pathophysiology of ASD (Bahrami et al. 2018). Dietary components such as curcumin and resveratrol have been reported to promote brain functions through histone acetyltransferases and histone deacetylase-mediated epigenetic mechanisms (Braidy et al. 2016). Deficiency in prenatal macro- and micronutrients has been associated with interruption of hippocampal H4K20 histone methylation. Iron deficiency disrupts histone demethylases that control hippocampal DNA methylation and brain-derived neurotrophic factor (BDNF) expression (Tran et al. 2015). Prenatal choline inhibits hippocampal BDNF suppression mediated by iron deficiency in rats (Tran et al. 2016). Surprisingly, much research suggests that epigenetic and environmental factors lead to alterations in glutamatergic, dopaminergic, and GABAergic systems. Especially, NMDA receptors are implicated in the pathogenesis of SCZ (Snyder and Gao 2020). In conclusion, epigenetic reprogramming is a fundamental strategy that underpins nutrition neurotherapeutics.

15.3.3 Nutrition and Microbiota-Gut-Brain Axis

The microbiome is made up of microorganisms that are present in/on the body. Over the past 20 years, advances in metabolomics have revealed the effects of gut microbiota on brain functions. Researches show that gut bacteria regulate brain function and behavior through a bidirectional pathway named the gut-brain axis (Naveed et al. 2021). Gut microbiota affects brain functions through the modulation of the HPA axis, synthesis of neurotransmitters, modulation of BDNF, synaptophysin, and immune function (He et al. 2018; Mao et al. 2021). Gut dysbiosis, changes in gut microbiota, is implicated in many psychiatric diseases like ASD, ADHD, anxiety, MDD, and SCZ (Wong et al. 2021). The nexus between the gut microbiota and CNS could be regulated through the modulation of neuroimmune function, neurogenesis, neuroendocrine, neuroplasticity, and some neurotransmitters such as serotonin, melatonin, GABA, histamine, acetylcholine, cytokines, hormones, and bacterial metabolites (Tognini 2017) (Fig. 15.2). Some gut microbiota such as *Bacillus subtilis*, *Bacillus mycoides*, *Proteus vulgaris*, *Escherichia coli*, and *Serratia marcescens* produce neurotransmitters like molecules that communicate with the CNS. A certain type of *E. coli* increases adrenaline and

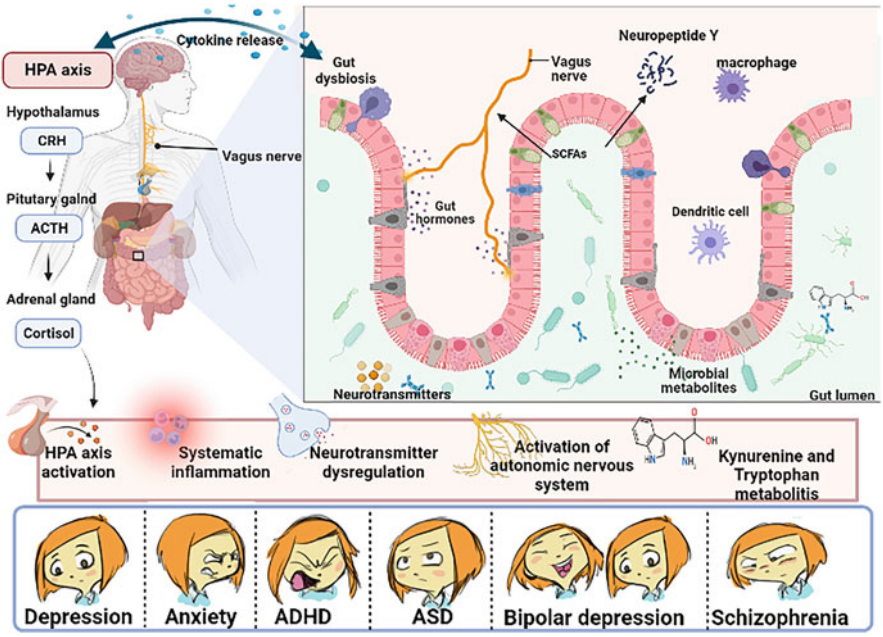

Fig. 15.2 Gut-brain axis and psychiatric diseases. Gut microbiota affects CNS via direct and indirect pathways including disruption of the HPA axis, stimulation of the vagal nerve, production of cytokines, SCFAs, neuropeptide Y, neurotransmitters, and tryptophan metabolites. *HPA axis* hypothalamic-pituitary-adrenal axis; *CRF* corticotrophin-releasing hormone; *ACTH* adrenocorticotropic hormone; *CNS* central nervous system; *SCFAs* short-chain fatty acids; *ADHD* attention deficit hyperactivity disorder; *ASD* autism spectrum disorder

activates genes required for colonization. Interestingly, the level of dopamine and norepinephrine in the gut is mediated by gut microbiota. Certain metabolites of spore-forming bacteria stimulate serotonin release (Sperandio et al. 2003).

Numerous studies have revealed that gut bacteria can influence depressive-like behavior (Gur et al. 2017). An increase in *Actinobacteria*, *Firmicutes*, and *Bacteroidetes* whereas a low level of *Lactobacillus* and *Bifidobacterium* have been found in patients with MDD (Zheng et al. 2016). A direct nexus between the gut microbiota and the HPA axis has been reported by the elevated levels of adrenocorticotropic hormone (ACTH) and corticosterone and reduced stress in microflora-deficient mice compared to controls (Sudo et al. 2004). A study demonstrated that dysregulation of the kynurenine pathway elevated IL-8 and IL-6 levels, reduced QA, IL-2, and serotonin, in postpartum depressive patients (Achtyes et al. 2020). *Faecalibacterium* has been known as a differentiating agent between patients with BPD and healthy controls. *Corynebacterium* and *Actinobacteria* were overrepresented, while *Faecalibacterium* and *Ruminococcaceae* were deficient (Painold et al. 2019). Also, the link between anxiety and gut dysbiosis has been known by the changes in gut microbiota diversity (Dinan and Cryan 2012). Gut dysbiosis was

found in patients with SCZ, and plenty of specific bacteria, such as *Corynebacterium* and *Succinivibrio* (Li et al. 2020b). Treatment of *Lactobacillus rhamnosus* and *Lactobacillus reuteri* could result in antidepressant and anxiolytic effects along with inhibition of corticosterone (Yano et al. 2015). SCZ and mania may result from *Toxoplasma gondii* infection of the gut microbiota (Naveed et al. 2021). *Corynebacterium* and *Actinobacteria* are higher in bipolar depressive patients relative to *Faecalibacterium* and *Ruminococcaceae* in controls (Painold et al. 2019).

Alterations in the gut microbiota structure are linked with exaggerated immunoinflammation in ASD patients. Recent researches have revealed increased levels of *Firmicutes phyla* and *Bacteroidetes*, *Clostridium phyla,* and *Lactobacilli*, along with a reduction in *Sutterella, Dorea*, and *Blautia*, emphasizing the gut dysbiosis in autistic children and consequently establishing a strong association between ASD and gut microbiota (Finegold et al. 2012; Azhari et al. 2019). Preclinical studies have revealed disrupted gut microbiota in ASD animal models, which can be reversed after treatment with probiotic strains such as *Lactobacillus reuteri* and *Bacteroidetes fragilis* (de Theije et al. 2014). Furthermore, antibiotic therapy decreased anxiety in autistic children, with short-term advantages in aggressive behavior through inhibition of increased cytokine levels and increase in BDNF (Hsiao et al. 2013). Moreover, the administration of probiotics has inhibited depressive-like symptoms in an animal model (Desbonnet et al. 2010). In summary, change in the diet greatly affects the composition of gut microbiota. Many preclinical studies have shown the effectiveness of probiotics in the amelioration of many psychiatric disorders. Therapeutic translation of these results is now required for food to be considered as a prospective treatment for various neuropsychiatric diseases.

Attention deficit hyperactivity disorder (ADHD) symptoms have been linked with gut dysbiosis and reduction in *Faecalibacterium* (Jiang et al. 2018). Moreover, a reduction in microbial diversity has also been found in ADHD, which may cause a leaky gut (Prehn-Kristensen et al. 2018). A randomized clinical study found that infection with *Streptococcus* or reduced levels of fecal *Bifidobacterium* in the postnatal period have been implicated in ADHD development (Pärtty et al. 2015). Gut microbiota influence the brain through stimulation of the vagus nerve and activation of the autonomic nervous system that has been implicated in ADHD (Negrao et al. 2011).

Nutrition has been demonstrated to modify the microbiome, controlling brain functions (Stilling et al. 2014). *Clostridium difficile* and *E. coli* are lower in the microbiota of breastfed babies relative to formula-fed infants (Penders et al. 2005). A Western diet with increased consumption of high-fat diets, refined sugars, and meat leads to alteration in the gut microbiota, contributing to an increased probability of psychiatric and inflammatory diseases (Naveed et al. 2021). Numerous studies have revealed that foods rich in PUFAs, DHA, and 3′ sialyllactose modulate gut microbiota, reducing HPA axis-mediated stress (Foster et al. 2017). In the future, targeting the gut-brain axis may underpin essential mechanisms of psychiatric diseases. Moreover, specific diets can restore the microbiota-gut-brain axis's balance and have therapeutic benefits on mental diseases.

15.4 Schizophrenia (SCZ)

Schizophrenia (SCZ) is a complicated range of neuropsychiatric disorders that are distinguished by abnormal cognition, altered perception, delusions, social isolation, hallucinations, loss of motivation, lack of communication, apathy, and decreased expression (Naveed et al. 2021). Although the etiology of SCZ has not been known, correlations among environmental, psychological, and genetic factors may be embroiled in the pathophysiology of SCZ (Imamura et al. 2020). Early neurodevelopmental variables may have a role in the etiology of SCZ (Weinberger 1987). High dopamine levels have been reported in SCZ (Howes and Kapur 2009). Also, glutamate dysfunction due to NMDA receptor hypofunction has been proposed to prompt SCZ (Nakazawa and Sapkota 2020). Neuroinflammation is an underlying cause of SCZ. Furthermore, inflammatory cytokines such as IL-1, IL-12, IL-6, transforming growth factor, and TNF-α were reported to be elevated in SCZ patients (Mongan et al. 2020). The main aims of antipsychotic drugs are alleviation of symptoms, prevention of relapse of SCZ, and regulation of dopamine levels. Nonetheless, antipsychotic drugs have side effects such as increased appetite and body weight. Dysregulation of dopamine may alter food consumption and increase body weight (Huang et al. 2020a).

15.4.1 Role of Amino Acids in Schizophrenia

Oxidative stress has been implicated in the pathogenesis of SCZ. This oxidative stress is further complicated by several processes such as inflammation, mitochondrial dysfunction, lipid peroxidation, apoptosis, and DNA mutation (Mansour et al. 2021c). Consequently, dietary antioxidants can be accepted as an adjuvant therapy in SCZ. L-theanine is a natural antioxidant and inhibits lipid peroxidation (Yokozawa and Dong 1997). As we hinted above, the dysfunction of the NMDA receptor has been involved in the pathogenesis of SCZ. Hence, administration of specific AAs, acting as NMDA receptor agonists such as D-serine, glycine, and D-cycloserine, has resulted in the amelioration of negative symptoms of SCZ (Ohnuma et al. 2008).

Tyrosine is the precursor of epinephrine, norepinephrine, and dopamine. Tryptophan is a major source of serotonin. High levels of tyrosine and tryptophan have been found in the plasma of SCZ patients treated with clozapine (Tortorella et al. 2001; De Luca et al. 2008). L-serine is a transmitter that regulates NMDA receptors. Previous studies examining the level of L-serine in SCZ have ended with inconclusive results. A previous study found an increased level of L-serine in the plasma of a patient with SCZ (Fiardi et al. 1990). Another study has found a low level of L-serine in the plasma of schizophrenic patients (Carl et al. 1992; Yamamori et al. 2014). Some other studies found normal levels of L-serine in patients with SCZ (Tortorella et al. 2001). D-serine is another NMDA receptor co-agonist that has been reduced in patients with SCZ (Yamamori et al. 2014). L-glutamate and L-aspartate are

excitatory AAs. They were elevated in the serum of patients with SCZ, which decreased after administration of clozapine (Tortorella et al. 2001). Glycine is an inhibitory neurotransmitter that modulates NMDA receptors. Some studies have reported high levels of serum glycine in patients with SCZ compared to controls (de Bartolomeis et al. 2020). Higher levels of histidine, L-isoleucine, citrulline, kynurenine, valine, GABA, homocysteine, ornithine, and arginine have been reported in patients with SCZ (Rao et al. 1990; Carl et al. 1992; Tortorella et al. 2001; Muntjewerff et al. 2006; Saleem et al. 2017; Leppik et al. 2018). The proline dehydrogenase gene, encoding the enzyme that increases proline catabolism, is present on human chromosome 22q11.2, an area associated with SCZ risk. Elevated proline levels have been linked to SCZ (Clelland et al. 2016). Depending on the foregoing, many studies have shed light on the importance of AAs in the treatment of SCZ. For instance, administration of 6 g/day of L-lysine for 4 weeks ameliorated positive symptoms of SCZ (Wass et al. 2011). Administration of L-theanine and N-acetyl cysteine reduced the positive symptoms of SCZ patients (Arroll et al. 2014).

15.4.2 Role of Fatty Acids in Schizophrenia

Schizophrenic patients have high levels of SCFA (He et al. 2018). Several studies have found that α-linolenic acid and DHA were lower in the red blood cells of schizophrenic patients (Cha and Yang 2020). TNF-α and triglyceride levels were reduced in SCZ patients with metabolic syndrome after 3 months of omega-3 FA administration (Xu et al. 2019). In another study, patients treated with omega-3 fatty acids for nearly 6 months had a decrease in the intensity of their SCZ symptoms (Cha and Yang 2020). Administration of omega-3 for 26 weeks lowered the severity of symptoms and relapse in SCZ patients (Pawełczyk et al. 2015). Although omega-3 FAs have been shown to improve symptoms of SCZ, there is some conflicting evidence. Administration of a high dose of omega-3 FAs for 4 months did not affect symptoms of SCZ (Fenton et al. 2001).

15.4.3 Role of Vitamins in Schizophrenia

Many epidemiological studies implicate a low maternal concentration of vitamin D as a risk factor of SCZ. In contrast, prenatal and postnatal administration of vitamin D decreases the possibility of having SCZ later in life (McGrath et al. 2004). People born in the winter and spring seasons have a higher risk of getting SCZ due to reduced levels of vitamin D (Davies et al. 2003). Also, a cohort study revealed that dark-skinned people are more likely to have vitamin D deficiency due to higher melanin concentration in the skin, increasing the possibility of developmental vitamin D deficiency in their children (McGrath et al. 2003). In another cohort

study, a group of Finnish male children who got appropriate vitamin D supplementation throughout their first year of life had a lower chance of developing SCZ (McGrath et al. 2004). A low concentration of vitamin D in infants is attributed to a twofold greater risk of SCZ later in life (McGrath et al. 2010). The therapeutic efficacy of vitamin D is attributed to its effect on inflammatory molecules like TNF-α and IL-6 (Cha and Yang 2020). This evidence, taken together, supports the concept that vitamin D shortages during development may raise the risk of schizophrenia, although further research is needed.

A meta-analysis has detected lower levels of vitamins B6, B8, and B12 in schizophrenic patients compared to the control group. Nevertheless, no effect of B vitamins was noticed on negative and positive symptoms of SCZ (Firth et al. 2017). Vitamin C is an antioxidant that plays a role in protection from inflammation. Low intake of vitamin C, vitamin B3, and vitamin B9 was linked with SCZ symptoms in Korean patients (Kim et al. 2017). Administration of vitamin B9 as an adjuvant therapy to antipsychotic drugs may be beneficial in patients with a genetic vulnerability (Roffman et al. 2013a). Vitamin C given at a dose of 200 mg per day for 8 weeks displayed substantial enhancement of ascorbic acid levels and a brief psychiatric rating scale score, suggesting enhancement in psychopathological status (Dakhale et al. 2005). In patients with a genetic vulnerability, administration of vitamin B9 as an adjuvant therapy to antipsychotic drugs may be beneficial (Roffman et al. 2013b). Also, co-administration of vitamins E and C reduced many psychiatric scores in SCZ patients treated with haloperidol (Sivrioglu et al. 2007).

15.4.4 Role of Minerals in Schizophrenia

Patients with SCZ have a high level of magnesium. The magnesium level was reduced after treatment with haloperidol (Jabotinsky-Rubin et al. 1993). Also, calcium levels in schizophrenic patients were elevated compared to controls (Mauri et al. 2013). Furthermore, low levels of iron, sodium, potassium, and selenium have been reported in patients with SCZ (Uddin et al. 2021). As dopamine disruption is implicated in the pathogenesis of SCZ, copper elevation may be related to dopamine dysregulation. A higher level of copper has been found in schizophrenic patients as compared to controls. In line with this result, a previous study reported an elevation in the copper level of SCZ patients along with a reduction in manganese and iron levels relative to controls. However, the plasma levels of selenium and zinc did not vary between groups (Wolf et al. 2006). A recent study revealed the decreased level of zinc in SCZ patients relative to controls (Joe et al. 2018). Another clinical study demonstrated that treatment with zinc for 6 weeks ameliorated symptoms of SCZ as compared to controls (Mortazavi et al. 2015). A previous study displayed that maternal iron deficiency increased the susceptibility of SCZ in the offspring (Sørensen et al. 2011). More research is required to understand the therapeutic potential of minerals in SCZ.

15.5 Autism Spectrum Disorder (ASD)

Autism spectrum disorder (ASD) is a disease of altered brain connectivity. ASD affects around 1% of the world's population (Manivasagam et al. 2020). It is a complicated heterogeneous neurodevelopmental condition with significant genetic and environmental origins. Several gene mutations of proteins involved in synaptic transmission, cell function, transcriptional/posttranscriptional mechanisms, and excitatory and inhibitory neurons are embroiled in the pathophysiology of ASD, like neuroligin, multiple ankyrin repeat domains 3, SH3, neurexin, and contactin-associated protein-like (Pangrazzi et al. 2020). In ASD, gene mutations, poor detoxification, oxidative stress, aberrant neurotrophic factors, neuroinflammation, immunological dysregulation, seizures, and neurotransmitter levels have been suggested (Rossignol and Frye 2014). Also, environmental factors like maternal drugs, gut microbiota, socioeconomic status, and nutrition have been engaged in the etiology of ASD (Bölte et al. 2019). ASD is characterized by repetitive or restrictive behavior, reduced social interaction, social behavior deficit, self-injury, sleep-wake disorders, multiple sensory deficits, convulsions, and often fatal gastrointestinal complications (Sandhu et al. 2017). Much research has shown that oxidative stress and neuroinflammation may be underlying causes of ASD. ASD patients display a higher level of proinflammatory and oxidative stress molecules like IL-6 and TNF-α (Whiteley 2015). ASD has been linked with several triggers such as pollution, chemicals, stress, and nutrition (de Theije et al. 2014). Because of the wide range of ASD symptoms, no single treatment approach is completely successful. Unfortunately, the currently available drugs for ASD are geared to the amelioration of behavioral symptoms only. They do not affect the language and social issues that are central to ASD (Hartman and Patel 2020). Interestingly, many studies show that nutritional intervention enhances the nonverbal intelligence quotient in ASD (Wang et al. 2020).

15.5.1 Effect of Peptides and Amino Acids in Autism Spectrum Disorder

Increased urine peptide levels indicate that autistic children have impaired protein digestion because of high intestinal permeability. ASD symptoms are caused in part by food hypersensitivities. Gluten is present in oats, wheat, and barley. Casein is present in milk. Gluten and casein have been proven to elicit an immune and inflammatory response in autistic patients. Children with ASD have more lipopolysaccharide and proinflammatory cytokines after the consumption of milk or wheat. Likewise, gluten and casein can increase immunoglobulin G and A antibodies in patients with ASD (Lau et al. 2013). Casein-free and gluten-free diets have been demonstrated to decrease the symptoms of ASD, including social interaction, motor, language, and behavioral deficits (Stangl and Thuret 2009). Another hypothesis

called "excess opioid" suggests that casein and gluten are converted in the intestine into peptides known as casomorphins and gluteomorphins, which are analogous to endorphins and also have opiate agonist effects. In the healthy gastrointestinal tract, the intestinal mucosa prohibits such peptides from reaching the blood. But, in patients with ASD, a leaky gut possibly permits these exorphins into the blood and eventually into the brain to stimulate opiate receptors (White 2003). A randomized clinical trial reported that eating a gluten-free diet for 6 weeks significantly decreased repetitive behavior and gastrointestinal side effects in autistic children compared to the control consuming a regular diet (Ghalichi et al. 2016). Another research found that consumption of a milk-free diet for 8 weeks improved ASD symptoms in children. According to a Cochrane review, there is no actual proof of the benefit of gluten- and casein-free diets in ASD. As a result, a large-scale, randomized trial would yield more precise findings (Whiteley 2015).

Many AAs act as neurotransmitters like glutamate and aspartate or as precursors for neurotransmitter synthesis such as tryptophan and tyrosine. Disturbances in the levels of these AAs have been embroiled in ASD (Sanctuary et al. 2018). Autistic children have higher levels of glutamate and decreased levels of glutamine. Concentrations of these AAs act as an indicator of intelligence quotient in those children relative to control (Shimmura et al. 2011). In addition, L-tryptophan precursors are present in meat, eggs, bananas, cereal, milk, shellfish, plums, and fish. Also, AAs are produced by gut microbiota, which contributes to modified tryptophan metabolism, resulting in higher levels of indolyl lactate and indole-3-acetic acid (Richard et al. 2009). Indole derivatives are found to increase in ASD patients (Delgado et al. 2021). Regardless of the exact pathways via which certain proteins may increase ASD symptoms, research shows that limiting their intake may be beneficial. In addition, the levels of lysine, aspartic acid, and taurine were found to be elevated in autistic children (ElObeid et al. 2020). Continued research on the nexus between personalized diet and ASD is required.

15.5.2 Fatty Acids and Autism Spectrum Disorder

Short-chain fatty acids (SCFAs) have been stated to increase in fecal samples of autistic children. Nevertheless, the involvement of SCFAs in ASD is not completely understood. For example, treatment with butyrate in ASD animal models has been reported to decrease repetitive behavior (Peng et al. 2007). Conversely, cerebroventricular administration of propionic acid was stated to induce ASD-like signs in rats (MacFabe et al. 2011), suggesting conflicting roles of SCFAs in ASD. It has been stated that patients with autism have more disrupted SCFA levels than their non-autistic counterparts. Interestingly, a previous study demonstrated that gut microbiota transfer from ASD patients to germ-free mice could induce ASD-like symptoms, suggesting that the gut-brain axis contributes to the pathogenesis of ASD (Sharon et al. 2019). In agreement with these results, a previous study has reported that an increase in propionate-producing bacteria and a reduction in butyrate-

producing bacteria in the microbiome may influence the incidence and severity of ASD (Finegold et al. 2010). Further investigation on the involvement of SCFAs in autism is required.

Valproic acid is another example of SCFAs. It is derived from valerian root. Recent studies have revealed that valproic acid has potential neuroprotective effects in Alzheimer's disease, ischemia, and Parkinson's disease through various mechanisms (Monti et al. 2010; Suda et al. 2013). Despite the aforementioned neuroprotective effects of valproic acid, epidemiological studies in children exposed to valproic acid in utero have noticed autism and other neurodevelopmental disorders (Chomiak et al. 2013). As a result, careful consideration must be given to whether or not valproic acid would be an appropriate treatment, particularly in pregnant women or women wanting to conceive.

15.5.3 Therapeutic Potential of Vitamins in Autism Spectrum Disorder

Vitamin D deficiency, whether in prenatal or neonatal stages, is a significant risk factor for ASD (Cannell 2008). A previous meta-analysis revealed that patients with ASD have lower vitamin D concentrations than controls (Mazahery et al. 2016). Vitamin D deficiency has been associated with ASD severity (Saad et al. 2016). Activated vitamin D is an immunomodulatory agent. It has been shown to suppress T-helper cells (Borges et al. 2011). The capability of vitamin D to regulate neurotrophic factors and inflammation has led to the recommendation that vitamin D is neuroprotective. Previous studies have shown that treatment with vitamin D can suppress glutamate-derived cell toxicity in the culture of hippocampal and cortical neurons. These effects have been attributed to an increase in vitamin D receptor level (Taniura et al. 2006) and a reduction in Ca^{2+} channel levels (Brewer et al. 2001). Many studies have established a low level of vitamin D in children with ASD relative to their counterparts (Bjørklund et al. 2019). Administration of vitamin D could decrease the high level of serotonin and gastrointestinal inflammation in patients with ASD (Patrick and Ames 2014). Together, these results suggest that vitamin D has favorable therapeutic benefits in ASD.

Researchers have found an absence of the gene encoding vitamin A production. Vitamin A supplementation has enhanced language and vision abilities in patients with ASD (Parikh et al. 2009). Vitamin A boosts oxytocin levels in patients with autism through the upregulation of the CD38 signaling pathway. Consequently, brain activity and communication skills in autistic patients may be considerably improved by oxytocin (Riebold et al. 2011). Another research revealed that around 80% of autistic children are vitamin A deficient (Guo et al. 2018). It was also demonstrated that vitamin A supplementation could be a potential agent for ASD patients to aid in the maintenance of numerous biochemical responses in autistic children (Bjørklund et al. 2019).

Vitamin B1 deficiency may be implicated in ASD through several mechanisms such as apoptosis, oxidative stress, and mitochondrial dysfunction (Bjørklund et al. 2019). Interestingly, a patented device used as therapy for ASD provides patients with a thiamine derivative (Lonsdale and Frackelton 2002). Administration of vitamin B6 has been proven to ameliorate behavioral and gastrointestinal symptoms in patients with ASD (Gogou and Kolios 2017).

Maternal abnormalities in vitamin B9 have been associated with the development of ASD (Wiens and Desoto 2017). Also, patients with ASD have decreased levels of vitamin B9 because antibodies inhibit vitamin B9 synthesis by competing with folate receptors and blocking folate transport. Consequently, dietary administration of vitamin B9 has been preferred for ASD patients (Alfawaz et al. 2018). Administration of vitamins B6, B9, and B12 in children with ASD reduced homocysteine levels that are engaged in the pathophysiology of ASD (Ali et al. 2011). A randomized clinical study revealed that administration of methyl vitamin B12 in children with ASD significantly improved the symptoms of ASD compared to the control group, as confirmed by the clinical global impression improvement score (Hendren et al. 2016). Finally, it is significant to emphasize the importance of using B vitamins in prospective clinical research as a neuroprotective approach for ASD.

Vitamins C and E are crucial antioxidants in the CNS. Individuals with ASD were shown to have lower levels of vitamin C, indicating the necessity of vitamin C supplements in ASD patients (Adams and Holloway 2004). According to another research, children with vitamin E deficiency exhibit autism-like behavioral characteristics (Krajcovicova-Kudlackova et al. 2009). In previous clinical studies, the administration of high doses of vitamin C enhanced the behavior of patients with ASD (Shaltout et al. 2020). Vitamin E and vitamin C have neuroprotective effects because they can scavenge free radicals. They are engaged in copper, zinc, and iron chelation (Monacelli et al. 2017). A meta-analysis reported lower levels of both vitamin E and glutathione in autistic children, proving the antioxidant effects of vitamin E (Frustaci et al. 2012).

15.5.4 Therapeutic Potential of Minerals in Autism Spectrum Disorder

Low iron is more common in children with ASD, suggesting defective absorption or metabolism of iron in these children. Also, low iron intake during gestation and little iron consumption fold the risk of having ASD (Schmidt et al. 2014). The deficiency of zinc, potassium, calcium, magnesium, and copper during pregnancy has been associated with an increased incidence of ASD (Curtin et al. 2018). In the maternal phase, zinc and iron deficiencies alter the expression of genes responsible for neuroplasticity and neurogenesis, like PSD-95, BDNF, CamKIIa, and SDF-1 (Hagmeyer et al. 2018). Administration of zinc ameliorated impaired vocalization and social interaction in a rat model of ASD (Cezar et al. 2018). Magnesium

improves sleep and behavioral and gastrointestinal symptoms in patients with ASD (Adams and Holloway 2004).

15.6 Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder is a neurodevelopmental disease with a genetic origin and a suboptimal fetal nutritional environment (Lahti et al. 2006). ADHD is distinguished by hyperactivity, impulsivity, dysregulated cognition, excessive motor activity, and persistent inattention (Klein et al. 2016). Disturbance of brain maturation, structure, and connectivity in patients with ADHD has been observed. In particular, delayed maturation of the frontal cerebral cortex has been found in ADHD patients (Shaw et al. 2007). DRD5, the gene that encodes the dopamine receptor D5, has recently been identified as a potential gene for ADHD. ADHD is characterized by changes in neurochemistry and neurobiology accompanied by disrupted dopamine and noradrenaline signaling (Tripp and Wickens 2009). Many studies show that changes in glutamatergic signaling pathways may lead to ADHD (Levy and De Leon 2015). In this context, it has been found that ADHD patients have a lower level of glutamate and glutamine in the basal ganglia and striatum (Carrey et al. 2007). An increase in glutamate level in the anterior cingulate cortex was associated with impulsivity and hyperactivity in ADHD patients. Genome analysis for ADHD genes showed a changed expression of genes linked to glutamatergic neurotransmission (Bauer et al. 2018).

Therapeutic approaches for ADHD primarily work to enhance the function of dopamine and noradrenaline in the prefrontal cortex, which is crucial for maintaining attention and cognitive control. Stimulants such as amphetamine inhibit noradrenaline and dopamine reuptake, methylphenidate inhibits dopamine reuptake, and atomoxetine inhibits noradrenalin reuptake (Andrade 2010). Most currently used drugs for ADHD are effective (Klein et al. 2016). Some drugs fail in 20–30% of children with ADHD (Abbasi et al. 2011). However, they are linked with adverse effects like hypertension, QT interval prolongation, headache, psychotic symptoms, potential abuse, seizures, anxiety, stomachaches, insomnia, and impaired growth. Moreover, atomoxetine has been correlated with a high risk of suicidal behavior in adults. Hence, dietary intervention is being studied to ameliorate ASD symptoms (Graham et al. 2011).

15.6.1 Role of Amino Acids in Attention Deficit Hyperactivity Disorder

A previous study demonstrated that children with ADHD had lower concentrations of proline, glutamine, and lysine, suggesting impaired metabolism of these AAs.

They had high levels of glutamate, aspartate, and hydroxyproline relative to their healthy counterparts, suggesting altered neurotransmission and collagen catabolism, respectively (Skalny et al. 2021). In a prospective US birth study, elevated cord levels of valine, leucine, and isoleucine were related to a higher probability of developing ADHD (Anand et al. 2021). Acetyl-L-carnitine is vital for optimum fatty acid oxidation. Treatment with acetyl-L-carnitine increased norepinephrine. In the medial frontal cortex and cingulate cortex, the metabolite/serotonin (5HIAA/5HT) ratio is lowered in impulsive rats (Adriani et al. 2004). L-carnosine is present in brain tissues. L-carnosine has been implicated in ADHD symptoms (Ghajar et al. 2018). Larger scale research is needed to investigate whether or not intake of different AAs may be a therapeutic approach for ADHD.

15.6.2 Role of Fatty Acids in Attention Deficit Hyperactivity Disorder

ADHD has also been associated with single nucleotide polymorphisms in the fatty acid desaturase 1 and 2 genes, which code for delta-5 and delta-6 desaturases, respectively. These enzymes are responsible for PUFA metabolism (Brookes et al. 2006). The studies supporting PUFAs for the treatment of ADHD have been inconclusive. Numerous studies suggest that PUFAs may have a role in reducing the risk and cure of ADHD. A cohort study showed that low maternal dietary intake of seafood may increase the susceptibility of neurobehavioral, neurodevelopmental, and social communication problems in offspring later in life (Hibbeln et al. 2007). Evidence has established that a deficiency of FAs is correlated with ADHD symptoms (Händel et al. 2021), proving the importance of PUFAs in regulating neurotransmitter synthesis and modulation of immunity via the regulation of lipid signaling pathways as well as their anti-inflammatory effects (Yaqoob and Calder 2007). A previous clinical trial showed that treatment of ADHD children with omega-3 and omega-6 FAs, zinc, and magnesium improved ADHD symptoms and emotional problems. However, a meta-analysis showed the inadequate effect of PUFAs on the amelioration of ADHD symptoms. The authors also suggested that PUFA deficiency in ADHD patients' baseline is thought to be required for effective PUFA therapy (Händel et al. 2021). A long-term investigation of the effects of giving PUFA as a supplement to ADHD patients is required.

15.6.3 Role of Vitamins in Attention Deficit Hyperactivity Disorder

Various studies have studied vitamins as an alternative non-pharmacological therapeutic approach for ADHD. Vitamin D can influence dopamine levels through

various mechanisms, including antioxidant effects, calcium transition, and gene expression. Hypovitaminosis D has been implicated in the pathophysiology of ADHD in children and adults (Mohammadpour et al. 2018). A recent cohort study in Greece reported a nexus between a high level of maternal vitamin D and a decrease in the risk of ADHD development (Daraki et al. 2018).

Previous studies on the nexus between B vitamins and ADHD have shown inconclusive results (Sourander et al. 2021). A cohort study revealed that maternal administration of vitamin B9 late in the first trimester of gestation was associated with enhanced offspring neurodevelopment and neurobehavioral outcomes at the age of 4 years such as motor, inattention, verbal, and social competence symptoms. Another pre-birth cohort study showed that maternal intake of vitamin B2, vitamin B9, and vitamin B6 was negatively correlated with children's low prosocial behavior, hyperactivity, and emotional problems (Miyake et al. 2020). Nevertheless, a recent population-based study revealed that there was no relationship between maternal deficiency of vitamin B12 and risk of ADHD in offspring (Sourander et al. 2021).

15.6.4 Role of Minerals in Attention Deficit Hyperactivity Disorder

Iron and zinc deficiency has been found in children with ADHD as compared to controls (Granero et al. 2021). Genetic, neuroimaging, and experimental investigations have also revealed that lower dopamine transporter levels are associated with lower brain iron and zinc levels (Swanson et al. 2007). The deficiency of these minerals could be associated with a dopaminergic disturbance, which could be the underlying cause of attention and hyperactivity in ADHD (Khan et al. 2017). Moreover, zinc plays vital functions in the metabolism of melatonin, regulating dopamine metabolism. Hence, zinc is regarded as a dopamine reuptake inhibitor. Iron is a cofactor in the synthesis of serotonin, dopamine, and noradrenaline. Moreover, brain iron deficiency has been associated with impaired adenosine neurotransmission, which has been associated with the pathogenesis of ADHD (Granero et al. 2021). A longitudinal study reported that the administration of zinc and iron improved attention and concentration in children (Vazir et al. 2006). Also, a positive nexus between serum zinc level and symptoms of inattention in children with ADHD has been established in a cross-sectional study (Arnold et al. 2005). Decreased magnesium level has been found in children with ADHD (Nogovitsina and Levitina 2007). A randomized clinical trial showed that administration of magnesium and methylphenidate in 40 children with ADHD ameliorated ADHD symptoms (Noorazar et al. 2021).

15.7 Anxiety Disorders

Anxiety is a negative emotional mental state defined by unfavorable internal conflicts, which is frequently accompanied by anxious behavior such as physical complaints, walking back and forth, and brooding (Naveed et al. 2021). The symptoms of anxiety disorders include impaired concentration, fatigue, restlessness, irritability, heart palpitations, muscle aches, and sleep disorders. Anxiety disorders include selective mutism, separation anxiety disorder, specific phobias, agoraphobia, generalized anxiety, social phobia, and panic disorder (Bhandari et al. 2020). Anxiety is associated with decreased GABA or increased excitatory glutamine. Other neurotransmitters are implicated in the pathogenesis of anxiety such as vasopressin, cholecystokinin, neuropeptide Y, galanin, corticotrophin-releasing factor, and oxytocin (Casseb et al. 2019).

15.7.1 Role of Amino Acids in Anxiety

A systematic review revealed that a low level of tryptophan did not correlate with anxiety (Schopman et al. 2021). A higher concentration of glutamine and lower level of glutamate were reported in the thalamus of patients with social anxiety disorder relative to controls (Pollack et al. 2008). The administration of glutamine may represent a useful approach for treating anxiety (Wang et al. 2007). Acute depletion of both tyrosine and phenylalanine in healthy women resulted in increased anxiety as compared to the control group (Leyton et al. 2000). Administration of a low L-histidine diet in C57BL/6 J mice for 2 weeks resulted in reduced histamine levels in the brain with a contaminant increase in anxiety-like behavior relative to the control group (Yoshikawa et al. 2014).

15.7.2 Role of Fatty Acids in Anxiety

In 2018, Hollis et al. studied the effect of 15 days of consumption of MCFAs on anxiety in a rat model. MCFA-fed rats had a lower level of beta-hydroxybutyrate, altered energy metabolism in the brain, and reduced anxiety in the light-dark box test, indicating the anxiolytic effects of SCFA-containing diets (Hollis et al. 2018). Also, a linear association between DHA and anxiety has been described (Jacka et al. 2013).

15.7.3 Role of Vitamins in Anxiety

A low level of vitamin D was associated with anxiety in 51,003 Korean adult participants (Kim et al. 2020). Some studies state that the administration of vitamin D is correlated with lower anxiety (Narula et al. 2017). Vitamin C has been reported to have anxiolytic and antioxidant effects (Kocot et al. 2017). Nevertheless, other studies failed to establish a nexus between vitamin D and anxiolytic effects (Wepner et al. 2014). In a clinical study, a reduced level of vitamin B6 was found in 3362 anxious patients relative to controls (Kafeshani et al. 2020). Another study showed that the administration of vitamins B1, B5, B6, B7, and B9 was correlated with a lower risk of depression and anxiety (Mahdavifar et al. 2021).

15.7.4 Role of Minerals in Anxiety

Many enzymes and cellular functions implicated in stress are magnesium dependent. In a randomized clinical trial, administration of magnesium alone or combined with vitamin B6 for 8 weeks in patients with severe stress ameliorated anxiety scores from baseline (Noah et al. 2021). Insomnia is common in anxiety disorders (Staner 2003). Magnesium has been demonstrated as an adjuvant therapy in insomnia because magnesium is an NMDA antagonist, GABA agonist, relaxant, and melatonin regulator. As a result, sleep is improved (Abbasi et al. 2012). A higher concentration of Cu^{2+} and a lower concentration of Zn^{2+} were reported in 38 patients with anxiety compared to controls (Russo 2011).

15.8 Obsessive-Compulsive Disorder (OCD)

Obsessive-compulsive disorder is a psychiatric disease marked by reoccurring unpleasant thoughts or images, as well as repetitive activities. Obsession is characterized by repetitive and persistent thoughts, desires, or emotions that are seen as invasive and undesired and that produce significant anxiety. Compulsion is characterized by behavioral or mental activities such as handwashing, ordering, and checking, which are examples of recurrence that an individual feels driven to execute (Bhandari et al. 2020). Insufficiency of the serotonin level and serotonin receptor availability has been embroiled in the pathophysiology of OCD (Kellner 2010). A high concentration of glutamine, GABA, and glutamate in the caudate nucleus has been detected in patients with OCD. In addition, the NMDA receptor has been embroiled in OCD (Chakrabarty et al. 2005). The available therapies for OCD are tricyclic antidepressants and selective serotonin reuptake inhibitors. The ineptitude and potential adverse effects of current medicines have prompted the quest for new approaches. Nutritional deficiencies have been detected in patients with OCD. As a

result, dietary modifications are regarded as useful in therapy (Kuygun Karcl and Gül Celik 2020).

15.8.1 Role of Amino Acids in Obsessive-Compulsive Disorder

Compulsive behaviors, present in OCD, are related to a low level of serotonin and its receptors. Administration of a tryptophan-free diet in rats resulted in increased compulsive behavior due to changes in the serotonergic system (Merchán et al. 2017). Glycine is linked with glutamatergic function in the cerebral cortex. Glycine ameliorates OCD symptoms because it acts as an NMDA receptor agonist (Singer et al. 2010). Administration of 60 g/day of glycine to 24 patients with OCD ameliorated OCD symptoms. However, the dropout rate was high because of the side effects of glycine (Greenberg et al. 2009).

15.8.2 Role of Vitamins in Obsessive-Compulsive Disorder

Vitamin D deficiency has been implicated in OCD pathophysiology. There is a direct nexus between vitamin D and tyrosine hydroxylase that is vital for the production of dopamine, adrenaline, and noradrenaline. In addition, vitamin D has antioxidant properties that inhibit the nitric oxide synthase enzyme, with consequent protection from deleterious free radicals present in OCD (Behl et al. 2010). Hence, hypovitaminosis D has a direct role in the development of OCD. Deficiency in vitamin D has been found in patients with OCD (Cui et al. 2015).

Vitamins B9 and B12 are vital in carbon transfer metabolism that regulates the methylation of some neurotransmitters, proteins, and neural membrane phospholipids. Thus, deficiency of these vitamins affects neurotransmitter levels. Deficiency of vitamins B9 and B12 increases homocysteine levels that result in apoptosis, oxidative stress, DNA damage, mitochondrial dysfunction, and ultimately OCD (Bottiglieri 2005). Hypovitaminosis B12 has been reported in OCD patients in some studies (Sharma and Biswas 2012; Türksoy et al. 2014). Another study found a lower concentration of vitamin B9 and a higher concentration of homocysteine in patients with OCD relative to healthy counterparts (Atmaca et al. 2005). Clinical research found that giving vitamin B9 plus fluoxetine to 36 individuals with OCD for 12 weeks did not make a meaningful impact when compared to a placebo group that got both placebo and fluoxetine (Tural et al. 2019).

15.8.3 Role of Minerals in Obsessive-Compulsive Disorder

There is little data about the levels of minerals in OCD patients. A reduction in levels of magnesium, zinc, and iron has been reported in OCD patients as compared to the control group (Botturi et al. 2020). In contrast, calcium and manganese levels were higher in OCD patients as compared to controls (Shohag et al. 2012). Zinc regulates some neurotransmitters such as NMDA and GABA. In a randomized clinical trial, administration of zinc and fluoxetine for 8 weeks enhanced symptoms of OCD relative to the control group that received placebo and fluoxetine (Sayyah et al. 2012). Selenium is a dietary mineral that has antioxidant properties (Wolonciej et al. 2016). Former research found that OCD patients had lower levels of selenium than the control group. They also established a link between selenium levels and glutathione peroxidase action (Ozdemir et al. 2009). A clinical study showed that administration of a combination of selenium and selective serotonin reuptake inhibitor in 30 OCD patients for 12 weeks enhanced OCD symptoms relative to the control group that received placebo and selective serotonin reuptake inhibitor (Kuygun Karcl and Gül Celik 2020).

15.9 Major Depressive Disorder (MDD)

Depression is a major cause of disability all around the world, and it contributes significantly to the overall global disease burden as well as a considerable economic cost. At least 8–12% of the population suffers from depression at least once in their lives. Depression is characterized by behavioral, psychological, and physical symptoms such as a feeling of worthlessness, guilt, sleep disturbance, weight change, difficulty in concentration, and suicidal tendencies (Küpeli Akkol et al. 2021). Depression is a stress-induced emotional disease that is frequently accompanied by a reduction in monoamines such as norepinephrine and serotonin, a dysfunctional HPA axis, inflammation, oxidative stress, and disrupted immune response (Sandhu et al. 2017). Tricyclic antidepressant drugs and selective serotonin reuptake inhibitors have interactions with other drugs, side effects such as gastrointestinal effects, sexual dysfunction, increased appetite, weight gain, insomnia, drowsiness, fatigue, and prompt suicide (Huang et al. 2019). One of the most promising approaches to avoiding the side effects of these drugs is the consumption of balanced nutrition as an alternative.

15.9.1 Role of Amino acids in Depression

As we hinted above, the underlying cause of MDD is a disturbance in neurotransmitters such as serotonin, dopamine, epinephrine, and norepinephrine. Nutritional

intake of certain AAs affects the synthesis of these neurotransmitters. Tryptophan is the precursor of serotonin. The recommended daily dose of tryptophan is 100 mg three times daily. In a previous study, consumption of a drink free from tryptophan in 15 patients with a history of MDD worsened their symptoms. In contrast, the addition of tryptophan enhanced mood (Khanna et al. 2019). Epinephrine and norepinephrine are synthesized from dopamine. Phenylalanine is the precursor of dopamine. The level of phenylalanine was reduced in patients with MDD relative to control (Teraishi et al. 2018). Tyrosine has been shown to be beneficial in the management of MDD. Administration of L-tyrosine in a rat model of depression ameliorated depressive-like symptoms by restoring levels of norepinephrine in the cerebral cortex (Bulut et al. 2016).

Low levels of tryptophan, tyrosine, methionine, phenylalanine, phenylalanine, tyramine, GABA, and kynurenine are associated with MDD (Van der Does 2001; Parker and Brotchie 2011; Pan et al. 2018; Islam et al. 2020). Conversely, concentrations of leucine, valine, and isoleucine increased in patients with MDD (Fellendorf et al. 2018). A low level of L-histidine has been reported in a patient with anxiety and MDD since L-histidine regulates neurotransmitters (Solís-Ortiz et al. 2021). A higher level of glutamate and glutamine has been related to depression in postmenopausal women (Huang et al. 2020).

15.9.2 Role of Fatty Acids in Depression

Depressed patients had lower SCFA levels than controls, according to clinical evidence (Szczesniak et al. 2016). Butyrate has antidepressant and anti-inflammatory effects, and it also ameliorates depressive-like behavioral changes in mouse models (Valvassori et al. 2015). In comparison to the control group, depressive individuals had lower levels of eicosapentaenoic acid (EPA), DHA, and n-3 PUFA, according to a meta-analysis. There was no statistically significant change in n-6 PUFA or arachidonic acid levels (Lin et al. 2010). The content of n-3 PUFAs in plasma is inversely related to the risk of psychological disorders. A lack of fish and seafood consumption has been linked to a greater incidence of depression (Nabavi et al. 2017). It has also been stated that enough PUFA consumption has benefits for unipolar and bipolar depression (Wu et al. 2015). Dietary administration of omega-3 may protect from depression. Moreover, a reduction of the level of omega-3 has been embroiled in postpartum depression (Sandhu et al. 2017). Administration of omega-3 has been established to improve and ameliorate symptoms of depression in clinical studies (Chang et al. 2020). Administration of eicosapentaenoic acid or DHA for 16 weeks alleviated depression symptoms following the Brief Psychiatric Rating Scale (Robinson et al. 2019). The antidepressant effects of n-3 PUFAs may be contributed to antioxidant properties, adjustment of serotonin, modulation of proinflammatory cytokines, and BDNF (Huang et al. 2019).

15.9.3 Role of Vitamins in Depression

A cross-sectional study revealed that higher consumption of dietary B vitamins was related to a lower incidence of anxiety, depression, and stress symptoms (Mahdavifar et al. 2021). Nicotinamide is the active form of vitamin B3. Wheat, meat, and fish are often high in nicotinamide, but plants are low in nicotinamide. The deficiency of nicotinamide leads to depression. Surprisingly, nicotinamide is neuroprotective and antioxidant at low doses, but at high concentrations, it causes neurotoxicity, particularly dopaminergic toxicity (Williams and Ramsden 2005). More investigation is required to determine the optimum neuroprotective dose of vitamin B3. Vitamin B6 (pyridoxine) affects the serotonergic, glutamatergic, and adrenergic systems. Neurological symptoms of pyridoxine insufficiency include depression (Lotto et al. 2011). Vitamins B9 and B12 participate in the synthesis of monoamines and other vital methylation reactions in the CNS (Gilbody et al. 2007). The deficiency of vitamins B6, B9, and B12 prevents the transformation of homocysteine into methionine, leading to hyperhomocysteinemia that is associated with cytotoxicity, oxidative stress, apoptosis, and ultimately depression (Sangle et al. 2020). Nonetheless, studies considering the effects of vitamin B9 on depression have generated inconclusive findings. An epidemiological study revealed that serum level of vitamin B9 was not related to depression status. However, vitamin B12 deficiency is correlated with a twofold increased risk of severe depression (Penninx et al. 2000). Accordingly, a diet rich in B vitamins could decrease the risk of depression.

Epidemiological studies demonstrated that hypovitaminosis D was related to an 8–14% increased susceptibility of depression (Hoang et al. 2011). Vitamin D could protect the brain from the reduction of serotonin and dopamine (Cass et al. 2006). Moreover, vitamin D could increase serotonin hydroxylase 2 and inhibit tryptophan hydroxylase 1 (Berridge 2013). Vitamin D could also ameliorate depression symptoms by regulating Ca^{2+} concentration. This effect is mediated through overexpression of Na+/Ca^{2+} exchanger 1 (NCX1) and Ca^{2+}-ATPase (PMCA), which remove Ca^{2+}, and parvalbumin, calbindin D-9 k, and calbindin D-28 k, which neutralize Ca^{2+} (Huang et al. 2019).

15.9.4 Role of Minerals in Depression

Zinc is required for neuromodulation and regulation of neurotransmitters involved in MDD, such as dopaminergic, glutaminergic, and serotonergic systems (Yi et al. 2011). It also increases the expression of BDNF (Bitanihirwe and Cunningham 2009). Several epidemiological studies have correlated zinc deficiency with depression (Miki et al. 2015). A meta-analysis indicated that dietary consumption of iron and zinc was connected to a lower incidence of depression (Li et al. 2017). In a previous study investigating the levels of minerals in the rat model of depression, iron, copper, and manganese were found to be increased in the diseased group than

in the control group (Sahin et al. 2021). A magnesium-deficient diet has been related to alterations in the gut microbiota, leading to abnormalities in the gut-brain axis and, as a result, depression in rats (Winther et al. 2015). In depressed patients, magnesium level has been decreased relative to controls (Botturi et al. 2020). Magnesium deficiency has been implicated in disruption of the HPA axis, which is implicated in the pathogenesis of depression and anxiety disorders (Sartori et al. 2012). Magnesium supplements have been suggested to be beneficial in the treatment of MDD. Antidepressant drugs like amitriptyline and sertraline have been reported to increase magnesium levels (Serefko et al. 2013). A systematic review demonstrated that higher magnesium intake was correlated with reduced depression (Derom et al. 2013). Administration of 500 mg of magnesium for 2 months in 46 depressed patients enhanced Beck's test score relative to controls (Afsharfar et al. 2021). Also, prepartum administration of magnesium was correlated with decreased postpartum depression (Miller et al. 2021).

15.10 Bipolar Depression (BPD)

Bipolar disorder (BPD) is a serious, debilitating, and even fatal psychiatric disorder with a genetic origin. Many genes, such as CACNA1A and ANK3, are implicated in the pathogenesis of BPD (Ferreira et al. 2008). BPD is distinguished by a predisposition to mania and episodic depression (Goodwin and Jamison 2007). Physical and psychological stimuli can exacerbate the progression of BPD into a vulnerable stage and provoke mood swings in susceptible individuals (Post and Leverich 2006). Excess acetylcholine receptors are one of the major causes of manic symptoms in BPD (Skutsch 1981). Psychostimulants such as corticosteroids and monoamine depletion can trigger such episodes (Goodwin and Jamison 2007).

15.10.1 Role of Amino Acids in Bipolar Depression

A previous study reported a pronounced increase in the concentration of glycine and glutamate and reduction in tryptophan in 20 patients with BPD as compared with control (Hoekstra et al. 2006). Another recent study found higher levels of alanine and glycine in 83 BPD patients relative to controls (Wan Nasru et al. 2021). A significant association between proline and negative signs of BPD has been addressed (Clelland et al. 2016). A lower level of leucine was found in patients with BPD (Fellendorf et al. 2018). Taurine deficiency is associated with BPD (Beyer and Payne 2016). Lower levels of D-serine and L-serine have been detected in patients with BPD compared to healthy counterparts. D-serine was higher in patients with BPD that were treated with mood stabilizers relative to control, supposing dysregulated metabolism of serine in BPD (Hashimoto 2016).

15.10.2 Role of Fatty Acids in Bipolar Depression

Butyric acid is present in milk, cheese, and butter. Sodium butyrate has been displayed as an anti-inflammatory, antioxidant, histone deacetylase inhibitor in different in vitro and in vivo models of mania (Lei et al. 2016). The deficiency of omega-3 may be associated with BPD (Lakhan and Vieira 2008). Administration of 1 to 2 gm of omega-3 FAs in patients with BPD for 6 months decreased manic/depressive disorders (Osher et al. 2005). In brain autopsy of postmortem patients with BPD, low levels of DHA in the orbital frontal cortex have been detected. Also, DHA was inversely proportional to stearic acid metabolism (McNamara et al. 2008). Administration of omega-3 FAs enhanced depressive symptoms in patients with BPD (Sarris et al. 2011).

15.10.3 Role of Vitamins in Bipolar Depression

The deficiency of vitamin D has been associated with BPD. However, no research has been conducted to investigate the efficacy of vitamin D therapy in BPD (Lakhan and Vieira 2008). Eighty percent of BPD patients are vitamin B deficient. Folate is used effectively in the treatment of BPD. It may affect BPD by improving DNA methylation and regulating neurotransmitter synthesis by modulating S-adenosyl methionine and homocysteine (Crider et al. 2012).

15.10.4 Role of Minerals in Bipolar Depression

Zinc may be involved in the pathogenesis of BPD. An elevated serum zinc level was reported in patients with BPD in the depressive phase relative to controls (Siwek et al. 2016). Another study revealed a nonsignificant difference in serum Zn^{2+} and Cu^{2+} levels in 110 patients with BPD relative to the control group (Styczeń et al. 2018). Another study found lower levels of Zn^{2+} and Se^{2+} and a higher level of Fe^{3+} in patients with BPD as compared to controls (Santa Cruz et al. 2020). Brains from postmortem patients with BPD revealed high levels of Fe^{3+} and Cu^{2+} and a low level of Zn^{2+} relative to controls (Mustak et al. 2010).

15.11 Summary and Conclusion

Psychological well-being is a critical element in improving health, boosting productivity, lowering medical costs, and enhancing the quality of health. Though psychiatric diseases are complicated, and some are multigenic owing to hereditary factors,

research has shown that nutritional elements could mitigate symptoms. In recent years, many studies have demonstrated that dietary nutrition is an intriguing strategy for psychiatric disorder therapy (Bekdash 2021). This book chapter reviews literature investigating the role of dietary nutrition such as AAs, vitamins, and minerals in different psychiatric disorders (Fig. 15.3). It also gives particular attention to SCZ. This chapter also summarized the underlying relationships between nutrition and

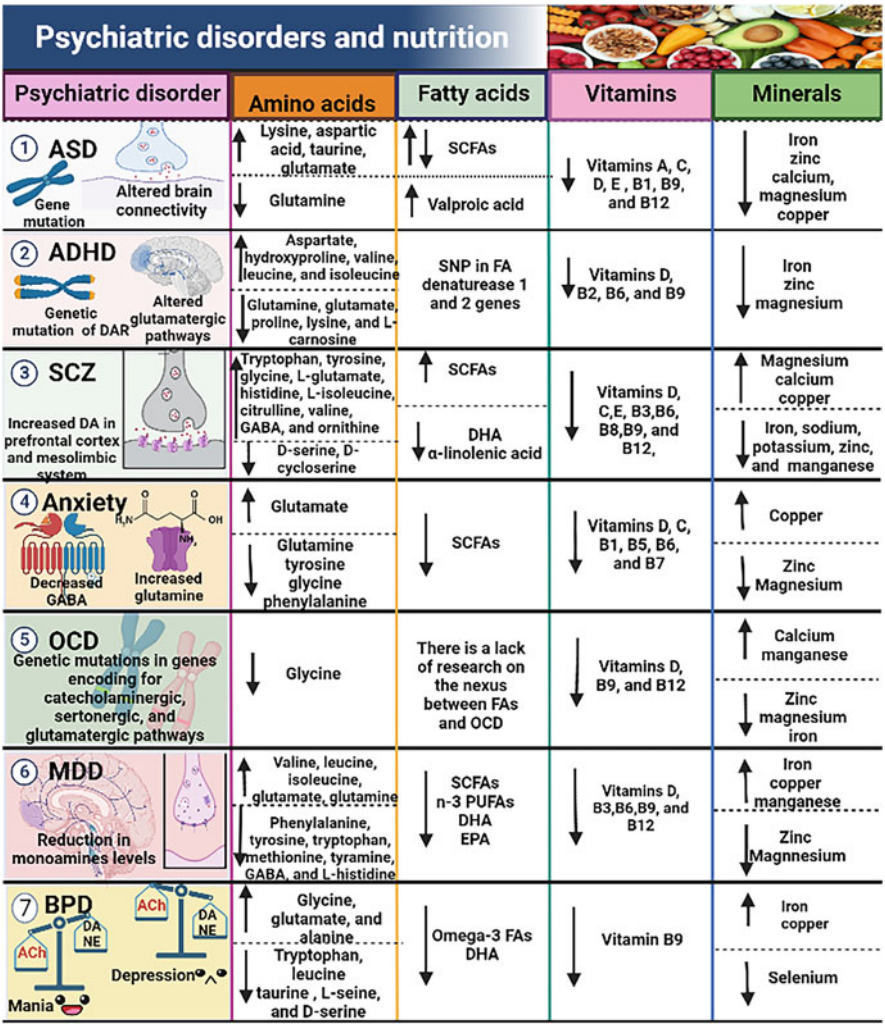

Fig. 15.3 Graphical abstract. *ASD* autism spectrum disorder; *SCFAs* short-chain fatty acids; *ADHD* attention deficit hyperactivity disorder; *SNP* single nucleotide polymorphism; *FA* fatty acid; *SCZ* schizophrenia; *SCFAs* short-chain fatty acids; *DHA* docosahexaenoic acid; *OCD* obsessive-compulsive disorder; *MDD* major depressive disorder; *PUFAs* polyunsaturated fatty acids; *EPA* eicosapentaenoic acid; *BPD* bipolar depression

psychiatric disorders, including metabolic regulation, nutrigenomics, and gut-brain axis. This insight has the potential to enhance individual health outcomes and maybe reduce or prevent disease symptoms. Practitioners should instead use different approaches to understand the etiology of psychiatric diseases, such as epigenetically based strategies to interpret how a particular diet or controlled micronutrient dietary supplements during early life interact with genes and mental health outcomes.

Recent research has revealed the overarching beneficial role of certain gut microbiota such as Akkermansia, Bifidobacterium, and Lactobacillus in mental health. Certain nutrients have been found to boost the proliferation of specific bacterial species, implying that gut bacteria could be guiding human eating preferences. Inter-individual variability in intestinal microbiota could underlie why there is often a variance in results and why one-size-fits-all nutrients are often not appropriate (Delgado et al. 2021). One unanswered scientific concern is what makes an optimum health-promoting microbiota, and how people with different initial microbiota can develop such microflora. Future studies will need to identify the alterations in microbiota composition that precede various psychiatric disorders, as well as the accompanying gene expression profiles relative to nutritional status in both microbiota and host genes. Consequently, determining the whole diet-microbiota interactions will lead to breakthroughs in tailored treatment, personalized nutrition, and development of probiotics suited to the individual.

Although the area of nutritional psychiatry is still in its infancy, it is now receiving extensive investigation, which has resulted in some favorable research findings. Numerous nutrients modify biomarkers as well as molecular pathways involved in the etiology of several mental illnesses, as with many other diseases, and this can be effective in controlling disease development, including prevention. While the exact mechanisms of many nutritional therapies remain unclear, the evidence-based strategy justifies the use and recognition of nutrition in the treatment of psychiatric diseases. This could drive corrective approaches using dietary nutrients that may hold promise for the avoidance of psychiatric disorders and their progression. According to this viewpoint, the approach of a personalized diet may be effective for identifying individuals who may benefit from nutrients that improve brain functions in health and disease.

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Chapter 16
High-Fat Diet and Psychiatric Disorders: What Is the Interplay?

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Contents

Abstract Many neurological conditions have been treated using diet and metabolic therapy, including epilepsy, headaches, neurotrauma, Alzheimer's, Parkinsonism, and sleep disorders. Both the lack of efficacy of pharmacological treatments and an inherent attraction to a more "natural" approach motivate people to use diverse nutrition to treat—or moreover relieve the symptoms of—such diseases. Using a low-carbohydrate, high-fat diet, the ketogenic diet has been around for over a century to treat children with refractory epilepsy. Research on a ketogenic diet for various metabolic, neurological, and neurodevelopmental diseases has lately increased in prominence. This thorough chapter objectively examines the possible therapeutic benefits of a ketogenic diet and ketogenic agents on neuropsychiatric and mental illnesses in humans and translationally viable animal models. According to preclinical studies, there is remarkable corroboration in the involvement of ketogenic diet in the treatment of a number of neuropsychiatric conditions in animals. There is some promising clinical evidence in the areas of schizophrenia, psychosis, and

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autism spectrum disorders, but it is restricted to case studies and pilot trials. The lack of randomized, controlled clinical trials makes it impossible to come to a definitive judgement regarding the efficacy of the ketogenic diet in the treatment of psychiatric diseases. This wide range of pathology suggests that energy metabolism, oxidative stress, and immune/inflammatory processes are all possible targets for ketogenic therapy in these conditions. While preclinical evidence suggests that the ketogenic diet and related compounds may be effective in treating a number of neurological and mental illnesses, more research, particularly randomized controlled clinical trials, is needed to determine their clinical usefulness and any possible side effects.

Keywords Ketogenic diet · Neuropsychiatric disease · Autism spectrum disorder · Schizophrenia · Oxidative stress · Energy metabolism · Inflammatory processes

16.1 Introduction

For millennia, people have relied on dietary therapy to heal a wide range of ailments. Hippocrates and Galen, two of the most prominent ancient Greek physicians, both held the view that one's diet had the potential to either cause or treat disease. A ketogenic diet-like metabolic state was recommended by the ancient Greeks as a treatment for a wide range of conditions, including seizures. Long-chain triglycerides and low-carbohydrate diets are the main components of the ketogenic diet (Bough and Rho 2007).

As a consequence, a ketogenic diet lowers both the amount of insulin in circulation and the amount of insulin signaling, which leads to a change in the body's metabolism toward the consumption of fatty acids (Paoli et al. 2013). Ketone bodies, including ß-hydroxybutyrate, are produced by dietary intake and provide an alternate energy origin for glucose, which is specifically relevant to the energy utilization in the brain because fatty acids are rarely utilized as an energy resource in the brain (Bough and Rho 2007; Hartman et al. 2007).

There are numerous studies which have revealed that the ketogenic diet has a wide range of effects on metabolic functions such as reduction in body weight, glucose tolerance, and low-density lipoproteins (LDL), as well as triglycerides, cholesterol, and insulin (Cunnane et al. 2002; Dashti et al. 2004; Cantello et al. 2007; Yudkoff et al. 2001), and by increasing high-density lipoproteins (HDL). The ketogenic diet (KD) has been found to be an effective treatment for epilepsy that is resistant to drugs (Vining et al. 1998; Neal et al. 2008; Yancy Jr. et al. 2005).

Despite the fact that the mechanisms underlying its anti-seizure effects are still not fully known (Hartman et al. 2007; Bough and Stafstrom 2010; Rho and Stafstrom 2011), increasing experimental evidence points to its broad neuroprotective capabilities, with new researches supporting its usage in many neuron-related disorders (Baranano and Hartman 2008). Clinical trials have shown that patients with fits and absence seizures who have been seizure-free on the KD for

2 years can safely cease their anticonvulsant drugs and the diet without experiencing a return of their paroxysm (Freeman et al. 2007).

This fascinating clinical evaluation serves as a foundation for a concept that the KD may show qualities that inhibit the development of epileptic seizures. Research on the ketogenic diet has shown some encouraging results in the therapy of myocardial illnesses (Cantello et al. 2007; Cunnane et al. 2002; Modan et al. 1985; Reilly et al. 2003; Sumithran et al. 2013; Thio et al. 2006; Yudkoff et al. 2001), cancer (Wright and Simone 2016), brain damage (Stafstrom and Rho 2012), and glioblastoma (Seyfried and Mukherjee 2005). Since the 1920s, doctors have been using the ketogenic diet to treat medically refractory pediatric epilepsy.

Ketogenic diet had fallen out of favor following the invention of anticonvulsant medicines; nevertheless, the rise of drug resistance in the 1990s led to the comeback of KD as a therapy for childhood epilepsies. Recent meta-analyses conveyed to the idea that a KD can help treat the symptoms of this illness (Youngson et al. 2017; Zhang et al. 2018). This extensive chapter centers on the usage of ketogenic intake for a number of CNS diseases in both humans and animals. We conduct a literature review on the efficacy of ketogenic ingredients, focusing on the mechanisms underlying their therapeutic effects.

16.2 Involvement of KD in Neuroprotection

Researchers have uncovered a plethora of potential pathways in the KD that may be responsible for its neuroprotective effect during the course of the past 10 years. However, even if detailed examination of these pathways is included in the chapter, a brief review is needed because it has a common trait of consecutive destruction of neurons followed by cellular bioenergetic failure (Gasior et al. 2006; Acharya et al. 2008; Masino and Geiger 2008).

An increase in the generation of ketone bodies by the hepatocytes and a decrease in blood sugar levels are two distinguishing characteristics of the ketogenic diet treatment. Ketone levels rise primarily as a result of the breakdown of fatty acids. It has been demonstrated that ketone bodies, on their own, possess neuroprotective effects. These qualities include an increase in ATP levels, a reduction in ROS production via improved oxidation via oxidative enzymes, and a suppression of mitochondrial transformation (Kim et al. 2007). In a manner that is analogous to the enhancement of bioenergetics, it has been demonstrated that the KD promotes the synthesis of mitochondria, which ultimately results in the maintenance of synaptic physiology (Bough et al. 2006). The second main neurochemical hallmark of KD is a limited glycolytic flow, which occurs during the disease.

Glycylation reduction is a key component of less energy storage, which has been proven to reduce convulsions (Greene et al. 2001) and extend the longevity of many species, including monkeys (Kemnitz 2011; Redman and Ravussin 2011). Although the link between reduced energy storage and KD intake is still debatable (Yamada 2008; Maalouf et al. 2009), it is undeniable that both treatments result in a lower

blood glucose level, most likely due to a reduction in the amount of glycolytic flux. 2-Deoxy-D-glucose (2DG), a sugar analogue that inhibits phosphor-glucose isomerase and thus glycolysis, has been demonstrated to suppress epileptogenesis in the rat kindling model by reducing the expression of brain-derived neurotrophic factor (BDNF) and its primary receptor, tyrosinase B (Garriga-Canut et al. 2006). There are a number of other key processes that contribute to the neuroprotective effects of calorie restriction. These mechanisms include better mitochondrial function and lower oxidative stress (equivalent to that seen with ketones and PUFAs), decreased activity of pro-apoptotic proteins, and suppression of inflammatory mediators such as interleukins and tumor necrosis factor alpha (Maalouf et al. 2009).

These mechanisms all work together to produce the neuroprotective effects of calorie. After all is said and done, the KD's neuroprotective qualities are likely due to a variety of additional processes. It is known that the majority of these pathways are primarily related to the anticonvulsant effects of the KD; nevertheless, some of them, if not all of them, could contribute to the maintenance of cellular balance followed by prevention of neuronal injury or dysfunction. Moreover, it is possible that unrecognized processes may be at work in disorders other than epilepsy, and this potential provides new avenues for studying the pleiotropic effects of this metabolism-based treatment at a molecular level.

16.3 Neuroprotective Role of Ketogenic Diet in Various Neuropsychiatric Disorders

16.3.1 Anxiety and Depression

It has been postulated that the KD has mood-stabilizing characteristics (El-Mallakh and Paskitti 2001); however, as of the time of this writing, no clinical investigations have been carried out to test the hypothesis. The possible involvement of the KD in anxiety has been investigated using the forced choice model of depression in rats, which resulted in a therapeutic effect that was comparable to that provided by conventional antidepressants (Murphy et al. 2004; Murphy and Burnham 2006).

There are currently no clinical studies for analyzing the effects of a ketogenic diet on anxiety and serious depression. For the purpose of this study, researchers examined the behavioral effects of prenatal ketogenic diet exposure. Sussman and his colleagues fed CD-1 pregnant mice a regular diet or a ketogenic diet. When the pups were 21 days old, half of them were MRI-scanned, and the other half were assessed for behavioral traits at 8 weeks. In comparison to offspring raised on a regular diet, those exposed to the ketogenic diet during pregnancy had lower levels of activity and anxiety, as well as decreased depressive-like behavior. In a study, adult offspring exposed to a ketogenic diet prenatally showed bilateral increases in various parts of the brain (Sussman et al. 2013). For 7 days, 40 Wistar rats were fed either a normal diet or a ketogenic diet (Murphy et al. 2004).

Animals fed a ketogenic diet were found to be more active (Murphy et al. 2004). Ketogenic agents have been shown to have a variety of distinct effects on rats, including Sprague-Dawley and WAG/Rij rats. Ketone derivatives combined with triglycerides were administered to Sprague-Dawley rats at both chronic and subchronic doses (KSMCT). In both strains of rats, chronic administration of KSMCT and subchronic ketone monoester both showed anxiolytic effects (Ari et al. 2016). Animals administered with BHB and LY294002 intracerebroventricularly in in vivo studies reduced microglial process elongation. Moreover, GPR109a does not play a role in BHB's in vitro effect on microglial cell morphology. However, suppression of histone deacetylases was associated with BHB's effects on microglial morphology change. Histone H3 and H4 acetylation was elevated in cells treated with BHB and a histone deacetylase inhibitor (Huang et al. 2018).

Pro-inflammatory cytokines were reduced in cells treated with lipopolysaccharides (BHB) and LY294002 (protein kinase B inhibitor) that had been exposed to lipopolysaccharides, BHB, and LY294002. An acute LPS-induced depression model and a chronic stress protocol were used in this study to examine the effects of BHB administration over 3 days, and the results showed that BHB was effective even in long-term depression models. BHB was able to normalize symptoms in models of depression. BHB's antidepressant impact was eliminated by LY294002 suppression of protein kinase B, which prevented BHB's enhanced phosphorylation of protein kinase B. LY294002 reversed BHB's pro-ramification actions in mice treated with lipopolysaccharides and under prolonged stress (Huang et al. 2018).

In clinical reports, the ketogenic diet has not yet been studied for depression. Anxiety and depression-like behaviors were reduced by the ketogenic diet. BHB was able to ameliorate major depression in combination with reduction in inflammation in the chronic stress and lipopolysaccharides. Preclinical evidence suggests that ketogenic medications may be an effective therapy for depression (Huang et al. 2018; Murphy et al. 2004; Sussman et al. 2013).

16.3.2 Autism

Autism is a neurological condition that impairs a person's ability to communicate verbally and socially (Ciernia and LaSalle 2016; Fuccillo 2016; Hampson and Blatt 2015; Li and Zhou 2016). No particular medicine exists for social deficiencies and repetitive behaviors; therefore treatment choices follow initiatives and/or antipsychotic therapy (Anagnostou et al. 2014; Kern et al. 2015). Chronic neuronal injury and altered ATP production are two of the numerous potential processes that have been postulated to lay at the root of some parts of the pathophysiology of autism spectrum disorder (ASD). These components may be prone to responding favorably to a therapeutic KD (Herbert and Buckley 2013; Kern et al. 2015; Rho 2017).

The benefits of a modified gluten-free ketogenic diet supplemented with medium-chain triglycerides, which resulted in ketosis, were investigated for 3 months in

15 children diagnosed with autism spectrum disorder (ASD) in a small clinical trial. Children's comparison scores, total scores, and social affect categories on the Autism Diagnostic Observation Schedule improved significantly after 3 months of treatment, as did imitation and physical function on the Childhood Autism Rating Scale. On the Autism Diagnostic Observation Schedule, ten of these people were still exhibiting evidence of improvement 6 months later. Restricted and repetitive behaviors, on the other hand, did not demonstrate any differences. Supervisors noticed changes in socializing, memory, and hyperactivity.

Regardless of the fact that these medical trials indicate the efficacy of ketogenic therapy in the treatment of ASD, they are restricted by small sample sizes and lack of appropriate controls. A number of preclinical studies using mutant mouse models have looked into the ketogenic diet (Newell et al. 2016; Verpeut et al. 2016). Young Black and Tan BrachyuryT+tf/j (BTBR) and wild-type littermates were fed either a regular or a ketogenic diet, which resulted in metabolic ketosis. The ketogenic diet was able to normalize BTBR mice's aberrant behaviors, such as reduced sociability, increased repetitive behavior, and diminished social communication. As shown by the findings of this trial, the ketogenic diet reversed all signs of ASD in BTBR mice (Ruskin et al. 2013). The risk of their child developing autism spectrum disorder (ASD) rises when pregnant women take VPA, making it an appropriate rodent model (Mabunga et al. 2015).

The male offspring of dams treated with VPA were allocated randomly to a standard diet or a ketogenic diet, both of which resulted in ketosis. VPA offspring had a higher nociceptive threshold, more repetitive activity, more grooming behavior, poor social abilities, and abnormal social memory (Castro et al. 2017). All of the VPA-induced actions were able to be inhibited by following a ketogenic diet (Castro et al. 2017). Gender differences were identified when the autistic seizure-prone EL (epilepsy 1 gene) mutant mice were submitted to a rigorous behavioral assessment. A ketogenic diet cured both reduced sociability and increased home cage grooming. However, this experiment had no effect on public acceptance or propagation of dietary preferences (Ruskin et al. 2017a).

When EL female mice were fed a 6:1 ketogenic diet, social recognition improved and grooming (a three-chamber test of sociability) decreased since there was no target mouse present. Maternal immunological stimulation has been suggested as a viable animal study for autism spectrum disease. Following intraperitoneal infusions of polyinosinic-polycytidylic acid, all C57Bl/6 pregnant females were randomized to receive either a conventional diet or a ketogenic diet (PIPCA). Following the ketogenic diet, male offspring's sociability and grooming behaviors became more normal (Ruskin et al. 2017b). Every group preferred the new mouse in the social novelty task, which was part of a three-chamber test of sociability. The response to changes of food choice task remained unchanged (Ruskin et al. 2017b).

These findings imply that a ketogenic diet can help cure ASD-like behavioral phenotypes by increasing sociability and decreasing repetitive behavior. The following study investigated the possible impact of a ketogenic diet on the neurobiology of autism spectrum disorders. In human experiments, the ketogenic diet has been proven to be effective in the management of social inadequacies, problems with

communication, and repetitive behavior patterns (Evangeliou et al. 2003; Herbert and Buckley 2013). This has also been discovered in the animal models of ASD (Ahn et al. 2014; Castro et al. 2017; Ruskin et al. 2013, 2017a, b; Verpeut et al. 2016). A ketogenic diet also reduces cortical excitability, recovers bioenergetic dysfunctions (Ahn et al. 2014), improves myelin formation and white matter growth (Mychasiuk and Rho 2017), and improves intestinal flora (Newell et al. 2016).

16.3.3 Attention Deficit Hyperactivity Disorder (ADHD)

Attention deficit hyperactivity disorder (ADHD) is the most common type of pediatric mental problem, according to multiple recent studies (Dutra et al. 2016). Impaired neurotransmission and reduced metabolism in the prefrontal cortex cause symptoms such as restlessness, impatience, and lack of attention in children with ADHD (Dutra et al. 2016; Howard et al. 2011; Thapar and Cooper 2016; Wilens et al. 2002). In the treatment of ADHD, psychostimulants such as methylphenidate and d-amphetamine have been used to increase catecholamine release (Faraone and Buitelaar 2010). The noradrenaline reuptake inhibitor is another possibility, but it comes with a slew of drawbacks (Thapar and Cooper 2016). Despite the fact that no human studies have looked at the effect of a keto on ADHD, a case study looked at the behavior and growth of children with severe seizures before they started a ketogenic diet. After a year on the ketogenic diet, seizure frequency dropped drastically. After following a ketogenic diet, children who had aberrant emotional and behavioral responses at the outset of the experiment but did not get a medical diagnosis of ADHD saw significant improvements in motor control, personality skills, attention, and social skills (Pulsifer et al. 2001).

According to one study, a ketogenic diet can help youngsters with ADHD-like symptoms and abnormal emotional and behavioral activities (Pulsifer et al. 2001). As a result, more research is needed to assess the usefulness of a ketogenic diet in treating ADHD. Despite various preclinical studies showing the effects of a ketogenic diet on overall rat behavior, the interpretation of such findings is limited because of the lack of suitable ADHD experimental animals (Kraeuter et al. 2015). After 7 days on a ketogenic diet, Long-Evans rats' exploration and activity were significantly reduced (Murphy and Burnham 2006). Due to the paucity of data to support metabolic ketosis, this study should be considered with care. Wistar rats were fed a conventional diet, a balanced ketogenic diet, and a standard diet for 18–19 days in a different study. The ketogenic diet made all rats less active than the usual diet (Murphy et al. 2005).

Control rats spent substantially more time grooming and much less time exploring than ketogenic diet rats, indicating dose-dependent inhibition and inappropriate behavior (Murphy et al. 2005). The majority of data now supports the use of a ketogenic diet to treat hyperactivity. These researches did not explore other indications of ADHD than impulsivity and attention problems, making it difficult to generalize the findings to ADHD therapy. According to a recent seizure study,

ketogenic diets have demonstrated considerable efficacy in the treatment of partial seizures (Murphy and Burnham 2006; Murphy et al. 2005; Packer et al. 2016). A ketogenic diet has been found to aid humans by reducing hyperactivity and inappropriate behavior in animal studies. To investigate the impact of a ketogenic diet on ADHD symptoms, human clinical studies and animal models of ADHD should be done.

16.3.4 Schizophrenia

Schizophrenia is a long-term, lifelong psychiatric condition with three main kinds of symptoms: positive, negative, and cognitive symptoms (Evensen et al. 2016). Antipsychotic drugs only help with positive symptoms in a limited way, and they come with a slew of negative side effects, including metabolic syndrome and eventual cardiovascular problems (Girgis et al. 2008; Lindenmayer et al. 2003; Melkersson and Dahl 2003; Zhang et al. 2004). Schizophrenia patients' brains exhibit an abnormal glucose metabolism, according to neuroimaging, postmortem samples, and animal research (Beasley et al. 2009; Dwyer et al. 2001; Fujimoto et al. 2007; Krivoy et al. 2008). Insulin resistance (Harris et al. 2013), decreased pyruvate and ATP synthesis, elevated lactate levels (Du et al. 2014), and a deterioration in glucose metabolism have all been observed in the inferior and lateral frontal lobes, respectively (Martins-de-Souza et al. 2010). As a result, a ketogenic diet could be able to bypass glucose metabolism entirely, instead relying on ketone bodies as a fuel source.

Several case studies have suggested that the ketogenic diet could be used to treat schizophrenia. Ten female patients with severe chronic treatment-resistant schizophrenia were studied in the limitations of a small clinical trial (Pacheco et al. 1965). Patients exhibited significant reductions in symptoms following a 2-week ketogenic diet, as judged by the Nursing Checklist and the Minimal Social Behavior Scale. Seven people's symptoms deteriorated after they stopped eating, but they were more controlled than they were at the start of the study (Pacheco et al. 1965). After 7 days, a treatment-resistant patient with severe chronic schizophrenia that adopted a ketogenic diet began to show symptoms of recovery, including increased energy and an overall sense of well-being (Kraft and Westman 2009). She said that she had no longer experienced any hallucinations after a 1-year period (Kraft and Westman 2009). After a 1-year follow-up period for the male patient and 4 months for the female patient, both patients exhibited significant improvement on the Positive and Negative Syndrome Scale (PANSS). When the individuals were not in ketosis, however, symptoms progressively deteriorated until ketosis was achieved. Two more case studies were published in 2019 that looked at the long-term effects of the ketogenic diet. These examinations took place during a 5- and 12-year period, respectively (Palmer et al. 2019).

The effects of a ketogenic diet on opposite-sex twins were recently investigated for 6 weeks. Throughout the study, the patients struggled to stick to the food plan

and hence failed to enter ketosis for long periods of time. Both patients' PANSS scores dropped considerably after ceasing the ketogenic diet, and their overall psychopathology improved (Gilbert-Jaramillo et al. 2018). A ketogenic diet seems to have potential results for persons suffering from psychosis. In a schizophrenic mouse model, Kraeuter and his colleagues discovered that a ketogenic diet alleviated positive and negative symptoms as well as cognitive deficiencies (Kraeuter et al. 2015, 2019).

In summary, case reports on people with schizophrenia and schizoaffective disorder found that the ketogenic diet was beneficial in improving clinical symptoms and quality of life; however there were some compliance issues. A ketogenic diet has been demonstrated to effectively cure a wide spectrum of schizophrenia-like disorders in preclinical studies (Sarnyai et al. 2019).

16.3.5 Obsessive-Compulsive Disorder

The ketogenic diet (KD), now a popular fad diet, is a high-fat, low-carbohydrate diet that has been used to treat refractory epilepsy for years. In animal models, aging, obsessive-compulsive disorder, and autism are among the newest therapy options for KD. These diseases have been associated to life-threatening and stigmatizing stereotypic behaviors (repetitive, unchanging behaviors with no apparent function). However, little is known about their underlying mechanisms, and there are no active pharmaceutical treatments available at this time. In an inbred mouse strain (FVBN/J) with a prominent repetitive circling behavior, Beltramini et al. 2020, explain how KD can be used to reduce biased behavior. Beltramini et al. 2020, found that a 3-week treatment with KD reduced overall stereotypic behavior in aged (18 months) mice in Experiment 1. In Experiment 2 ($N = 14$ cages), adult (6–8 months) females were matched to keep a "spinner" mouse and a non-spinning control mouse together. Using an ABAB design, the author examined stereotypic behavior between evaluation periods on a standard food diet and a KD. These data imply that stereotypic behavior is influenced by timing and diet.

16.3.6 Bipolar Disorder

Bipolar disease (BD) is a polygenic, episodic mood disorder marked by manic and depressed episodes that can last a lifetime. For the treatment of BD symptoms in the early stages of the infection, mood stabilizers and antipsychotics should be administered jointly (Grande et al. 2016; Vallarino et al. 2015). Some of the BD's hypothesized causes, such as inflammation and apoptosis, as well as mitochondrial abnormalities, may be prevented by following a ketogenic diet. As a result, the efficacy of case studies that were presented varies.

The first case study looked at two female BD-II patients on lamotrigine who were resistant to treatment. Both individuals said that being in a state of high ketosis helped them feel better. One patient reported feeling calmer, more confident, and kinder to others as a result of the treatment. Two patients were taken off lamotrigine, but when their ketone levels dropped, one of them restarted it (Phelps et al. 2013).

The effects of the ketogenic diet were less equivocal in a patient with early-onset increased blood pressure who subsequently had manic-depressive episodes that alternated. The patient did not improve on a ketogenic diet, likely because ketosis was not maintained. To get the body into ketosis, medium-chain triglyceride oil was used instead of dietary fats. However, there was no proof of urine ketosis or clinical improvement after a month (Yaroslavsky et al. 2002).

Finally, the results of these studies are mixed, with two indicating a beneficial response to the ketogenic diet and one indicating no effect. The challenge is most likely attributable to the lack of preclinical evidence. The difficulties of mimicking bipolar disease in animal research are most likely due to the lack of preclinical data.

16.4 Conclusion

According to this comprehensive review of the research, ketogenic therapies have been shown to be beneficial in a range of psychiatric diseases. Despite the availability of a number of mechanistic ideas, such as those mentioned here, future study into potential paths of ketogenic therapy for these severe disorders is hampered by a dearth of suitable animal studies in these severe disorders. The ketogenic diet has a high rate of noncompliance. These preclinical findings (Gasior et al. 2006; Maalouf et al. 2009) are largely based on the fundamental idea that metabolic changes can contribute to restorative benefits. Toward what extent may changing one's diet help with illnesses with such a wide range of pathophysiological mechanisms? Changes in energy metabolism appear to be a recurring theme. While the mechanisms by which the KD causes these effects are likely to be diverse (Rho and Stafstrom 2011), one or more mechanistically comparable pathways may exist. Finally, the precise processes by which altered metabolism reduces neuronal excitability, avoids further neurotoxicity, or negates cognitive deficits remain unknown.

As a result, future research should concentrate on substances that mimic the effects of a ketogenic diet, such as BHB, ketone monoesters, triheptanoin, and caprylic triglycerides. There is no research on their impact in brain conditions at the moment. Future research, particularly in human trials, should give more full information of dietary patterns and reporting of glucose levels and ketone levels to allow us to compare and evaluate studies (Zilberter and Zilberter 2018). More scientific proof investigation on the modes of action of the keto diet and ketogenic medicines is needed to better inform researchers and practitioners. Most importantly, there are yet no randomized, controlled clinical studies in the literature to investigate the efficacy of ketogenic therapy in mental diseases.

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