Principles of Neurochemistry

Fundamentals and Applications

Bijo Mathew
Della Grace Thomas Parambi
Editors

Springer

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Preface

The first neurochemist ***Thudichum***, in his early days, defined neurochemistry as the branch of science devoted only to neurochemicals. Over the years this definition lost its identity and researches have moved far beyond from this holistic approach because of the improved technology. This new diversity of technology has given more focus on the emerging disciplines of neuroscience branches like neurophysiology and neuropharmacology. However, the perspective of the neurochemist remains the same as molecules form the foundation from which all the studies of the nervous system emerge.

The first edition of "***Principles of Neurochemistry: Fundamentals and Applications***" emphasizes our belief that the increased knowledge and basics of neurochemistry will ultimately lead to an understanding of the coding experiences that relate to the human behavior and mind. Advances in the field of neurochemistry and flourishing it derive from correlations among neurological events in multiple levels and also encourage fetching new knowledge in the field of neurobiology. This book is a copious set of ten chapters written by eminent academicians, researchers, and scientists who were engaged in neurochemical research. We believe that this book can enhance the basic knowledge and succinct and thorough understanding of the basics of neurochemistry and neuropharmacology with important neurodegenerative diseases with an excellent presentation.

This book is mainly intended for professionals, academicians, students, researchers, scientists, and industrialists around the world. Biomedical, health, and life science departments can use this book as a crucial textbook. Researchers and scientists from research institutes can use this book as efficient research info. Pharmacists, physicians, and other healthcare professionals can use this book as a complete reference book. Furthermore, for interested readers, this book is a storehouse of knowledge to comprehend the fundamentals of basic principles of neurochemistry. The organizations of this book provide a profound knowledge and also maintain the reader's interest.

This book contains ten chapters with two parts as (i) Basics of Neurochemistry and (ii) Revisiting Neurodegenerative Diseases.

Chapter 1 is Molecular Biology of the Nervous System, which describes the dynamic nature of the brain, colossal network of neurons, resting membrane potential, action potential and propagation of action potential, synapses, synaptic transmission, synaptic cleft, and neuropeptides. This chapter serves as a brief introduction to neurotransmission and the many types of neurotransmitters.

Chapter 2 is Basics of Neurotransmitters and Signal Transmission, and this chapter illustrates the chemical makeup of the brain and endogenous agents involved in CNS which are capable of modulating the chemical makeup in brain and are used in pharmacotherapy for their wide range of therapeutic benefits.

Chapter 3 is Chemistry of Psychopharmaceuticals, Neurochemicals, and Neuropeptides, and it also deals with how psychopharmaceuticals, neuropeptides, and neurochemicals affect the function of neurons, synapses, and neural networks by binding to different receptors and produce changes in brain-behavioral conditions.

Chapter 4 is Role of Chemical Agents in Nervous System: A Paradigm. This chapter enlightens the various aspects of neuromodulators like dopamine, GABA receptors, glutamate, noradrenaline, and serotonin that are involved in controlling the major functions of the body. This also deals with various theories of the chemical transmitters of the nerve impulses and their neurosecretions with a broad text of the metabolism and degradation.

Chapter 5 is Pathophysiology of Neurodegenerative Diseases: Basics to Advanced. This chapter illustrates the underlying pathological mechanisms behind diseases like Alzheimer's disease (AD) and Parkinson's disease (PD) that are the most common types. Other examples include Huntington's disease (HD), motor neuron diseases (MND), spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), and prion disease.

Chapter 6 is Current Perspectives in the Management of Neurodegenerative Alzheimer's Disease: Preclinical and Clinical Status. This mainly focuses on the pathophysiology of AD, drug targets, amyloid peptide-targeted drugs, tau protein-targeted drugs, neurotrophin-based drugs, multitargeted drugs, and mitochondrial targeted drugs. This chapter also deals with the relationship of neurochemical alteration and restoration strategy of neuron in AD, advantages and disadvantages of AD drug therapy, and future challenges too.

Chapter 7 is Revisiting the Alzheimer's Disease. This chapter speaks about the need for AD for the development of targeted and effective drug delivery as the number of these patients continues to increase. It also deals with the classification of AD, three major hypotheses proposed to explain AD pathology, current treatment modality, potential therapeutic interventions and animal models, clinical diagnosis, potential biomarkers, and recent clinical trials.

Chapter 8 is Advancement and Challenges in the Treatment of Parkinson's Disease (PD): A Recent Outlook. This chapter emphasizes the alternative approaches, strategies, studies, and researches that have been pursued in various areas in the treatment of PD. Authors also emphasize the need for exploring the new therapeutic approaches like cell transplantation therapy and gene engineering to meet the challenges.

Chapter 9 is Post-traumatic Disorders (PTSD), and PTSD is a common mental and psychological instability among different kinds of population that needs much interest and professional care of both psychotherapy and pharmacotherapy. This chapter mainly deals with the clinical picture of PTSD, categories of post-traumatic stress disorders, pathophysiology and biological features, management, counseling, and pharmacotherapy of PTSD.

Chapter 10 is Neuropharmacology: Looking Forward to the Future. This review illustrates the different approaches like omics technology, neural engineering, stem cells, gene therapy, and antiviral therapies for the successful understanding of the pathology of disease that leads to the discovery of medicines without side effects.

This book is a detailed excursion on the basics of the nervous system with detailed characterizations of chemical constituents of the nervous system, revisiting the topics like neurodegenerative disorders like AD, PD, PTSD, and neuropharmacology. We expect that readers shall find this book informative and profoundly useful. The editors are ebulliently ready to accept any comment, suggestion, advice, or critique.

Pallakad, India — Bijo Mathew
Sakaka, Saudi Arabia — Della Grace Thomas Parambi

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Bijo Mathew, MPharm, PhD is associate professor of Pharmaceutical Chemistry at the Ahalia School of Pharmacy, Palakkad, India. Dr. Bijo Mathew obtained his M.Pharm in Pharmaceutical Chemistry from The Tamilnadu Dr. M.G.R. Medical University, Tamilnadu, India in 2008 and Ph.D. in Pharmaceutical Sciences from Jawaharlal Nehru Technological University, Hyderabad, India in 2016. Mathew's primary areas of focus are in drug discovery of neurodegenerative disorders, cancer and molecular modelling. His main research interest is on the design of enzyme inhibitors, and especially monoamine oxidase and acetylcholinesterase inhibitors. He has published 130 papers, [h-index = 24; the number of citations: 1541 in Google scholar; h-index = 21; the number of citations: 1205 in Scopus [August 2020]. With 12 years of teaching and research experience, Mathew authored 1 book, 1 edited book, 5 book chapters and 23 invited talk in national and international level. Dr. B. Mathew serving as a chief executive guest editor of the journals of current drug targets and combinatorial chemistry and high throughput screening. He is a Section Editor of the journal of Coronaviruses [Bentham Science]. He received one patent from Korean Intellectual Property of Office in the topic of protective or therapeutic compositions of neurological disorders containing furano chalcones as effective agents.

Della Grace Thomas Parambi has 16 years of experience in the field of pharmacy education, and is currently serving as an Assistant Professor at the Faculty of Pharmacy, Jouf University, Saudi Arabia. For the past 8 years, her efforts have focused on the development of analytical methods and validation of synthetic, bio-, and phytomolecules using LC-MS/MS, UPLC, HPTLC, and spectrofluorimetric techniques. She has received several grants from various agencies of the Indian Government (Indian Council for Medical Research, Department of Science and Technology, and the Council of Scientific and Industrial Research).

Part I

Basics of Neurochemistry

Molecular Biology of Nervous System

M. K. Unnikrishnan, Akash Marathakam,
and Vimal Mathew

Abstract

Brain is the most complex organ in the body, and the nervous system, the knottiest enigma. The human brain has over a hundred billion neurons. More than the number of neurons, the complexity of the nervous system has more to do with how these neurons are connected to each other. The mind is believed to be the result of what the brain "does." But the neuronal microstructure of the brain is not architecturally static. The complexity runs deep. The dynamic nature of the brain allows it to be altered continuously throughout life, impelled by the very same mind that the brain creates. Thus, while mind is the functional result of the brain, the brain is also, at least partly, the construct of the mind's experiences, thoughts, and executive functions. This chapter is intended to serve as a brief introduction to neurotransmission and the many types of neurotransmitters.

1 Neurons

Neurons are the functional units of the nervous system. Brain processes information with the help of a colossal network of neurons that receive, process, integrate, and transmit bits of information [1]. A neuron can have multiple dendrites through

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B. Mathew, D. G. Thomas Parambi (eds.), *Principles of Neurochemistry*,
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which inputs enter but has only a single axon which sends out signals. Inputs from other neurons enter the neuron through these multiple dendrites. As many as hundreds of thousands of such neuronal signals could enter a given neuron through its many dendrites. The output signals exit the cell through the lone axon, and keep communicating with other neurons and various body parts. The consolidation and summation of the myriad signals that a neuron receives constitute a mind-boggling computational challenge [2]. There is considerable complexity in neuronal processing, both temporally and spatially. The output signal generated through the single axon is further capable of branching into hundreds of individual units (telodendria) that link up with the dendrites of other neurons.

Neurons are discrete cellular entities that share a lot in common with other cells of the body. The essential difference lies in the manner in which neurons are linked together into functional aggregates. The neuronal network is discontinuous, and yet constitutes a well-connected, functionally integrated, purposeful entity [3]. The structural discontinuity between the preceding axon and succeeding dendrite is the gap called synapse. Transferring information across the synapse is a very complex and elaborate phenomenon that comprises multiple molecular mediators and elaborates signal transduction devices. Synaptic transmission is critical for processing the inputs from the preceding axons. Signals emanating from each axon can divide into multiple branches and in turn feed multiple neurons downstream, eliciting further complexity in neuronal processing, output, and outcome behaviors. Synaptic transmission is based on the computational sum of inputs from multiple dendrites and is critical to decision-making in the nervous system [4]. Not all axons end up in a synapse; some are wired to a body part, eliciting purposeful responses such as muscular movement, glandular secretion, and metabolic functions. The nervous system embraces planning, decision-making, and executive action in a harmoniously synchronized manner. The complexity of neuronal wiring in the brain is mind-boggling. There are synapses between the axon and its own dendrites (Fig. 1).

Neurons communicate using both chemical and electrical signals. While communication between neurons, via the synaptic cleft, is dominantly chemically mediated, nerve impulses move along the neuron as electrical signals. Although neurons do not conduct electricity per se, the nerve impulses are nothing but propagating electric pulses. This chapter would briefly outline neuronal conduction and synaptic transmission, the most important processes that sustain the functional integrity of the nervous system.

How did the nervous system originate in the first place? What made nerves capable of generating nerve impulses? On closer examination, we can see that the basic molecular equipment for the generation and transmission of electrical impulses were already present from the beginning of life on earth. For instance, the sodium potassium ATPase pump and the voltage-gated potassium channel have been integral components of the cell membrane since prokaryotes. Precursors to many molecules that participate in neuronal conduction can be seen in all clades of the evolutionary tree. Even bacteria possess gene homologues that code for the proteins that guard voltage-gated ion channels and synaptic structures. Therefore, molecular beginnings for the ultimate development of the nervous system must have begun

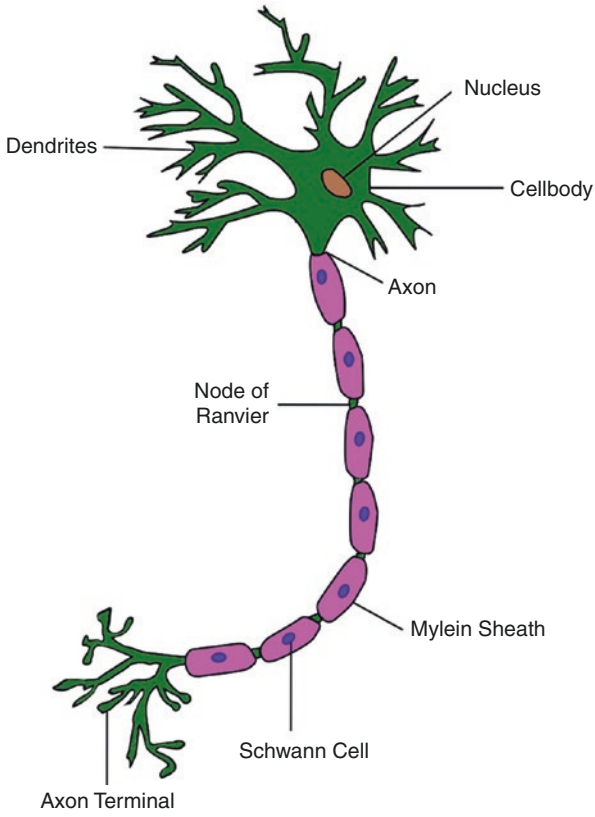

Fig. 1 A typical neuron

with prokaryotic/eukaryotic ancestors 4 billion years ago. The nervous system was merely an adaptive upgrade that came with the redeployment of preexisting cellular processes.

2 Resting Membrane Potential

Neuronal conduction is the fundamental process that impacts all attributes of brain function [5]. Neurons communicate with the help of electrical pulses that propagate along the neuron. Understanding the molecular mechanisms that generate and propagate electrical signals in the neuron is the first step towards understanding the functioning of the nervous system. Some fundamental concepts need explanation before we go further (Fig. 2).

First and foremost, we must begin with how the concept of membrane potential is critical to neuronal conduction and transmission. The neuron, like other animal cells, is covered by a lipid bilayer membrane [6]. This protective barrier created by the lipid bilayer is also very selective to ions that can enter or leave the cell, much like international borders vigilantly screening immigrants at entry and exit points.

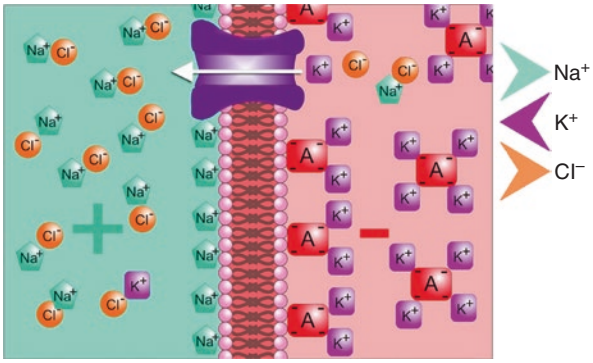

Fig. 2 Ionic distribution across neuronal membrane

Embedded in the lipid bilayer are transmembrane proteins that operate as ion transporters and ion pumps. Ion pumps actively push ions across the membrane and establish concentration gradients. Ion channels allow specific ions to move across the membrane along the concentration gradient. The sodium–potassium ATPase pumps out three sodium ions out of the cell and pulls two potassium ions into the cell. Thus, the intracellular concentration of potassium ions is much higher than the exterior. On the other hand, sodium is dominantly extracellular. The differences between the ionic gradients create a potential difference between the surfaces of the neurons. This is called membrane potential [7].

In steady-state conditions, the potential difference between the two surfaces of the neuronal membrane is called the resting membrane potential of the neuron. The resting membrane potential of the inner surface of the cell is slightly negative (it varies from −40 to −90 mV) [8]. Therefore, the inner membrane is negatively polarized or "depolarized" with respect to the exterior. The electrical potential is limited to the surface of the membranes. The flow of ions across the plasma membrane reaches steady state very quickly, keeping the membrane potential fairly constant for a given neuron.

There are two important ion transfer channels that govern the generation and propagation of the nerve impulse. These are the voltage-gated sodium channels and leaky channels that allow potassium to leak out of the cell, along the concentration gradient. The term "voltage gated" implies that such channels open and close in response to changes in the membrane potential. In the resting state, the cell membrane is relatively impervious to sodium because the voltage-gated sodium channels are designed to stay shut at the resting membrane potential. The leaking potassium channel allows a little potassium to leak out, rendering the inner surface of the neuronal membrane negatively charged with respect to the outer surface. The depolarized state of the neuron in steady state may be attributed to the leaky potassium channels [9].

Resting membrane potential varies between neurons and also within various parts of the same neuron. In steady state, the resting membrane potential varies between –40 and −80 mV. Membrane potential is what endows an electrical

property to the neuron. This electrical property is redeployed to create action potentials, the major means of electrical conductivity that links neurons.

3 Action Potential

Action potential is the engine that drives neuronal conduction in the nervous system. It is the abrupt, well-scripted, and temporally orchestrated rise and fall of the membrane potential of a neuron. Action potential is not an isolated event, but a propagating unidirectional electrical pulse that enables neurons to communicate with each other. The various phases of the action potential and the accompanying electrochemical events were discovered by Alan Hodgkin and Andrew Huxley, for which they won the Nobel Prize in 1963.

Action potential begins with the sudden pulse of depolarization, in which membrane potential rises towards zero. This pulse of depolarization would then stimulate adjoining locations on the neuron to depolarize in a similarly synchronous fashion. In this manner the action potential can propagate along the axon in the form of a traveling nerve impulse [10]. It is important to note that action potentials are not exclusively devoted to enable communication between neurons. Action potentials can also elicit executive functions such as muscle contraction and secretion of insulin by pancreatic beta cells.

The time course of the action potential can be described in four phases. To begin with, consider the neuron in the resting state. In the resting state, the neuronal membrane is impervious to sodium ions because voltage-gated sodium channels stay shut at the resting membrane potential. However, at the resting membrane potential, the leaky potassium channels allow potassium ions to leak out of the cell along the concentration gradient [11]. The next phase is the depolarization phase. Action potential kicks in only when the cell depolarizes to reach the threshold value of about –55 mV for a typical neuron. The threshold value of depolarization varies with neurons, and even with different parts of the same neuron. When membrane potential reaches the threshold value, the voltage-gated sodium channels would suddenly open and admit a large amount of sodium ions from the extracellular space. The sudden entry of positively charged sodium ions into the neuron would raise the membrane potential towards zero [12]. This phase involves a positive feedback loop in which the rise in membrane potential also serves to accelerate the opening of more and more voltage-gated sodium channels. Therefore, any rise in membrane potential above the threshold would result in a rapid rise in intracellular sodium, generating an explosive surge in membrane potential. Further and further influx of sodium ions into the cell would reverse the polarity of the neuronal membrane until depolarization reaches its peak (Fig. 3).

The third phase, namely the repolarization phase, begins when the depolarization reaches its peak. The reversal of membrane polarity, at the peak of depolarization, rapidly inactivates the voltage-gated sodium channels. Sodium influx ceases with the closing of the voltage-gated sodium channels [13]. The sodium ions that entered the cell are then pumped out into the extracellular space by the sodium pump. The

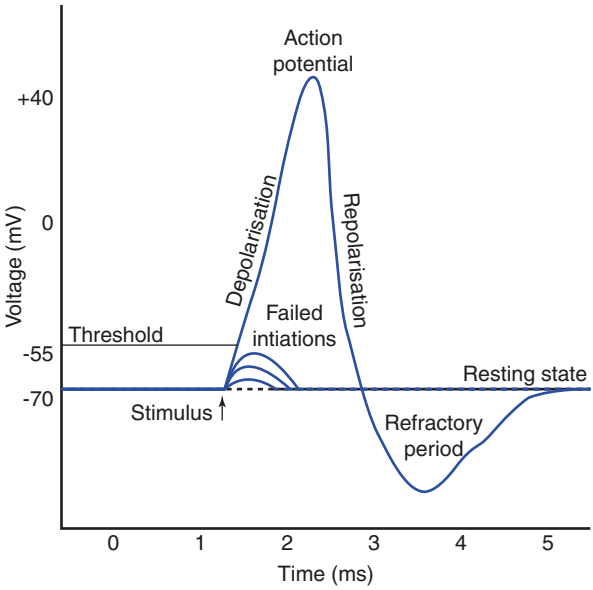

Fig. 3 Action potential

potassium channels are then activated, leading to an outward flow of potassium ions, eventually returning the membrane potential to steady state.

The repolarization phase extends to a brief and transient phase of hyperpolarization, during which membrane potential falls below the resting membrane potential. During this period, the neuron cannot be activated to trigger another action potential. This is called the refractory period. The refractory period is further divided into absolute and relative refractory periods. It is impossible to trigger an action potential during the absolute refractory period. During the relative refractory period, an action potential is still possible but much more difficult to trigger [14].

All synaptic inputs do not result in an action potential. Only a fraction of synaptic inputs that enter a neuron would raise the membrane potential above the threshold. Some synaptic inputs can also hyperpolarize a neuron, further lowering the membrane potential below the resting membrane potential, where no action potential will form. Neurons receiving multiple signals from multiple dendrites would respond with an action potential only if the sum of all signals reaches a threshold. This is called summation of nerve impulses. Not all the signals that feed into the neuron (via multiple dendrites) are excitatory in nature. Some might be inhibitory. That is why summation of nerve impulses is necessary for neuronal decision-making. Summation of multiple impulses can be temporal or spatial. Spatial summation is positive when many simultaneous signals, each of them too weak to raise the threshold individually, add up to reach the threshold [15]. Temporal summation is positive when multiple input signals come in quick succession, raising the membrane potential to the threshold sufficient to trigger an active potential. The summative function and the initiation of action potential are believed to occur at the "axon hillock" and the initial segment, the part that connects the axon to the neuronal cell body.

The action potential constitutes an all-or-none phenomenon. There is nothing like a fractional action potential. In other words, neuronal transactions are similar to those used by computers that employ a binary code. The time course and intensity of the action potential are generally uniform and invariant. The patterns in the amplitude as well as the scheduling of the rise and fall of membrane potential are more or less similar for all action potentials in a given cell. Another remarkable property of action potential is that they are all equivalent in producing effect. It is an all-or-none response. Stronger stimuli do not produce "stronger" action potentials. A very strong stimulus leading to suprathreshold membrane potentials can generate multiple action potentials in quick succession, even as many as 10–100/s [16].

3.1 Propagation of the Action Potential

The inward current at the summit of the action potential can spread forward (only forward!) along the axonal membrane, thereby depolarizing the segments immediately contiguous to the locus of the action potential. If the depolarization reaches the threshold, a similar action potential can be generated in the neighboring segments of the membrane. Experiments have shown that the action potential can even jump across a short segment of injury along the axon. In other words, an action potential is capable of raising the threshold of adjoining areas on the axonal membrane, propagating the nerve impulse further and further, till the nerve impulse traverses the entire length of the axon [17].

The time course of the action potential is about a millisecond. Axonal conduction ranges from 1 m/s to as much as 100 m/s in large myelinated axons. Myelin is a lipid-rich multilayered insulating material that wraps around the axons in a discontinuous fashion. The unmyelinated patches on the axon are called nodes of Ranvier. The axonal membrane covered by myelin is impervious to ions. Therefore, action potential cannot occur upon the myelinated segments because ions cannot cross the myelin sheath. And yet, paradoxically enough, myelin sheaths increase the speed of axonal conduction by letting the action potential skip the myelinated patch, directly jumping from one node of Ranvier to the next. This rapid mode of axonal conduction along myelinated nerves is called saltatory conduction [18] (Fig. 4).

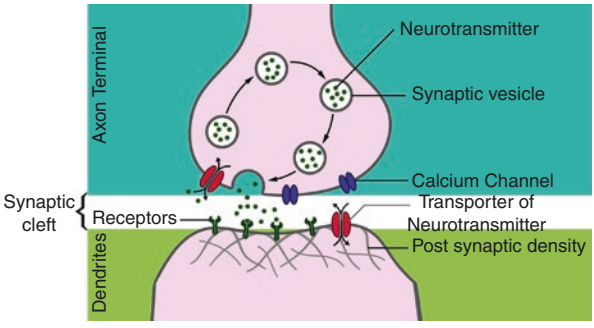

Fig. 4 Synapse

The cytoplasm, not the axonal membrane, carries the current between the nodes of Ranvier [19]. Myelination also makes axonal conduction more energy efficient. Axons with larger diameters can conduct nerve impulses faster because of lower resistance. Nonmyelinated nerve fibers are slower because action potential has to traverse the entire stretch of axonal membrane. The nervous system has both myelinated and nonmyelinated nerve fibers. For instance, axons of the neuron in the autonomous nervous system are generally unmyelinated. On the other hand, the skeletal muscles are wired to myelinated nerves for rapid action [20].

An important aspect of neuronal conduction is that it proceeds forward, and is unidirectional. The axonal segment that has just witnessed an action potential would be in the refractory period. Quite by contrast, the membrane patch ahead of the spike can be easily activated to threshold levels. The absolute refractory period would prevent activation of the membrane patches that precede the locus of the action potential and thereby prevent conduction in reverse [21].

4 Synaptic Transmission

As mentioned previously, synapses are gaps between neurons, across which neuronal signals should flow. The transfer of information across all synapses is not identical, neither spatially nor temporally [22]. The discretionary nature and the selectivity of synaptic transmission are essential features in neuronal decision-making.

There are two types of synapses: electrical synapses and chemical synapses. Electrical synapses are also called gap junctions which permit passive current flow through open pores that interconnect adjacent neurons. On the other hand, chemical synapses employ chemical mediators (neurotransmitters) to enable interneuronal communication. Electrical synapses are fewer than chemical synapses [23].

5 Chemical Synaptic Transmission

Grasping the structural features of the synapse is important for understanding chemical neurotransmission [24]. The synapse consists of the presynaptic and postsynaptic neuronal membranes, with a gap in between. The presynaptic terminal contains the neurotransmitters synthesized by the neuron and stored in synaptic vesicles. The synaptic vesicles are either floating in the synaptic cleft or "docked" along the presynaptic neuronal membrane. When an action potential reaches the presynaptic terminal, ensuing changes in membrane potential would lead to the opening of voltage-gated Ca++ channels. Calcium ions being dominantly extracellular, the opening of calcium channels generates a steep concentration gradient across the plasma membrane for Ca++. Thus, the Ca++ would rush into the presynaptic terminal and bring about the fusion of "docked" vesicles with the presynaptic plasma membrane along the synaptic cleft. Vesicular fusion would release the stored neurotransmitter into the synaptic cleft. The neurotransmitter thus released into the synaptic cleft would bind postsynaptic receptors sitting on the dendrites of the next

neuron. Neurotransmitters, upon binding to the receptors, would trigger events that change the membrane potential, precipitating depolarization or hyperpolarization, thereby driving the signal forward to the next neuron [25]. If the postsynaptic membrane is depolarized, opening of the voltage-gated Na+ channels is sufficient to depolarize the membrane to the threshold, and the postsynaptic neuron will fire an action potential. On the other hand, if the postsynaptic membrane is hyperpolarized, the postsynaptic neuron is prevented from firing an action potential [26].

The neurotransmitter is not allowed to remain in the synaptic cleft after its job is done. There are many ways in which the action of the neurotransmitter is neutralized. Some neurotransmitters are removed by glial cells or by presynaptic reuptake. Some of them are degraded by specific enzymes. More than one mechanism might operate in conjunction in some situations. Many drugs that affect the nervous system are designed to interfere selectively with synaptic transmission [27]. The molecular mechanism that leads to release of neurotransmitters consists of a number of tightly regulated steps, starting with the synthesis of the neurotransmitter. Once the neurotransmitters are synthesized, they are enclosed in membranous vesicles. These vesicles are first "trafficked" to the vicinity of the presynaptic neuronal membrane by engaging motor proteins. When the vesicles reach the vicinity of the presynaptic terminal membrane, they are "tethered" to the membrane, thereby concentrating the vesicles at the border, in order to facilitate ready exocytosis [28]. The next step is docking, where the tethered vesicles are temporarily docked at the plasma membrane. Priming of the vesicles is the penultimate step, where the vesicles are rendered ready for fusion with the neuronal membrane at the entry of calcium ions.

The fusion of the vesicles and the release of neurotransmitters involve a highly complex molecular interplay between SNARE proteins and the vesicle. The mammalian SNARE complex is an assembly of more than 60 different proteins. Calcium plays a critical role in triggering vesicle fusion. Depolarization of the presynaptic membrane elicits the opening of voltage-gated Ca++ channels, admitting the entry of calcium into the intracellular compartment, which is both necessary and sufficient for the fusion of vesicles to the presynaptic membrane and the subsequent release of neurotransmitters. Fusion of the vesicles to the presynaptic membrane is the result of a well-synchronized chain of coordinated events in which a plethora of molecules are distributed upon vesicular membrane, presynaptic cytosol, and presynaptic terminal membrane. Ca++ influx is the trigger that orchestrates these interactions. Calcium binds to synaptotagmin, a protein expressed on the vesicles. The SNARE complex is then activated to accomplish the fusion of docked vesicles. The formation of a "fusion pore" involves the union of the vesicular membrane and presynaptic terminal membrane and the release of the neurotransmitter [29]. The vesicular membrane, now fused to the presynaptic neuronal membrane, is then internalized into the neuronal cytosol. This happens with the help of the formation of a clathrin coat over the vesicular membrane, and eventually the pinching off of the clathrin-coated vesicular membrane. This process constitutes the recycling of the vesicular membrane. The cycle of events associated with the exocytosis of the neurotransmitters can be quick, in a matter of milliseconds [30].

Many toxins and drugs target the proteins involved in the exocytosis of the neurotransmitters. Botulinum and tetanus toxins work by targeting the SNARE components. "Botox" is a commercial formulation of the botulinum toxin that is especially useful clinically to treat spasticity and other forms of involuntary muscle fasciculation and twitching [31].

6 Electrical Synapses

Unlike the chemical synapse, the electrical synapse transmits information by an electrically conductive link between the incoming axon and the dendrites of the receptive neuron [32]. The narrow gap between the pre- and postsynaptic neurons is known as a gap junction. The gap junctions are much narrower (only a few nanometers) than chemical synapses which can be as much as 20–40 nm.

Electrical synapses conduct nerve impulses faster than chemical synapses. Electrical synapses operate for faster responses, for instance defensive reflexes. Unlike chemical synapses, electrical synapses admit bidirectional flow of information. In other words, the incoming axons can pick up signals from the dendrites linked by electrical synapses. Gap junction channels with a diameter of up to 2 nm are transfixed across the membranes of both cells [33]. The pores through the gap junction channels allow ions and medium-size molecules (e.g., signaling molecules) to flow from one cell to the next. The passage of ions can occur when the membrane potential of one cell changes, when ions may move through gap junctions from one cell to the next, carrying positive charge with them and depolarizing the postsynaptic cell [34]. The vertebrate gap junctions are hemichannels contributed by the two cells.

Electrical synapses are faster but can produce only simple behaviors. The more complex chemical synapses are involved in complex processes. Signal transmission at electrical synapses is faster than across chemical synapses, which constitute the majority of synapses in the nervous system. Chemical transmission is accompanied by synaptic delay whereas electrical transmission is must faster. Electrical synapses do not involve receptors to recognize chemical messengers. The presence of neurotransmitters and the corresponding receptors can make chemical neurotransmission a lot more amenable to modifications and processing [35].

7 Neurotransmitters and Synaptic Neurotransmission

There are two broad classes of neurotransmitters based on molecular size and chemical class, namely the small-molecule neurotransmitters and neuropeptides. Among the first category falls the small-molecule neurotransmitters that typically mediate rapid synaptic effects by binding ionotropic receptors. Also there are small-molecule neurotransmitters that can elicit long-lasting effects when they bind to metabotropic receptors. It is important to understand that the actions of a given neurotransmitter are not determined by its chemical structure but the postsynaptic receptors, second messenger systems, associated types of channels, and their location (Fig. 5).

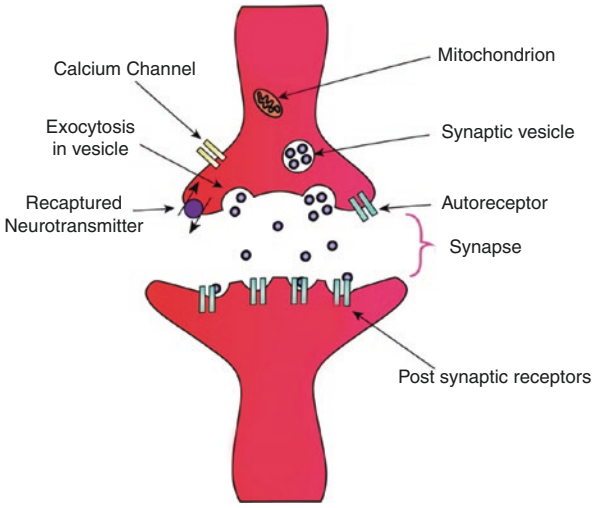

Fig. 5 Synaptic cleft

The most important representatives of small-molecule neurotransmitters are acetyl choline, noradrenaline, glutamate, GABA, glycine, etc. Discussing these individually would be outside the scope of this chapter. Noradrenaline (also called norepinephrine) is a neurotransmitter in the sympathetic ganglia and acts on target cells by binding to and activating noradrenergic receptors located on the cell surface. Acetylcholine plays multiple roles: It is the excitatory neurotransmitter of somatic motor neurons, major excitatory neurotransmitter in autonomic ganglia, and postganglionic parasympathetic fibers [36]. Additionally, acetyl choline also plays a role in modulatory systems in the CNS. Glutamate is the major excitatory neurotransmitter in the CNS, whereas GABA is the major inhibitory neurotransmitter in the brain. Glycine is the major inhibitory neurotransmitter in the spinal cord [37].

Nitric oxide (NO), being a gas, is unique in the list of neurotransmitters. This gaseous neurotransmitter, a metabolic by-product of the metabolism of arginine, can diffuse freely across neuronal and glial cell membranes. NO activates guanylyl cyclase, producing the second messenger, cGMP. Owing to the ability of NO to diffuse across membranes, this neurotransmitter can transgress the cell boundary membranes to produce a pervasive effect that ignores obstructive barriers [38].

Biogenic amines (dopamine, serotonin) are involved in motivation and reward systems and also linked to several neuropsychiatric disorders and movement disorders [39]. There are many more molecules with neurotransmitter function. ATP, co-released with other small-molecule neurotransmitters into the extracellular spaces, gets converted into adenosine, considered to modulate arousal. The stimulating effect of coffee can be attributed to xanthines that block adenosine receptors.

Endocannabinoids bind the very same receptors that bind to psychoactive components of cannabis. Being hydrophobic, these molecules readily diffuse through neuronal membranes and interact with membrane-bound receptors on other cells, engaging in the plasticity of inhibitory circuits [40].

8 Neuropeptides

Neuropeptides are smaller proteins (peptides) that help neurons to communicate with each other. Neuropeptides participate in neuronal signaling in specific ways. Neuropeptides are analogous to peptide hormones. Some peptides that function as hormones can also possess neuronal functions. Those peptides secreted into blood by neuroendocrine cells function as hormones [41]. On the other hand, those peptides secreted primarily by neurons and glia in some cases, and participate in neuronal transmission, are called neuropeptides. Thus, distinction between neuropeptide and peptide hormone depends on the origin and signal to neighboring cells (primarily neurons). Both neuropeptides and peptide hormones may be synthesized by the same enzymes such as prohormone convertases and carboxypeptidases. These enzymes cleave the peptide precursor at specific sites into neuropeptides. Sometimes neuropeptides are co-released with other neurotransmitters.

There are many ways in which the neuropeptides differ functionally from other neurotransmitters. Neurotransmitters are synthesized by enzymes and packaged into vesicles closer to the synaptic cleft. On the other hand, neuropeptides are synthesized as pre- or pro-peptides in cell bodies away from the site of release. While neurotransmitters are released even in response to neural activity of low frequency and with lower levels of calcium influx, the release of neuropeptides requires high-frequency neural activity and high levels of calcium influx. Thus, the neurotransmitters generate a rapid onset, and neuropeptides produce a slower onset. Unlike neurotransmitters like dopamine, glutamate, and serotonin, neuropeptides are not recycled back into the cell after they are secreted. Additionally, neuropeptides are modified by extracellular peptidases, which can either attenuate or enhance affinity and biological activity of the neuropeptide [42].

Neuropeptides participate in a wide range of brain functions, such as punishment and reward, feeding behavior, pain perception, metabolism, reproduction, social behaviors, learning, and memory. Many of the above functions are long term. Peptide signals are different from those generated by conventional neurotransmitters. Many neuropeptides are associated with behaviors. Maternal behavior, pair bonding, social behaviors, etc. are affected by oxytocin and vasopressin.

Neuropeptides can alter the affinity of ligands to specific receptors, a feature that is consistent with the periodic physiological changes in the course of menstrual cycle. Such extracellular processing events add to the complexity of neuropeptides in cell-cell signaling [43].

The hypothalamus, the integrating hub of neuroendocrine regulation, expresses several peptides that alter feeding behavior, appetite, pain perception, reproductive behavior, etc., to name a few. These complex behavioral patterns are orchestrated by a plethora of peptides such as the α-melanocyte-stimulating hormone, neuropeptide Y, agouti-related peptide, β-endorphin, dynorphin, enkephalin, ghrelin, growth-hormone releasing hormone, and somatostatin. Going into details would be beyond the scope of this chapter.

9 Conclusion

The human brain is the culmination of an evolutionary process lasting eons. While trying to understand the mind—thought to be the product of brain function—we should also consider the fact that brain is, at least partly, the construct of the mind's experiences, thoughts, and functions. Nervous system, in evolutionary terms, can be considered as an "upgrade" from the phylogenetically more primitive endocrine systems. Early multicellular organisms depended on slow and lethargic hormonal signaling via secreted, diffusible chemical signals. The development of the nervous system has added greater speed, complexity, dexterity, ingenuity, and flexibility in being able to coordinate the complex communication network with central inputs. The nervous system should be understood as an evolutionary extension of the more primitive endocrine signaling in both function and structure. Many modern psychosomatic human conditions might be looked upon as a disruption in the harmony between the environment that initially supported the evolutionary integration of the neuroendocrine complex and the abrupt environmental changes associated with contemporary lifestyle. Endocrine disorders such as diabetes have been recently shown to demonstrate a neural etiology. In this context, it is important for the reader to integrate knowledge at multiple levels and appreciate the gaps in reductionistic epistemology. In matters of the brain and the nervous system, such an integrative approach is particularly useful.

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Neurochemicals in Nervous System and Exploring the Chemical Make-Up of Human Brain

Seetha Harilal, Rajesh Kumar, Githa Elizabeth Mathew, Jobin Jose, Md. Sahab Uddin, and Bijo Mathew

Abstract

This chapter focuses on the chemical make-up of brain, the endogenous agents involved in CNS such as acetylcholine, catecholamines including dopamine, norepinephrine and epinephrine, serotonin, histamine, glutamate, GABA and glycine. Many are neurotransmitters and are involved in neurotransmission. The chapter describes the chemistry of these agents, the presence of these receptors in various locations as well as their functions in the brain. The chapter also explains the synthesis, storage and release of these agents. It also discusses the metabolism and reuptake of these agents. Targeting each of the above steps modulates the neurotransmission and produces various pharmacological effects. The chapter also discusses the exogenous agents such as anticholinesterases, indirectly acting agonists, indirectly acting alpha-agonists and

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centrally acting sympatholytics which are capable of modulating the chemical make-up in brain and are used in pharmacotherapy for their wide range of therapeutic benefits.

1 Introduction: Chemical Control of Brain

Human brain is a very complex network which processes huge amount of information each second. Neurones are the fundamental unit of these information-processing complex networks and transmit electrical as well as chemical signals all over the brain. Neurones communicate with each other by releasing and receiving chemicals known as neurotransmitters. These chemicals help all parts of the brain coordinate and communicate while processing information.

The most studied three neurotransmitters are dopamine, norepinephrine and serotonin. Dopamine produces pleasure experiences and has relation to the reward learning process. If a person does some good things, dopamine is rewarded which produces euphoria. It teaches the brain the need to do that again. Serotonin is related to learning and memory. It also plays a role in the neuronal regeneration, which is associated with its antidepressant action. Serotonin-level imbalance produces an increase in depression, anxiety, anger and panic. Norepinephrine eases the mood controlling anxiety and stress.

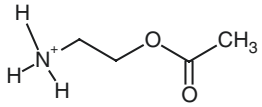
In the brain, if any abnormalities occur in receiving and processing the chemicals, a big effect is produced in the emotions. If a person does something rewarding, the brain part which processes that information interacts with dopamine. If the brain is unable to get dopamine naturally the person will feel less happy, or maybe sad. Studies in people suffering from major depressive disorder (MDD) show that there are lesser serotonin receptors in the brain.

2 Endogenous Agents in Nervous System

2.1 Acetylcholine

2.1.1 Chemistry

Acetylcholine is structurally an ester containing neurotransmitter which consists of choline and acetic acid [1].

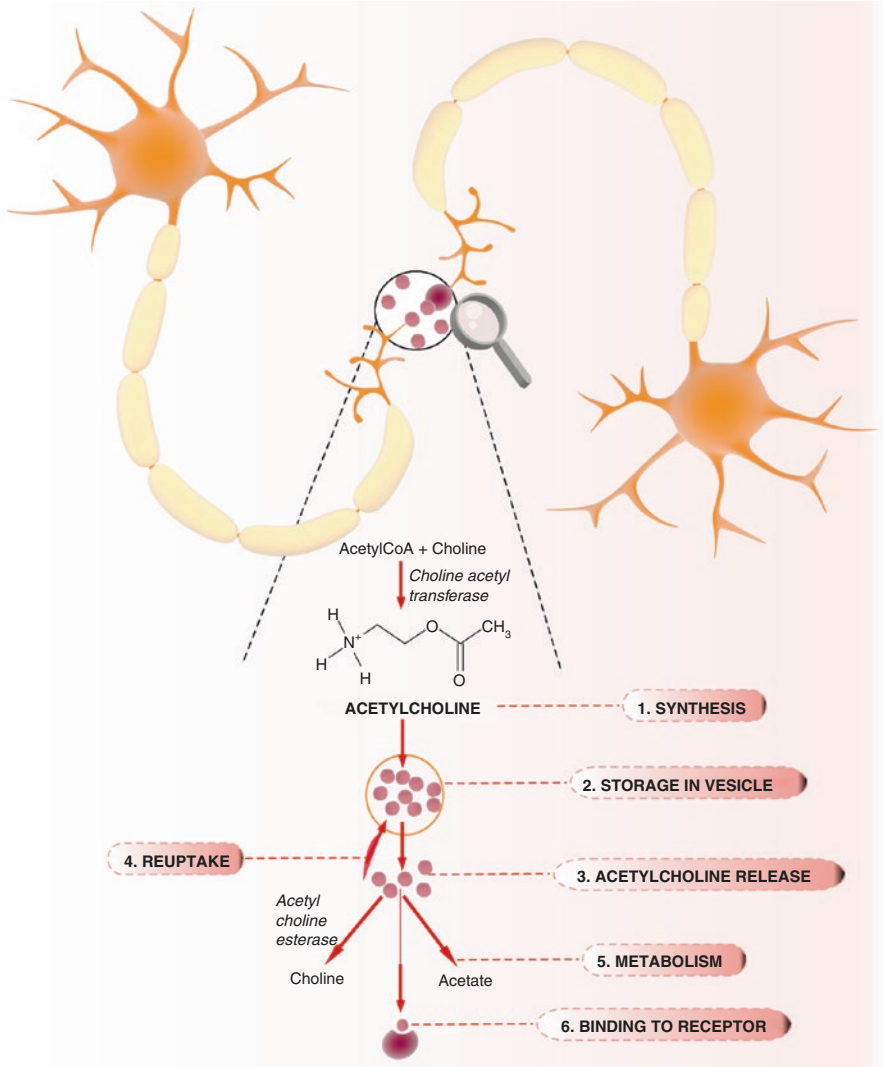


2.1.2 Location and Function

It is still a challenge to understand the complete distribution of cholinergic pathways in the CNS. Muscarinic and nicotinic receptors are widely distributed in the CNS. M1 receptors are seen mainly in the cerebral cortex and hippocampus. M2 receptors are seen mainly in the brainstem and cerebellum. M4 receptors are seen mainly in the striatum. Central nicotinic and muscarinic receptors are targets of great interest in Parkinson's disease, Alzheimer's disease and certain seizure disorders for their involvement in controlling abnormal neurological signalling. Nicotinic receptors are seen at prejunctional sites and regulate the neurotransmitter release [2, 3]. The nicotinic receptor is similar to various ion channels which are ligand gated. The muscarinic receptor comes under a group of seven transmembrane-spanning receptors [4], in which signal transduction is by interaction with GTP-binding proteins. Widespread M1 receptors in forebrain improve memory and learning tasks by interacting with GTP-binding proteins in G11 and Gq family. The α11 and G αq subunits activate phosphoinositide-specific phospholipase c (PI-PLC). Dopaminergic and muscarinic pathways in CNS communicate to regulate various pathways which have implication in diseases, mainly that control the involuntary motor system. Muscarinic action on the release of dopamine is mediated in many ways through different mAChR subtypes. The mAChR facilitates DA release and M4 receptors are involved on GABA projection neurones to the striatum. M3 receptors on DA neurons of striatum inhibit DA release in striatum [5]. The action of M3 mAChR and M5 receptors in the CNS is unclear and is seen in low quantities. Recent experiments with M5 receptor knockout mice prove that these receptors are located in endothelial cells of brain vessels and mediate their cholinergic relaxation [6].

2.1.3 Neurotransmission of Acetylcholine

The biosynthesis as well as storage of ACh include three processes where hydrolysed transmitter is recovered back by choline transport to the nerve ending and its acetylation to an active transmitter and stored in a vesicle for its release [7–12]. The single-step synthesis is catalysed by the enzyme choline acetyl transferase (ChAT). The ACh synthesis in mammalian brain uses acetyl CoA from pyruvate produced from glucose. The acetyl CoA produced in the mitochondrial inner membrane accesses the cytoplasmic ChAT but the mechanism remains unclear. ACh production is limited by choline concentration in intracellular region, which is determined by choline-active transport to the nerve terminals.

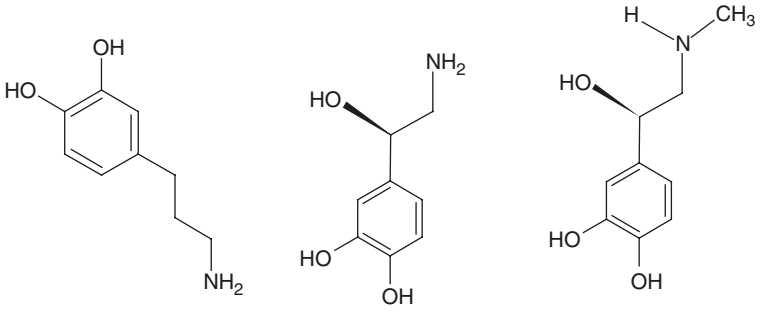


2.2 Catecholamines

The catecholamines epinephrine, norepinephrine and dopamine are the neurotransmitters present in CNS as well as in PNS. Norepinephrine is seen in the brain as well as in sympathetic postganglionic neurones. Norepinephrine undergoes *N*-methylation and forms epinephrine. It is a hormone secreted by adrenal gland. The catecholamine receptors in many organs are stimulated by epinephrine. Epinephrine in little amounts is seen in CNS especially in the brainstem.

2.2.1 Chemistry

Catecholamines are monoamine neurotransmitters consisting of a catechol ring accompanied by amine-containing side chain [13].



DOPAMINE NOREPINEPHRINE EPINEPHRINE

2.2.2 Location and Function

Dopamine

Dopamine receptors are primarily seen in the brain even though they are seen in the kidney [14]. Dopamine receptors include five primary subtypes and are members of G-protein-coupled receptor (GPCR). D_1 receptors stimulate and D_2 receptors inhibit the activity of adenylyl cyclase. D_1-like receptors include D_1 as well as D_5 receptors. They are coupled to adenylyl cyclase stimulation via G_s, producing an increase in cyclic AMP (cAMP) and PKA activation. D_2-like receptors are D_2, D_3 and D_4 receptors. D_2 receptors reduce adenylyl cyclase action via G_i, producing an increase in cAMP.

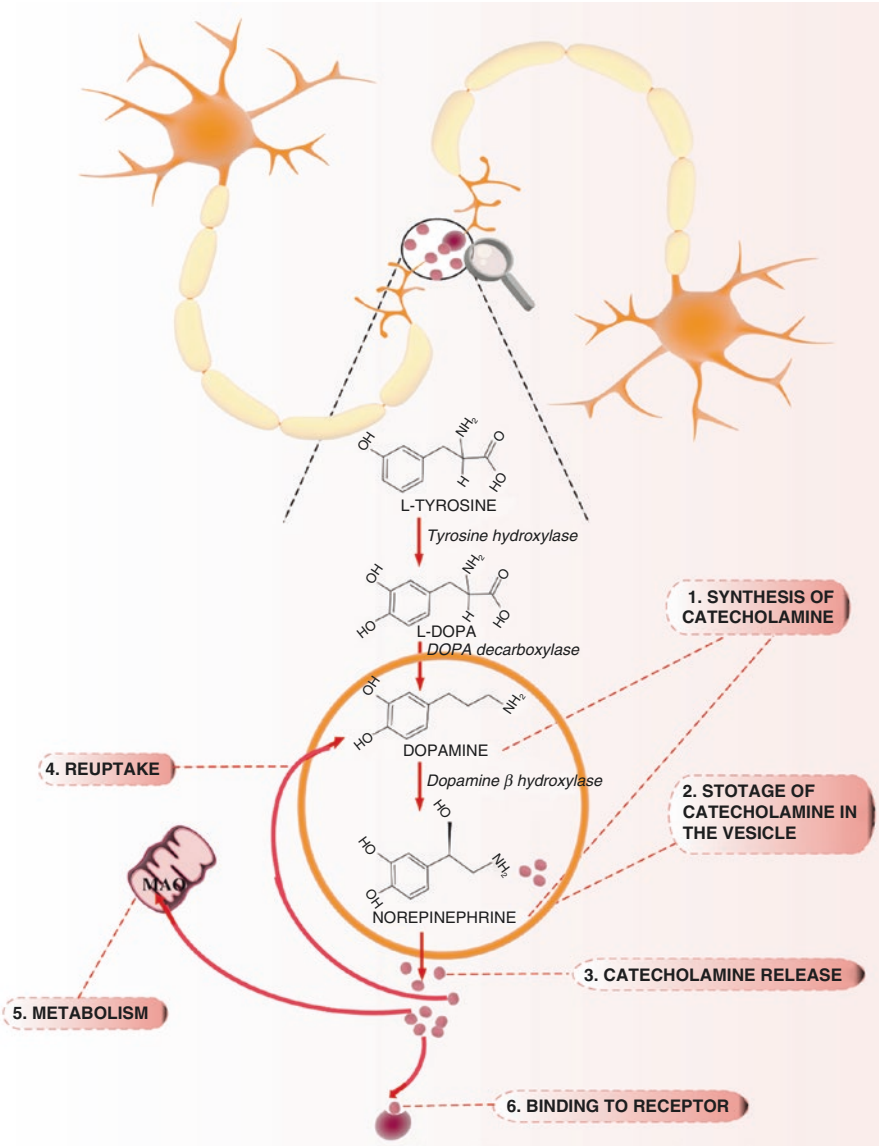
Norepinephrine

The effects of epinephrine and norepinephrine are mediated via nine receptors which are distinct and come under two families (α_1, α_2, β_1, β_2, β_3). α1-Adrenoceptor subtypes activate Gq/11, raising phospholipase C action, and release diacylglycerol and inositol 1,4,5-triphosphate. The action synergistically raises the activity of protein kinase c and produces various other effects due to an increase in the level of intracellular calcium. All adrenergic α_2 receptor subtypes activate G_i, thereby inhibiting adenylyl cyclase, an action similar to D_2-like receptors, producing decreased cAMP as well as protein phosphorylation by channels, producing an inhibition in their function [15], mainly when they act as autoreceptors. All of adrenergic β-receptor subtypes activate G_S to raise adenylyl cyclase activity, an action similar to D_1-like receptors, producing increased cyclic AMP and PKA activity. The important functions and wide distribution of adrenergic receptors have contributed to making them attractive therapeutic targets for new drug development. All of the adrenergic receptors are located in brain in varying patterns. Various subtypes coexist in cells of peripheral tissues, but one subtype is usually dominant. The action of various subtypes of adrenergic receptors in brain function

still remains unclear. Various subtypes are distributed differentially in various brain regions. Adrenergic α_1 receptor subtypes are seen in almost all brain regions. α_{1A} and α_{1B} subtypes are seen in higher concentration than α_{1D}. α_{2A} and α_{2C} receptors are seen in most parts of the brain while α_{2B} is seen mainly in thalamus. The subtypes β_1 and β_2 are widely seen but β_3 receptor expression is low in the brain [16].

2.2.3 Neurotransmission of Catecholamines

Synthesis: In catecholamine biosynthesis, tyrosine hydroxylase (TH) is the rate-limiting enzyme. It is present in all cells which synthesise catecholamines. It uses tyrosine and molecular oxygen as substrates and the cofactor biopterin. It is a mixed-function oxidase and can also hydroxylate phenylalanine to produce tyrosine, which is converted to L-DOPA. The hydroxyl group is added to meta-position of tyrosine, thereby forming 3,4-dihydroxy-L-phenylalanine (L-DOPA). The carboxyl group is removed from DOPA and is catalysed by DOPA decarboxylase (DDC) which is a pyridoxine-dependent enzyme, to form dopamine. The neurone which synthesises epinephrine or norepinephrine, the next step of biosynthetic pathway, is dopamine β-hydroxylase (DBH) which is a mixed-function oxidase that uses molecular oxygen to produce the hydroxyl group added to carbon on dopamine side chain [17]. The enzyme is present mainly in vesicles which store catecholamines. DBH is bound mainly to inner vesicular membrane but some are free in vesicles. DBH is released together with catecholamines and also from adrenal gland and is seen in plasma. In cells which synthesise epinephrine, the last step in pathway involves catalysis by the enzyme phenylethanolamine *N*-methyltransferase (PNMT) which is found in a small neuronal group in brainstem which uses epinephrine as neurotransmitter and in adrenal medullary cells, in which epinephrine secreted is the primary hormone. PNMT transfers a methyl group from *S*-adenosylmethionine to nitrogen in epinephrine, thereby forming a secondary amine [18]. The corticosteroids in adrenal gland as well as superior cervical ganglia regulate the PNMT activity.



Storage and release: Catecholamines are stored in vesicles which are densely present in nerve terminals. Low concentration is free in cytosol, where metabolism occurs by enzyme such as monoamine oxidase (MAO). In neurones which contain norepinephrine, final β-hydroxylation happens in vesicles. In adrenal gland, norepinephrine undergoes *n*-methylation by PNMT in cytoplasm. Epinephrine is trafficked for storage in chromaffin granules.

The vesicles maintain catecholamine supply at nerve terminal for release and mediate the release process. Action potential reaching the nerve terminal makes calcium channels open, producing an influx of cation which promotes the vesicle fusion to the neuronal membrane.

TH is the rate-limiting enzyme in the synthesis pathway. End-product inhibition modulates the enzyme [19]. Free catecholamines in neurone inhibit TH activity by competing for the site which binds pterin cofactor. Neuronal activity causes a release of catecholamines and a reduction in cytoplasmic concentration as well as disinhibition of enzyme. Catecholaminergic terminal depolarisation activates TH resulting from the enzyme-reversible phosphorylation [20]. cAMP-dependent protein kinase (PKA), Ca^{2+}/calmodulin-dependent protein kinases (CaMKs) and protein kinase C (PKC) can induce enzyme phosphorylation producing increased activity.

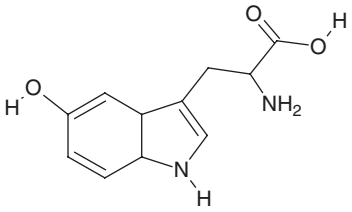
Metabolism: Catechol *O*-methyltransferase (COMT) and monoamine oxidase (MAO) are responsible primarily for catecholamine inactivation. They are seen throughout the body. MAO is seen on outer mitochondrial membrane and is a flavin-containing enzyme. Catecholamines are oxidatively deaminated to their aldehydes by the enzyme and can be converted to acids by aldehyde dehydrogenase, or to glycols by aldehyde reductase. MAO inactivates catecholamines which are free in nerve terminals. 3-Methoxy-4-hydroxyphenylglycol (MHPG) is a minor norepinephrine metabolite selectively formed in the brain. Norepinephrine is metabolised largely in periphery. MHPG in urine and CSF provide information about the turnover of norepinephrine in the brain.

Reuptake: The catecholamine action in synapse is affected by reuptake into presynaptic nerve endings. Catecholamines diffuse from release site, undergo receptor interactions and diffuse back into nerve terminal. Some amount of catecholamines are catabolised by COMT and MAO. The reuptake is mediated by transporter or carrier seen on catecholaminergic neurone outer membranes.

2.3 Serotonin

2.3.1 Chemistry

It is an indolamine molecule substituted by hydroxyl group at its fifth position. The primary amine nitrogen at physiological pH serves as a proton acceptor making 5-HT a hydrophilic substance which cannot pass the blood-brain barrier. Later the idea of 5-HT having a central role came to picture due to behavioural effects and hence it found a role in psychiatric disorders, particularly depression and schizophrenia [21].

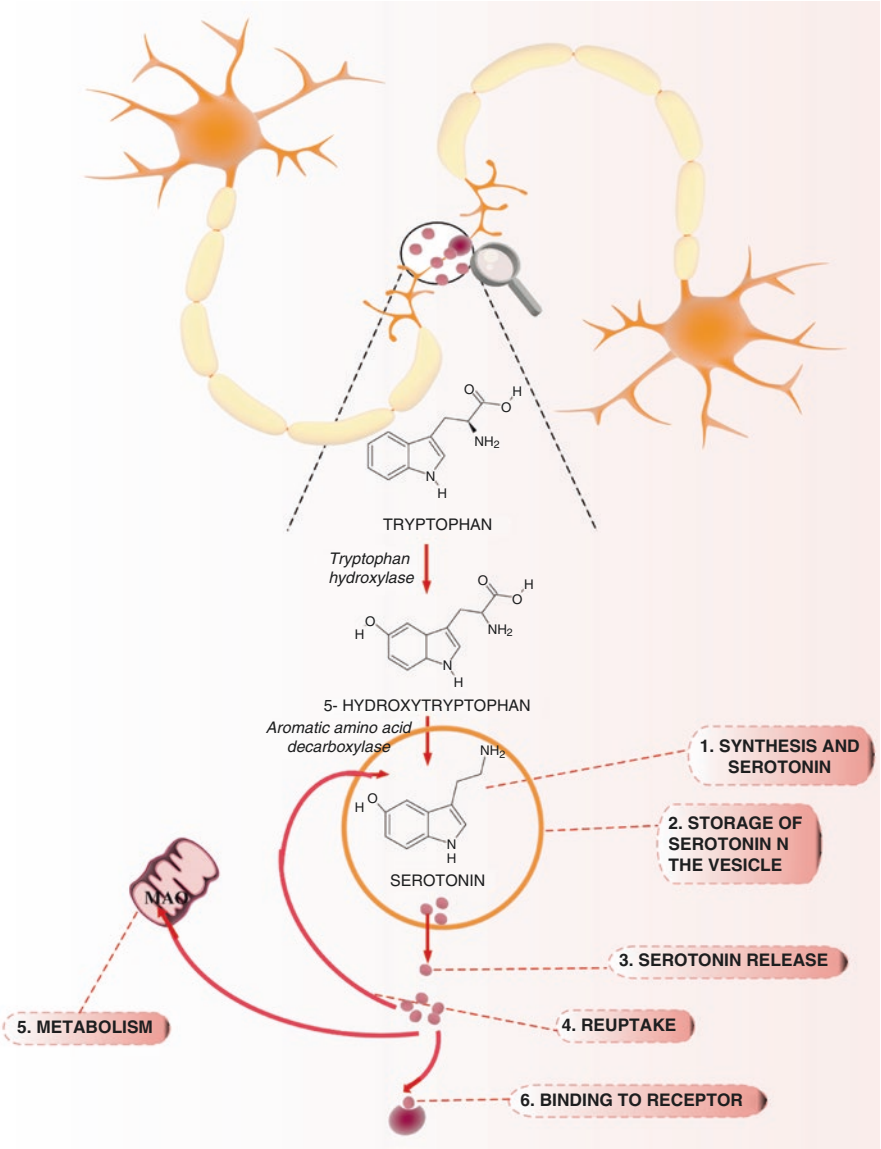


2.3.2 Location and Function

5-HT receptors couple to inhibit adenylyl cyclase through $G_{i/o}$ family of G-proteins [22]. 5-HT_{1A} receptor is seen mainly in limbic and cortical structures such as entorhinal cortex, amygdala, hippocampus, septum and frontal cortex. 5-HT_{1A} receptor has a role in cognitive and emotional functions. 5-HT_{1A} activation modulates sexual behaviour, body temperature and feeding and also stimulates adrenocorticotrophic hormone (ACTH) release. The receptor has a role in affective disorders such as depression and anxiety. 5-HT_{1D} receptor-binding sites are seen in basal ganglia including substantia nigra, caudate putamen, globus pallidus, cortex and hippocampus [23] and mediate trigeminal nociception and neurogenic inflammation. 5-HT_{1D} receptor is an important therapeutic target for migraine [24]. 5-HT_{1E} receptor was identified in human frontal cortex and is coupled to adenylyl cyclase inhibition [25]. The overall brain distribution is unknown. 5-HT_{1F} receptor inhibits adenylyl cyclase and is seen in trigeminal ganglia. 5-HT_{1F} agonists are potentially beneficial in migraine treatment. 5-HT_{2A} is seen in frontal cortex postsynaptically to serotonergic neurones. It may have a role in higher cognitive functions. 5-HT_{2A} receptor activation raises body temperature and raises the secretion of ACTH [26]. 5-HT_3 receptor is included in ligand-gated ion channel family. They are located in CNS and PNS postsynaptically to serotonergic neurones [27]. 5-HT_4 receptor stimulates adenylyl cyclase raising cAMP through G_s family of G-proteins. 5-HT_4 receptor may play a role in memory enhancement [28].

2.3.3 Neurotransmission of Serotonin

Synthesis: The precursor molecule is tryptophan which crosses blood-brain barrier and is supplemented to the body through diet. Tryptophan is converted into 5-hydroxytryptophan (5-HTP) in the presence of tryptophan hydroxylase, an enzyme present in serotonergic neurons. 5-Hydroxytryptophan gets converted to serotonin in the presence of aromatic L-amino acid decarboxylase (AADC) [29].



Storage: Serotonergic synaptic vesicles have a protein which binds 5-HT in the presence of Fe^{2+} with high affinity. The serotonin-binding protein (SPB) is packed along 5-HT in secretory vesicles. SPB is released along 5-HT through a calcium-dependent process [30].

Release: 5-HT release happens by exocytosis. Calcium produces stimulation of vesicular membrane and fusion with plasma membrane. Serotonin release is partly controlled by serotonergic soma firing rate in raphae nuclei. An increase in raphae cell firing improves the release of 5-HT in terminal fields.

Reuptake: The synaptic actions of various monoaminergic and amino acid neurotransmitters including 5-HT are stopped by these molecules binding to specific transporters. In the serotonergic neurones, the serotonin transporter (SERT) is present. 5-HT can diffuse from the release site before the termination of its action by reuptake into serotonergic neurones.

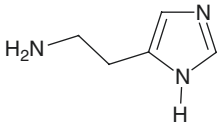
Metabolism: MAO helps in the conversion of serotonin to 5-hydroxyindoleacetaldehyde which is oxidised by NAD^+-dependent aldehyde dehydrogenase to 5-hydroxyindoleacetic acid (5-HIAA) [31, 32].

2.4 Histamine

Histamine is seen in CNS neurones and regulates many functions of the brain [33–35]. The well-established functions of histamine outside CNS hindered its acceptance as a neuronal messenger.

2.4.1 Chemistry

Histamine consists of an imidazole nucleus substituted by ethylamine at its second position which is common to most of the amine transmitters. The presence of imidazole nucleus distinguishes histamine from other transmitters which is the property of prototypic tautomerism permitting histamine to exist in chemically two different forms. This property is responsible for activation of some of its receptors.



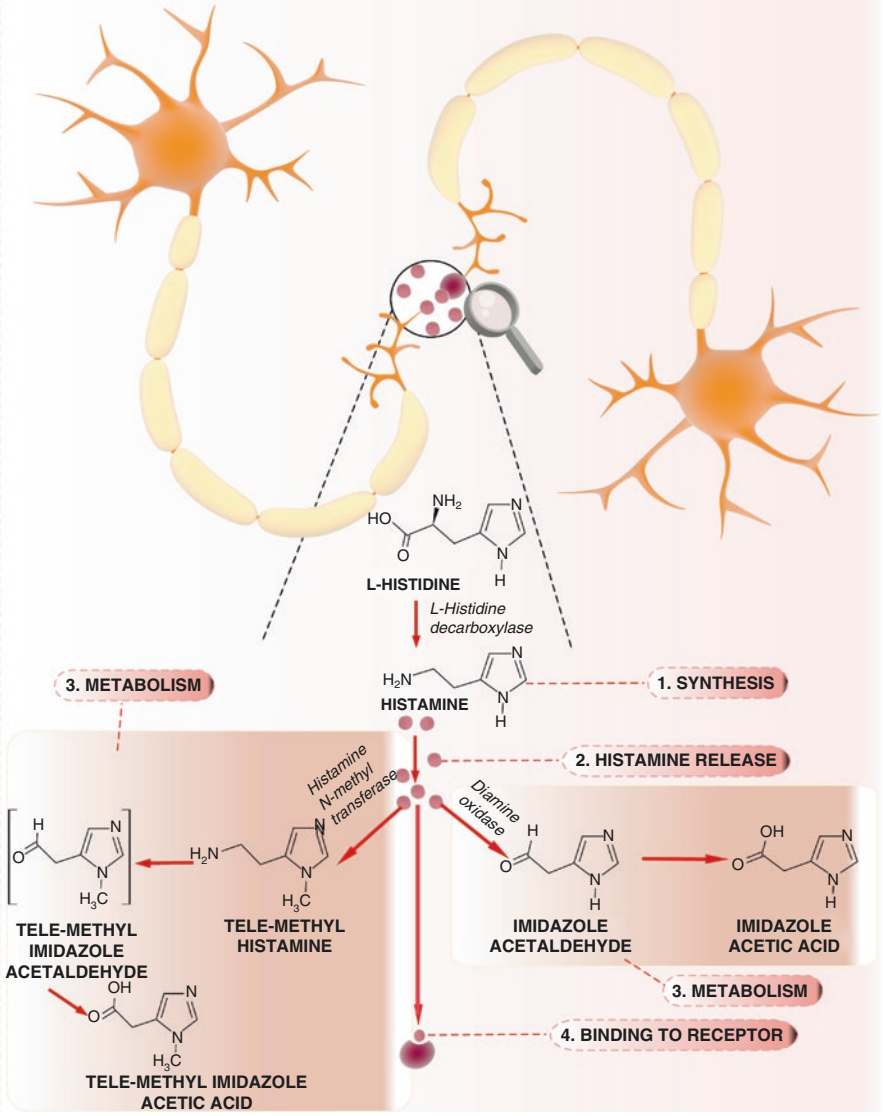
2.4.2 Location and Function

Histamine has activity on four GPCR, and out of these three are important in the brain. All subtypes of histamine receptors are G-protein coupled and are found outside and inside the brain. The H_1, H_2 and H_3 receptors are regionally distributed in the brain but none of them is localised alone to neurones. The brain localisation of H_4 receptors remains unclear. H_1 receptors are GPCRs which are intronless and linked to G_q and calcium mobilisation. H_1 receptors in brain slices can improve metabolism of glycogen [36] and modulate stimulation of cAMP. The brain cAMP synthesis activation by histamine is studied well and shows a positive interaction among histamine receptors [37]. H_1 receptor activation in brain stimulates cGMP synthesis and the mechanism remains unclear. It can lead to effects and depends on guanylyl cyclase activity [38]. Activation of H_1 receptors produces depolarisation in brain areas such as cerebral cortex, thalamus and hypothalamus and is mediated by cation channel opening. Changes in conductance induced by H_1 receptors are mediated by IP_3-Ca^{2+} cascade. H_2 receptors are GPCRs which are intronless and linked to cAMP synthesis and G_s proteins. Stimulation of H_2 receptors in hippocampus and cerebral cortex leads to excitation through inhibition of Ca^{2+}-activated K^+ conductance and can facilitate depolarisation by enhancement of 1H current, a cation conductance change by hyperpolarisation [34]. H_4 receptors are similar to H_3 in signal transduction and genetic structure but the expression is limited in the brain.

2.4.3 Neurotransmission of Histamine

Histamine synthesis and breakdown are controlled by specific subtypes.

Synthesis: In the presence of L-histidine decarboxylase histidine gets converted to histamine which is subjected to oxidation in the presence of diamine oxidase (DAO) that forms imidazole acetic acid (IAA) whereas on methylation in the presence of *N*-methyltransferase it leads to the formation of tele-methylhistamine (t-MH). t-MH undergoes metabolism by (MAO)-B leading to the formation of tele-methylimidazole acetic acid (t-MIAA). In CNS of vertebrates frequency of histamine methylation is more with respect to oxidation.



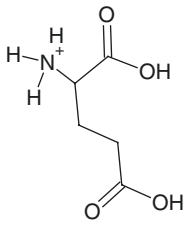
Storage and release: Storage of histamine is within neurones and then it is released. The neuronal transporter is not known. Newly produced neuronal histamine is trafficked to TM neuronal vesicles via vesicular monoamine transporter VMAT2 [39]. Nerve terminal depolarisation produces exocytosis of histamine via calcium- and voltage-dependent mechanism. The secreted histamine stimulates both presynaptic and postsynaptic receptors. Histaminergic nerve endings do not show high-affinity histamine uptake. Astrocytes may have a transport system for histamine [36, 40, 41]. Astrocytes may contain a histamine transport system.

Metabolism: Metabolism of histamine occurs via methylation. The histamine-methylating enzyme (HMT) uses methyl donor *S*-adenosyl-1-methionine. Methylation of histamine produces t-MH which is a substrate for MAO-B and is oxidised to t-MIAA which is the histamine metabolism end product in brain. Inhibitors of MAO raise t-MH concentration and reduce t-MIAA concentration in the brain, but no effect occurs on the concentration of histamine.

2.5 Glutamate

2.5.1 Chemistry

Glutamate consists of an amino and 2-carboxyl functional groups and can exist in two optical isomers due to the chirality of the C-atom remaining adjacent to NH_2 group.



2.5.2 Location and Function

The glutamate receptors come under one of the two main categories: Ionotropic receptors are cation channels. When glutamate interacts with the receptor, the opening of ionotropic receptors is enhanced. Metabotropic receptors do not transmit ion fluxes. They stimulate intracellular enzymes via G-proteins when bound to glutamate. The three ionotropic receptor classes are named after selective agonists a-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate (KA) and *N*-methyl-D-aspartate (NMDA). Metamorphic glutamate receptor (mGluRs) can be linked to various signalling enzymes of the cytoplasm. mGluR is classified into three groups. Group 1 increases the activity of phospholipase C and Ca^{2+} release from cytoplasm. Phospholipase C activation leads to IP_3 as well as diacylglycerol formation and activates protein kinase C. Group 2 and group 3 mGluR activation inhibits adenylate cyclase in which G_i family is involved (Table 1).

Table 1 Endogenous agents in nervous system

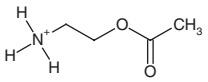
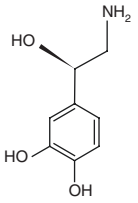
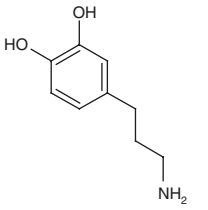
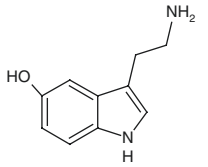
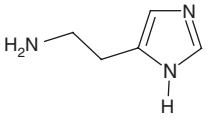
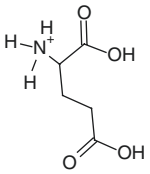
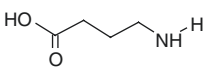
Endogenous agents in nervous system	Receptors present in CNS	Mechanism of action
Acetylcholine 	M_1, M_2, M_4 cholinergic receptors	$G_{\alpha q}$-stimulated protein receptor mechanism which activates phosphoinositide-specific phospholipase c (PI-PLC)
Norepinephrine 	α_{1A} and α_{1B} subtypes are seen in higher concentration than α_{1D}. α_{2A} and α_{2C} receptors are seen in most parts of the brain while α_{2B} is seen mainly in thalamus. β_1 and β_2 are widely seen but β_3 receptor expression is low in the brain	α_1 receptors—G_q → phospholipase C action → release diacylglycerol and inositol 1,4,5 triphosphate α_2 receptors—G_i → decreased production of cAMP
Dopamine 	D_1-like receptors (D_1, D_5); D_2-like receptors (D_3, D_4, D_5)	D_1 receptors—G_S → adenylyl cyclase stimulation → increase cAMP → PKA activation D_2 receptors—G_i → decreased production of cAMP
Serotonin 	5-HT_{1A}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{1F}, 5-HT_3, 5-HT_4 receptor	5-HT receptors → $G_{i/o}$ → inhibit adenylyl cyclase 5-HT_{1E} receptor → adenylyl cyclase inhibition 5-HT_{1F} receptor inhibits adenylyl cyclase 5-HT_3 receptor → ligand-gated ion channel 5-HT_4 receptor → G_s → stimulates adenylyl cyclase → raising cAMP
Histamine 	H_1, H_2 and H_3 receptors	H_2 receptors → Gs → cAMP synthesis and proteins H_2 receptors → excitation through inhibition of Ca^{2+}-activated K^+ conductance and can facilitate depolarisation

Table 1 (continued)

Endogenous agents in nervous system	Receptors present in CNS	Mechanism of action
Glutamate 	AMPA, KA, NMDA	AMPA-phospholipase C action → release diacylglycerol and inositol 1,4,5 triphosphate KA, NMDA-Gi → inhibits adenylate cyclase
GABA 	$GABA_A$ receptor	Both GPCRs and ligand-gated ion channels

2.5.3 Neurotransmission of Glutamate

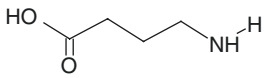
In the astrocytes, glutamate interacts with ammonia to produce glutamine through the activity of ATP-dependent cytosolic enzyme and glutamine synthetase which are expressed in oligodendrocytes and astrocytes, but not in neurones. Glutamine does not have neurotransmitter properties and is transported to extracellular fluid and then taken up by the neurones.

Glutamine is converted to glutamate in the neurones by glutaminase which is phosphate activated. It is a neurone-specific and mitochondrial enzyme in the brain. Glutamine and glutamate transport between astrocytes and neurones are known as the glutamine cycle. Glutamate release from nerve endings leads to α-ketoglutarate loss from tricarboxylic acid cycle. The glutamine cycle prevents α-ketoglutarate loss from TCA cycle in neurones. During neuronal release of glutamate, it is taken up by astrocytes and the neuronal TCA cycle loses α-ketoglutarate. The glutamine return for glutamate produces reduction in the loss of α-ketoglutarate in the neurones but does not prevent it fully due to astrocyte metabolising some glutamate via its TCA cycle as energy substrate. The level of glutamate and intermediates of TCA cycle in nerve terminal is maintained by glutamate reuptake from extracellular fluid to nerve terminals, and another mechanism is the reaction of pyruvate with CO_2 to produce malate, an intermediate of TCA cycle and the precursor of oxaloacetate, and the process is pyruvate carboxylation. Glutamate is accumulated in synaptic vesicles by vesicular glutamate transporters (VGLUTs). Zinc is seen along with glutamate in various glutaminergic vesicles, approximately 10% in hippocampus. Zinc accumulation in vesicles is through ZnT3 zinc transporter. Zinc modulates the glutamate receptor activation [42, 43].

2.6 GABA

2.6.1 Chemistry

γ-Aminobutyric acid **is** an inhibitory neurotransmitter in CNS consisting of an amino and carboxyl functional group [44].

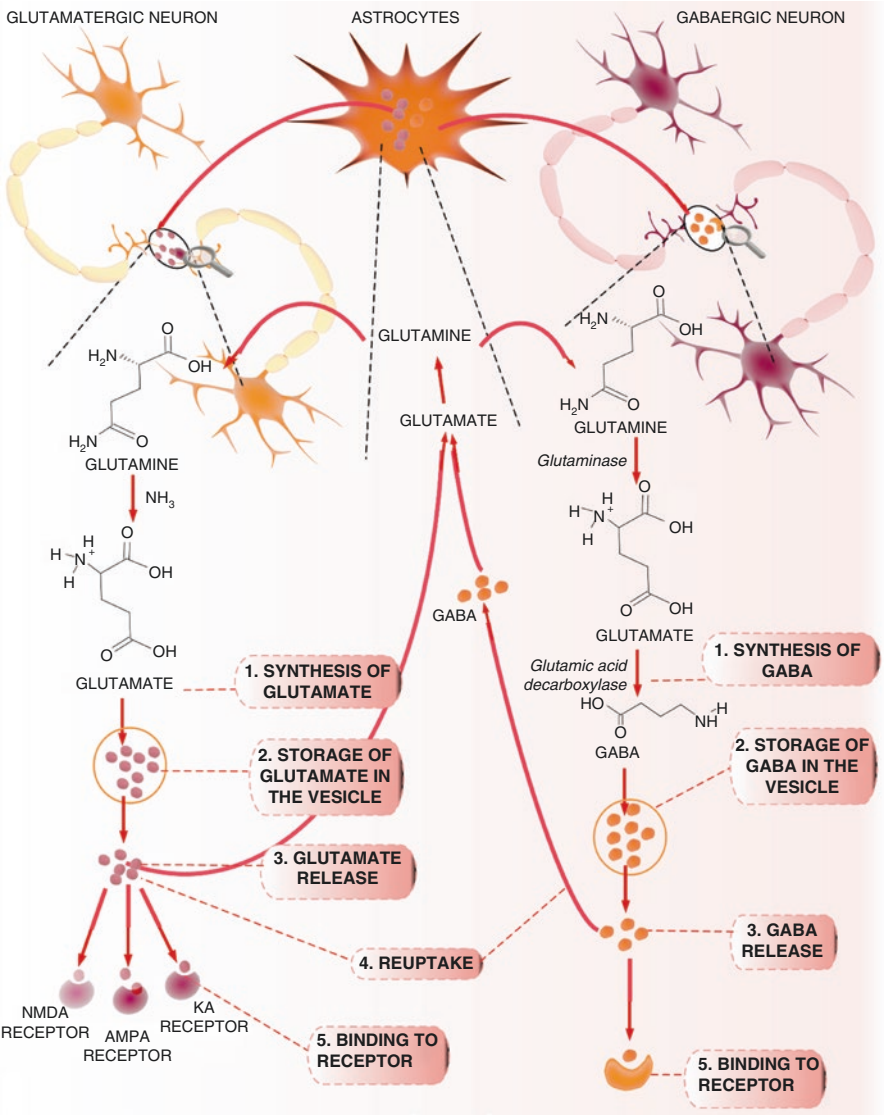


2.6.2 Location and Function

GABA is seen in high concentrations in various regions of the brain. GABA receptors involve both GPCRs and ligand-gated ion channels. Binding of GABA or structural analogues which are agonists produces opening of chloride ion channel [45–47]. The $GABA_A$ receptor is a main molecular target for various drugs in the brain.

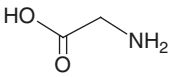
2.6.3 Neurotransmission of GABA

Glucose is the main precursor for synthesis of GABA, even though other amino acids and pyruvate act as precursors. In GABA shunt, the first step is transamination of α-ketoglutarate produced from metabolism of glucose in Krebs cycle, by GABA-A ketoglutarate transaminase (GABA-T) to produce L-glutamic acid [48, 49]. Glutamic acid is decarboxylated to GABA by glutamic acid decarboxylase (GAD) which is expressed only in cells which use GABA as neurotransmitter. GABA-T metabolises GABA to succinic semialdehyde. This transamination happens when α-ketoglutarate is present to accept the amino group removed from GABA, reforming glutamic acid. α-GABA molecule can only be metabolised if a precursor molecule is formed. Succinic semialdehyde dehydrogenase (SSADH) oxidises succinic semialdehyde to succinic acid. It can enter the Krebs cycle, thereby completing the loop [49]. Presynaptic neurone depolarisation releases GABA to synaptic cleft and diffuses towards postsynaptic receptors. GABA action at synapse is stopped by reuptake to glial cell as well as to presynaptic nerve terminals. The plasma membrane transport system which reuptakes GABA is ion dependent as well as temperature dependent. They require extracellular Na^+ ions and have a dependence on Cl^- ions. The GABA which undergoes reuptake to nerve terminals is available for utilisation again. GABA in glia undergoes metabolism to succinic semialdehyde by GABA-T and cannot be synthesised again from glutamate as glia lack GAD. GABA in glia becomes glutamine which is transported to neurone, where it is converted to glutamate by glutaminase and reenters GABA shunt.



2.7 Glycine

2.7.1 Chemistry



2.7.2 Location and function

Glycine is a major inhibitory neurotransmitter in CNS, mainly in spinal cord and brainstem, where it is important for motor neurone activity regulation [49]. Many amino acids activate the inhibitory glycine receptor. Glycine acts as a neurotransmitter in inhibitory ion channel receptors. It also activates ligand at excitatory ion channel receptor, the *N*-methyl-D-aspartate (NMDA) receptors.

3 Exogenous Agents in Nervous System

These include chemicals that can modify the general make-up of nervous system and are listed in Table 2 along with clinical applications.

Table 2 Exogenous agents modulating nervous system

Exogenous agents acting on nervous system	Mechanism of action	Therapeutic application
Anti-cholinesterases Tacrine Donepezil Rivastigmine Galantamine	Inhibit acetylcholine hydrolysis, thereby enhancing acetylcholine concentration	Treatment in Alzheimer's disease
Indirectly acting α-agonists Amphetamine Methamphetamine	CNS effect by releasing biogenic amines from storage vesicles in the nerve terminal	Treatment of ADHD, narcolepsy, obesity
Indirectly acting α-agonists Ephedrine	Enhance norepinephrine release by binding to both α and β receptors	Bronchodilator for treatment of asthma, nasal congestion, treatment of acute renal failure
Centrally acting sympatholytics Clonidine Guanabenz Methyldopa	Block adrenergic receptors centrally	Treatment of hypertension
Tizanidine		Treatment of spasticity
5-HT agonist		
Buspirone Ipsapirone	Binding on $5HT_{1A}$ produces partial agonistic action	Treat anxiety, depression
Sumatriptan	Ability of $5HT_{1B}$ and $5HT_{1D}$ receptors to cause constriction of intracranial blood vessels	Treatment of migraine
Methysergide Risperidone Ketanserin	Blockade of 5-HT_2 receptors (5-HT_{2A} and 5-HT_{2C})	Prophylactic treatment of migraine, depression, schizophrenia
DA receptor agonist (ergot alkaloids) Bromocriptine	D_2 receptor agonist	Treatment of Parkinson disease
Pergolide	Partial D_1 receptor agonist	Treatment of Parkinson disease
DA receptor agonist (non-ergot alkaloids) Apomorphine	Binding to DA receptors such as D_4, D_2, D_3, D_5	Treatment of Parkinson disease

Table 2 (continued)

Exogenous agents acting on nervous system	Mechanism of action	Therapeutic application
DA antagonist Chlorpromazine Clozapine Aripiprazole	Binding onto D_2 receptors and produce antagonism	Atypical antipsychotics
GABA agonists Muscimol Baclofen	Binding to $GABA_A$ produces agonistic action	Has been used to treat Parkinson disease and epilepsy in clinical trials
	Binding to $GABA_B$ produces agonistic action	
2-OH-Saclofen	Binding to $GABA_B$	Used to treat muscle spasms resulted from conditions such as spinal cord injury, multiple sclerosis
Benzodiazepines	Bind to benzodiazepine receptors in the site of GABA	General anaesthetics, sedative-hypnotics, antianxiety

4 Conclusion

The endogenous chemicals involved in the brain include acetylcholine, catecholamines including dopamine, norepinephrine and epinephrine, serotonin, histamine, glutamate, GABA and glycine. Many are chemical messengers known as neurotransmitters and are involved in the complex communication between neurons known as neurotransmission. The presence of these receptors in various locations of the brain and their presence outside the CNS in various cells, tissues and organs are responsible for the regulation of human brain and other vital organs as well as many vital processes happening in these organs. Any imbalance in the pathway of these neurotransmitters in various steps such as synthesis, storage, release, metabolism and reuptake leads to the development of variable diseases which can be treated or managed by various exogenous agents. Many are structural analogues of endogenous agents or other chemicals which modulate neurotransmission and modify any of the steps such as synthesis, storage, release, metabolism and reuptake, thereby increasing or decreasing the level of neurotransmitters, thereby treating or managing the disease conditions. Many of the endogenous agents play a crucial role in behavioural development, and have a close association with anaesthesia and neurological diseases such as depression, anxiety and psychosis. A touch of the molecular mechanism gives us the possible targets for treatment and its wide opportunity in future drug discovery.

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Chemistry of Neurochemicals: Psychopharmaceuticals and Neuropeptides

Gayatri Gopal Shetgaonkar and Lalit Kumar

1 Introduction

Neuropeptide signals are potentially more different than signals generated with more commonly expressed typical neurotransmitters with lower molecular weight and hence active pharmaceutical ingredients occupying neuropeptide receptors show highly selective pharmacological action and thus less side effects compared to active molecules acting on neurotransmitter receptors. The number of neuropeptides and their cognate receptors provide possibilities to define new objectives for targeting disorders of CNS. All antagonist and agonist subtypes of selective receptors are developed as well as the modulators of neuropeptide receptors. These ligands thus show effectiveness for preclinical/clinical model of pain as well as neuropsychiatric disease. This chapter thus discusses how psychopharmaceuticals and neuropeptide neurochemicals affect the function of neurons, synapses, and neural networks by binding to different receptors and produce changes in brain-behavioral conditions.

Chemistry of neurochemicals is the study of how the neurochemicals like neurotransmitters, psychopharmaceuticals, and neuropeptides influence the operation of neurons, synapses, and neural networks. Any changes in the electrophysiological activity of these neurochemicals can be responsible for changes in the brain and behavioral conditions [1]. For examples, food uptake and energy homeostasis are evoked by neuropeptide ghrelin expressed in brain and stomach [2]. Regulation of sleep is mediated by vertebrate hypothalamic RFamide neuropeptide VF (NPVF) [3]. Psychosis arises as a result of the dopaminergic activity imbalance in the brain [4].

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2 Neuropeptides

"Neuropeptides are small polypeptides produced and released by neurons through the regulated secretary route and thereby acting on neural substrates [5]. These type of neurochemicals influence the activity of the brain neuronal system and the peripheral nervous system. Neuropeptides are important factors in the brain, regulating activities like memory [6].

The neuron is the keyword to be considered with respect to the secretion of peptides [6]. However, glial cells also express neuropeptides [7].

3 Classification of Neuropeptide

The amount of human genome-encoded neuropeptides surpassed 250 molecules [8], with over 100 molecules present in the CNS [6]. Neuropeptides are categorized into distinct families on the basis of structural homology [8].

As discussed above neuropeptides are localized in a range of CNS neurons where they modulate neuronal functions. The classical neuropeptides secreted in the brain neurons of humans are highlighted in Table 1 [5].

4 Secretion of Neuropeptide

Neuropeptides are secreted along with the neurotransmitter's small vesicles as dense core vesicles (DCVs) or can be secreted individually as dense core vesicles. This is mostly observed in hypothalamus; however in the hippocampal region a surfeit of neuropeptides are synthesized, particularly by GABAergic neuron like neuropeptide Y, substance P, vasoactive intestinal polypeptide, cholecystokinin, enkephalin, somatostatin, neurokinin B, and dynorphin [9]. Following data focuses on the roles of some of the widely studied neuropeptides:

4.1 Apelins

Apelin is encoded by the gene APLN and binds to the APJ receptor. It is articulated on adipose tissue, gastrointestinal tract, brain, heart, lung, kidney, and liver [10, 11]. After cleavage from proprotein they are classified as apelin 36, apelin 17, and apelin 13. Expression of apelin in the brain controls food and water intake [12]. It leads to reduction in hypothalamic secretion of antidiuretic hormone vasopressin. The diuretic effect of this, in alliance with its hypotensive effect, participates in the maintaining of equilibrium of body fluid. It also helps in controlling appetite [13–15]. Structural formula of apelin is depicted in Fig. 1.

Table 1 Classification of neuropeptides (*Homo sapiens*) based on family

Family of neuropeptides	Neuropeptides	Number of amino acids
7B2	C-terminal peptide (by similarity)	13
7B2	N-terminal peptide (by similarity)	150
7B2	Neuroendocrine protein 7B2	186
ACBP	Acyl-CoA-binding protein	86
ACBP	Acyl-CoA-binding domain-containing protein 7	88
Adrenomedullin	Proadrenomedullin N-20 terminal peptide	20
Adrenomedullin	Intermedin-short (potential)	40
Adrenomedullin	Adrenomedullin-2	47
Adrenomedullin	Adrenomedullin	52
Apelin	Apelin-13 (by similarity)	13
Apelin	Apelin-28 (by similarity)	28
Apelin	Apelin-31 (by similarity)	31
Apelin	Apelin-36 (by similarity)	36
Bombesin/neuromedin-B/ ranatensin	Neuromedin-B	10
Bombesin/neuromedin-B/ ranatensin	Neuromedin-C	10
Bombesin/neuromedin-B/ ranatensin	Gastrin-releasing peptide	27
Bombesin/neuromedin-B/ ranatensin	Neuromedin-B-32	32
Bradykinin	Bradykinin	9
Bradykinin	Lysyl-bradykinin	10
Bradykinin	T-kinin	14
Calcitonin	Katacalcin	21
Calcitonin	Calcitonin	32
Calcitonin	Islet amyloid polypeptide	37
Calcitonin	Calcitonin gene-related peptide 2	37
Calcitonin	Calcitonin gene-related peptide 1	37
CART	CART(1–39)	39
CART	CART(42–89)	48
CART	Cocaine and amphetamine regulated	89
Cerebellins	[des-Ser1]-cerebellin	15
Cerebellins	Cerebellin	16
Cerebellins	Cerebellin-1	172
Cerebellins	Cerebellin-2	173
Cerebellins	Cerebellin-3	173
Cerebellins	Cerebellin-4	174
Chromogranin/secretogranin	WA-8	8
Chromogranin/secretogranin	AL-11	11
Chromogranin/secretogranin	WE-14	14

(continued)

Table 1 (continued)

Family of neuropeptides	Neuropeptides	Number of amino acids
Chromogranin/secretogranin	SS-18	18
Chromogranin/secretogranin	LF-19	19
Chromogranin/secretogranin	GV-19	19
Chromogranin/secretogranin	Secretoneurin	33
Chromogranin/secretogranin	ES-43	33
Chromogranin/secretogranin	ER-37	37
Chromogranin/secretogranin	GR-44	44
Chromogranin/secretogranin	Pancreastatin	48
Chromogranin/secretogranin	CCB peptide	57
Chromogranin/secretogranin	GAWK peptide	74
Chromogranin/secretogranin	Vasostatin-1	76
Chromogranin/secretogranin	EA-92	92
Chromogranin/secretogranin	Vasostatin-2	113
Chromogranin/secretogranin	Chromogranin-A	439
Chromogranin/secretogranin	Secretogranin-3	449
Chromogranin/secretogranin	Secretogranin-2	587
Chromogranin/secretogranin	Secretogranin-1	657
Cystatin	Low-molecular-weight growth-promoting factor	4
Cystatin	Kininogen-1 light chain	255
Cystatin	Kininogen-1 heavy chain	362
Cystatin	Kininogen-1	626
Endothelin/sarafotoxin	Endothelin-3	21
Endothelin/sarafotoxin	Endothelin-2	21
Endothelin/sarafotoxin	Endothelin-1	21
Endothelin/sarafotoxin	Big endothelin-1	38
FMRFamide-related peptide	Neuropeptide NPVF	8
FMRFamide-related peptide	Neuropeptide FF	8
FMRFamide-related peptide	Neuropeptide SF	11
FMRFamide-related peptide	Neuropeptide RFRP-2 (potential)	12
FMRFamide-related peptide	Neuropeptide RFRP-1	12
FMRFamide-related peptide	Neuropeptide AF	18
FMRFamide-related peptide	Prolactin-releasing peptide PrRP20	20
FMRFamide-related peptide	Prolactin-releasing peptide PrRP31	31
FMRFamide-related peptide	Neuropeptide NPSF (potential)	37
Galanin	Galanin	30
Galanin	Galanin message-associated peptide	59
Galanin	Galanin-like peptide	60
Gastrin/cholecystokinin	Cholecystokinin-5 (by similarity)	5
Gastrin/cholecystokinin	Gastrin-6	6
Gastrin/cholecystokinin	Cholecystokinin-7 (by similarity)	7
Gastrin/cholecystokinin	Cholecystokinin-8	8
Gastrin/cholecystokinin	Cholecystokinin-12	12

Table 1 (continued)

Family of neuropeptides	Neuropeptides	Number of amino acids
Gastrin/cholecystokinin	Gastrin-14	14
Gastrin/cholecystokinin	Gastrin-17	17
Gastrin/cholecystokinin	Cholecystokinin-18	18
Gastrin/cholecystokinin	Cholecystokinin-25	25
Gastrin/cholecystokinin	Cholecystokinin-33	33
Gastrin/cholecystokinin	Big gastrin (gastrin-34)	34
Gastrin/cholecystokinin	Cholecystokinin-39	39
Gastrin/cholecystokinin	Cholecystokinin-58 desnonapeptide	49
Gastrin/cholecystokinin	Gastrin-52	52
Gastrin/cholecystokinin	Cholecystokinin-58	58
Gastrin/cholecystokinin	Gastrin-71	71
Gastrin/cholecystokinin	Cholecystokinin	95
Glucagon	Secretin	27
Glucagon	Pituitary adenylate cyclase-activating polypeptide 27	27
Glucagon	Intestinal peptide PHM-27	27
Glucagon	Vasoactive intestinal peptide	28
Glucagon	Glucagon	29
Glucagon	Glicentin-related polypeptide	30
Glucagon	Glucagon-like peptide 1(7–36)	30
Glucagon	Glucagon-like peptide 1(7–37)	31
Glucagon	Glucagon-like peptide 2	33
Glucagon	Oxyntomodulin	37
Glucagon	Glucagon-like peptide 1	37
Glucagon	Pituitary adenylate cyclase-activating polypeptide 38	38
Glucagon	Gastric inhibitory polypeptide	42
Glucagon	Intestinal peptide PHV-42	42
Glucagon	Somatoliberin	44
Glucagon	PACAP-related peptide	48
Glucagon	Glicentin	69
GnRH	Gonadoliberin-1	10
GnRH	Gonadoliberin-2	10
GnRH	GnRH-associated peptide 1	56
GnRH	Progonadoliberin-1	69
GnRH	GnRH-associated peptide 2	84
GnRH	Progonadoliberin-2	97
Insulin	Insulin A chain	21
Insulin	Relaxin A chain (by similarity)	23
Insulin	Relaxin A chain	24
Insulin	Relaxin-3 A chain (by similarity)	24
Insulin	Relaxin-3 B chain (by similarity)	27
Insulin	Relaxin B chain	29

(continued)

Table 1 (continued)

Family of neuropeptides	Neuropeptides	Number of amino acids
Insulin	Insulin B chain	30
Insulin	Relaxin B chain (by similarity)	31
Insulin	Preptin	34
Insulin	Insulin-like growth factor II Ala-25 Del	66
Insulin	Insulin-like growth factor II	67
Insulin	Insulin-like growth factor I	70
KISS1	Kisspeptin-10	10
KISS1	Kisspeptin-13	13
KISS1	Kisspeptin-14	14
KISS1	Metastin	54
KISS1	Metastasis-suppressor KiSS-1	119
Leptin	Leptin	146
Melanin-concentrating hormone	Neuropeptide-glutamic acid-isoleucine	13
Melanin-concentrating hormone	Neuropeptide-glycine-glutamic acid (potential)	19
Melanin-concentrating hormone	Melanin-concentrating hormone	19
Melanin-concentrating hormone	Pro-MCH	144
Motilin	Motilin	22
Motilin	Obestatin	23
Motilin	Ghrelin-27	27
Motilin	Ghrelin-28	28
Motilin	Motilin-associated peptide	66
Motilin	Promotilin	90
NA	Ubiquitin-like protein 5	73
Agouti-related protein gene	Agouti-related protein	112
NA	Adiponectin	226
NAPRTase	Nicotinamide phosphoribosyl transferase	491
Natriuretic peptide	CNP-22	22
Natriuretic peptide	BNP(4–27)	24
Natriuretic peptide	BNP(5–29)	25
Natriuretic peptide	BNP(4–29)	26
Natriuretic peptide	BNP(5–31)	27
Natriuretic peptide	BNP(4–30)	27
Natriuretic peptide	BNP(3–29)	27
Natriuretic peptide	BNP(5–32)	28
Natriuretic peptide	BNP(1–28)	28
Natriuretic peptide	Atrial natriuretic factor	28
Natriuretic peptide	BNP(4–31)	28
Natriuretic peptide	BNP(3–30)	28
Natriuretic peptide	CNP-29	29
Natriuretic peptide	BNP(1–29)	29

Table 1 (continued)

Family of neuropeptides	Neuropeptides	Number of amino acids
Natriuretic peptide	BNP(4–32)	29
Natriuretic peptide	BNP(1–30)	30
Natriuretic peptide	BNP(2–31)	30
Natriuretic peptide	Cardiodilatin-related peptide	30
Natriuretic peptide	BNP(3–32)	30
Natriuretic peptide	Brain natriuretic peptide 32	32
Natriuretic peptide	CNP-53	53
Natriuretic peptide	Natriuretic peptide B	108
Neurexophilin	Neurexophilin-3	230
Neurexophilin	Neurexophilin-2	242
Neurexophilin	Neurexophilin-1	250
Neurexophilin	Neurexophilin-4	285
Neuromedins	Neuromedin-U-25	25
Neuromedins	Neuromedin-S	33
Neuropeptide B/W	Neuropeptide W-23	23
Neuropeptide B/W	Neuropeptide B-23	24
Neuropeptide B/W	Neuropeptide B-29	29
Neuropeptide B/W	Neuropeptide W-30	30
Neuropeptide S	Neuropeptide S	20
Neurotensin	Neuromedin N	5
Neurotensin	Tail peptide (potential)	5
Neurotensin	Neurotensin	13
Neurotensin	Large neuromedin N	125
NPY	Pancreatic icosapeptide	20
NPY	C-flanking peptide of NPY	30
NPY	Peptide YY(3–36)	34
NPY	Neuropeptide Y	36
NPY	Peptide YY	36
NPY	Pancreatic hormone	36
Nucleobindin	Nesfatin-1	82
Nucleobindin	Nucleobindin-2	396
Nucleobindin	Nucleobindin-1	435
Opioid	Met-enkephalin	5
Opioid	Leu-enkephalin	5
Opioid	Met-enkephalin-Arg-Phe	7
Opioid	Deltorphin I	7
Opioid	Met-enkephalin-Arg-Gly-Leu	8
Opioid	Dynorphin A(1–8)	8
Opioid	Beta-neoendorphin	9
Opioid	Alpha-neoendorphin	10
Opioid	γ-Melanocyte-stimulating hormone	12
Opioid	Rimorphin	13

(continued)

Table 1 (continued)

Family of neuropeptides	Neuropeptides	Number of amino acids
Opioid	Dynorphin A(1–13)	13
Opioid	Dynorphin A(1–17)	17
Opioid	Neuropeptide 2	17
Opioid	Nociceptin	17
Opioid	PENK(114–133)	20
Opioid	PENK(237–258)	22
Opioid	Leumorphin	29
Opioid	Neuropeptide 1 (probable)	30
Opioid	Big dynorphin	32
Opioid	PENK(143–183) (by similarity)	41
Opioid	Gamma-lipotropin	57
Opioid	Synenkephalin	73
Orexin	Orexin-B	28
Orexin	Orexin-A	33
Parathyroid hormone	Osteostatin	33
Parathyroid hormone	PTHrP[1–36]	36
Parathyroid hormone	Tuberoinfundibular peptide of 39 residues	39
Parathyroid hormone	PTHrP[38–94]	57
Parathyroid hormone	Parathyroid hormone-related protein	141
POMC	Melanotropin gamma	11
POMC	Melanotropin alpha	13
POMC	Melanotropin beta	18
POMC	Corticotropin-like intermediary peptide	21
POMC	Potential peptide	30
POMC	Beta-endorphin	31
POMC	Corticotropin	39
POMC	Lipotropin gamma	56
POMC	NPP	76
POMC	Lipotropin beta	89
ProSAAS	KEP (by similarity)	7
ProSAAS	Little LEN (by similarity)	10
ProSAAS	Big LEN (by similarity)	16
ProSAAS	Little SAAS (by similarity)	18
ProSAAS	PEN (by similarity)	22
ProSAAS	Big SAAS (by similarity)	26
ProSAAS	Big PEN-LEN (by similarity)	40
ProSAAS	ProSAAS	227
Resistin/FIZZ	Resistin-like beta	88
Resistin/FIZZ	Resistin	90
RFamide neuropeptide	QRF-amide	43

Table 1 (continued)

Family of neuropeptides	Neuropeptides	Number of amino acids
Sauvagine/corticotropin-releasing factor/urotensin I	Urocortin-3	38
Sauvagine/corticotropin-releasing factor/urotensin I	Urocortin	40
Sauvagine/corticotropin-releasing factor/urotensin I	Corticoliberin	41
Sauvagine/corticotropin-releasing factor/urotensin I	Urocortin-2	41
Serpin	Angiotensin 1–4	4
Serpin	Angiotensin 1–5	5
Serpin	Angiotensin-4	6
Serpin	Angiotensin-3	7
Serpin	Angiotensin 1–7	7
Serpin	Angiotensin-2	8
Serpin	Angiotensin 1–9	9
Serpin	Angiotensin-1	10
Serpin	Corticosteroid-binding globulin	383
Serpin	Serpin I2	387
Serpin	Serpin A12	394
Serpin	Serpin A11	403
Serpin	Angiotensinogen	452
Somatostatin	Somatostatin-14	14
Somatostatin	Cortistatin-17	17
Somatostatin	Somatostatin-28	28
Somatostatin	Cortistatin-29	29
Somatotropin/prolactin	Prolactin	199
Tachykinin	Substance P	10
Tachykinin	Neurokinin A	10
Tachykinin	Neurokinin-B	10
Tachykinin	Substance P	11
Tachykinin	C-terminal-flanking peptide	16
Tachykinin	Neuropeptide K	36
TRH	Thyrotropin-releasing hormone	3
TRH	Pro-thyrotropin-releasing hormone	218
Urotensin-2	Urotensin-2B	8
Urotensin-2	Urotensin-2	11
Vasopressin/oxytocin	Oxytocin	9
Vasopressin/oxytocin	Arg-vasopressin	9
Vasopressin/oxytocin	Copeptin	39
Vasopressin/oxytocin	Neurophysin 2	93
Vasopressin/oxytocin	Neurophysin 1	94
VGF	Antimicrobial peptide VGF[554–577]	24
VGF	Neuroendocrine regulatory peptide-1	26
VGF	Neuroendocrine regulatory peptide-2	38
VGF	Neurosecretory protein VGF	593

4.2 Neuropeptide Y

It is the most widely secreted neuropeptide in the CNS of humans along with neurochemicals glutamate and GABA. Neuropeptide affects physiological processes like stress reply, cortical excitability, food intake, circadian rhythms, and cardiovascular function. Also by modulating noradrenergic signaling neuropeptide Y regulates sleep [16]. Alteration in its gene function results in higher alcohol consumption, elevated cholesterol levels, and prone risks for metabolic and cardiovascular diseases [17–19]. Structural formula of neuropeptide Y is shown in Fig. 2.

4.3 Neuromedin

Neuromedin U is one of the omnipresent neuropeptides up in gastrointestinal tract and pituitary. It has been expressed for the control of contraction of smooth muscles, blood flow, blood pressure, movement of ions of intestine, tumor, gastric acid secretion stress control, feeding actions, and pronociception [20, 21].

Neuromedin B is another bombesin-related peptide present in CNS and gastrointestinal tract. Its binding to 7-TMR, the heterotrimeric G-protein, results in activation of cyclic AMP response element-binding protein, which has an impact on learning and long-term memory [22]. Structural formula of neuromedin is depicted in Fig. 3.

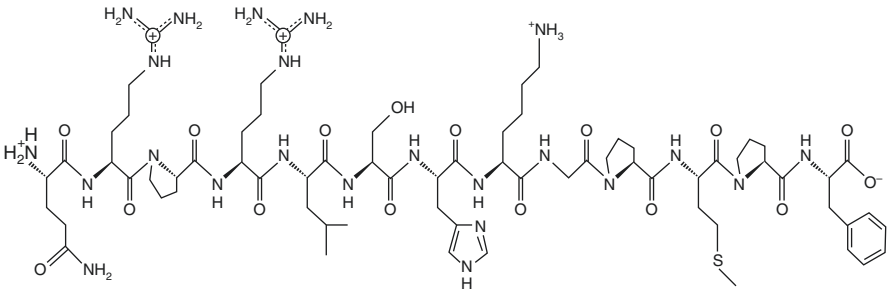

Fig. 1 Chemical structure of apelin

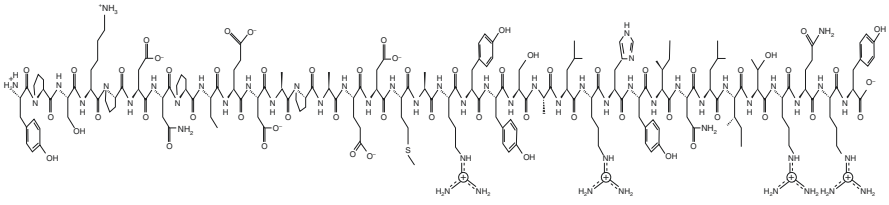

Fig. 2 Structural formula of neuropeptide Y

4.4 Enkephalins

It belongs to the class of endorphin-type neuropeptide. Enkephalins also are known as opioid growth factor. Chemical difference between two types of enkephalin is depicted in Fig. 4. Met-enkephalin produces action by binding to an δ-opioid receptor, and to a smaller extent the μ-opioid receptor, thus producing antidepressant and analgesic effects [23]. It is also found to produce an effect on human sperm motility [24]. L enkephalin also produces the same action with high affinity to δ-opioid receptor and μ-opioid receptor.

4.5 Orexin

Orexin or hypocretin is a peptide commonly expressed in appetite, arousal, and wakefulness as well as in the motivated behavior [25, 26]. Loss of orexin-producing neurons also leads to chronic sleepiness due to narcolepsy, an autoimmune disorder [27]. There are two isoforms of neuropeptide orexin-A and orexin-B. Structural formula of orexin is represented in Fig. 5.

Orexin-A generates neuronal signals by binding with approximately equal affinity to OX1 and OX2, while orexin-B has a strong affinity to OX2. Orexin has also shown to take part in the pathophysiology of ischemic stroke, drug addiction, and Alzheimer's disease (AD) [28, 29].

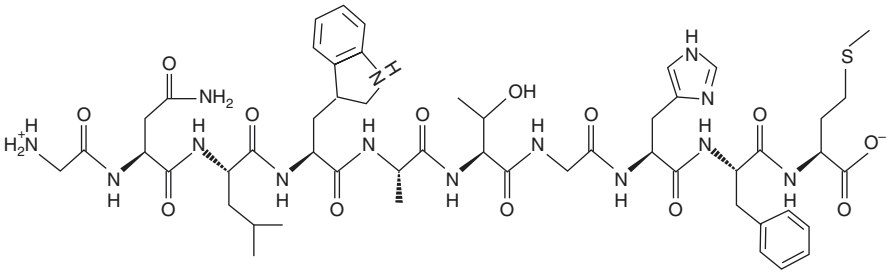

Fig. 3 Structural formula of neuromedin

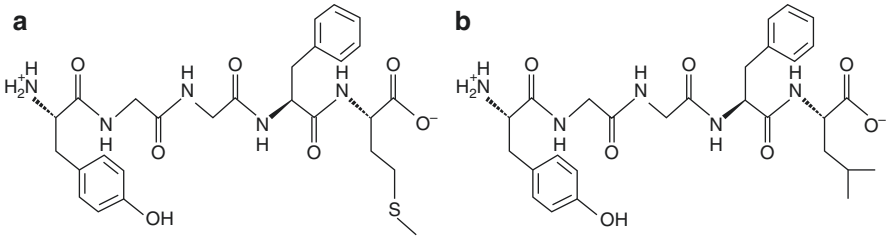

Fig. 4 Structural formula of (**a**) Met-enkephalin and (**b**) Leu-enkephalin

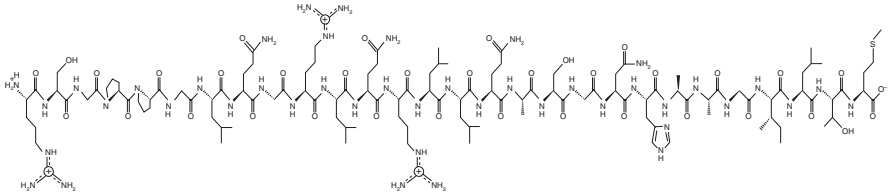

Fig. 5 Structural formula of orexin-B

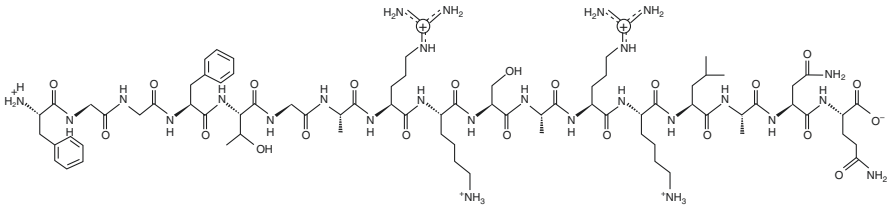

Fig. 6 Structural formula of nociceptin

4.6 Nociceptin

Nociceptin, 17-amino-acid-containing neuropeptide, is a ligand of the opioid receptor [30]. Nociceptin is widely distributed in the body enabling endogenous molecules to modulate its several physiological processes. Nociceptin is distributed in CNS parts like hypothalamus, brainstem, forebrain, and spinal cord [31]. Bonding FQ (N/OFQ), a neuropeptide with 17 amino acids, to the nociceptin receptor (NOP, ORL-1) covers the way for pain and fear learning in the brain. Nociceptin counteracts the effect of pain relievers, thus producing anti-analgesic action [32, 33]. Binding of nociceptin increases pain threshold and also reduces tolerance to analgesic opioids [34]. Structural formula of nociceptin is presented in Fig. 6.

Different animal studies demonstrate that nociceptin plays a role in anxiolysis and depression apprehension [35, 36].

4.7 Endothelin

The vasoconstricting peptides built into the endothelial are 21-amino-acid endothelin. They play a part in various organ systems, such as heart, lung, kidney, and brain, for vascular diseases [37, 38].

Endothelin has isoforms ET 1, 2, and 3 binding to receptors ET_A, ET_{B1}, ET_{B2}, and ET_C. Pituitary lobe expressing endothelin receptors shows increased metabolic activity when endothelin-1 in the blood or ventricular systems binds to it. Structural formula of endothelin is shown in Fig. 7.

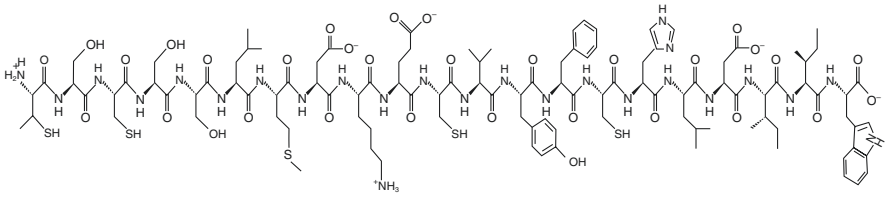

Fig. 7 Structural formula of endothelin

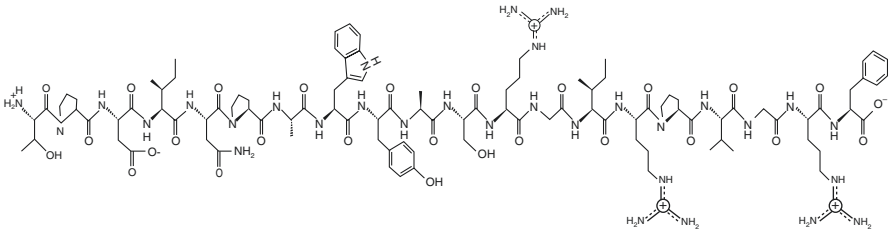

Fig. 8 Structural formula of prolactin-releasing peptide

ET-1 levels were shown to be increased 18 h after stroke in the cerebral spinal fluid and showed an impact on the patient's neurological outbreak [39].

4.8 Prolactin-Releasing Peptide

This neuropeptide binds to the PrRP receptor and plays a role in energy metabolism and endocrine regulation. The 31 (PrRP31) and the 20 (PrRP20) amino acids are two biologically active forms of receptors. It produces the action by MAPK/ERK1/2 (mitogen-activated phosphorylase/extracellular regulated kinase) phosphorylation and CREB (cAMP response element-binding protein), leading to the prolactin discharge. It is also found to reduce food intake and thus can be used in obesity [40, 41]. Structural formula of prolactin-releasing peptide is represented in Fig. 8.

4.9 Galanin

Galanin is broadly manifested in humans as well as other mammals in the brain, spinal cord, and intestine. It is programmed by the GAL gene, signaled by three GPCRs [42, 43].

Galanin is primarily engaged in modulating and inhibiting neuronal action potential. Galanin functions include nociception, cognition, feeding, regulation of

mood, regulation of blood pressure, and waking and sleep regulation, as well as acting as a trophic factor. It is associated with numerous illnesses such as Alzheimer's disease, epilepsy, depression, eating disorders, and cancer [44]. Galanin shows neuroprotective activity, which is especially observed during brain seizures by an increase in its biosynthesis. It is also involved in neurogenesis.

Galanin, hyperpolarizing neuropeptide, inhibits the release of neurotransmitters. Galanin is frequently coupled with conventional neurotransmitters like acetylcholine, serotonin, and norepinephrine, as well as other neuromodulators such as neuropeptide Y, substance P, and vasoactive intestinal peptide [35, 36]. Structural formula of galanin is revealed in Fig. 9.

4.10 Neurotensin

Neurotensin is a peptide with 13 amino acids, found in CNS, and is involved in digestive system. The endogenous peptide itself and the agonists produce its action through NT-1 and NT-2 receptors.

In the nigrostriatal and mesolimbic pathways, it involves analgesia, thermoregulation, and interaction with dopamine function [45]. It is predicted that it plays a part in schizophrenia, drug abuse, Parkinson's disease, pain mechanism, eating disorder, cancer, and inflammation. Structural formula of it is represented in Fig. 10.

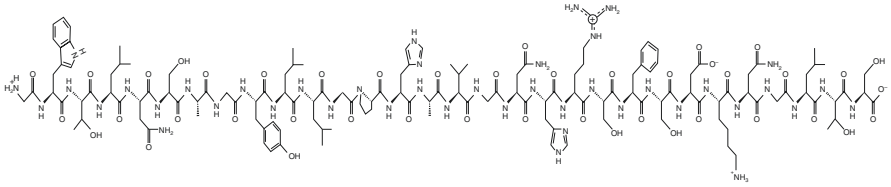

Fig. 9 Structural formula of galanin

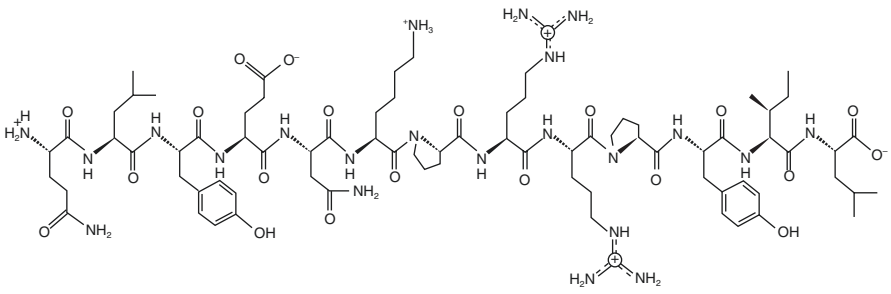

Fig. 10 Structural formula of neurotensin

4.11 Vasopressin

Vasopressin is implicated in cognitive enhancement and learning memory in the CNS. Structural formula of vasopressin is shown in Fig. 11.

It produces its action through V1a, V1b, and V2 receptors [46]. Vasopressin and V1a receptors are involved in maintenance of brain water and ion homeostasis, likely by aquaporin-mediated water transport via astrocyte plasma membranes [47].

4.12 Somatostatin

SRIF 14 and SRIF 28 are two isoforms of somatostatin. They are extensively dispersed in CNS and have a role in opening potassium channel, thus producing an inhibitory effect on neurons.

SRIF 14 produces action by binding to sst 2, 3, and 4 while SRIF 28 produces action by binding to sst 1 and 4. It produces antinociception action in the spinal cord and is involved in controlling the release of growth hormone [48]. Structural formula of somatostatin is depicted in Fig. 12.

Together with GABA, Somatostatin presence in dendritic targeting GABA neuron deficit, it is involved in cortical local inhibitory circuit deficit, which leads to abnormal cortical limbic network activity and clinical mood symptoms across neurological disorder [49].

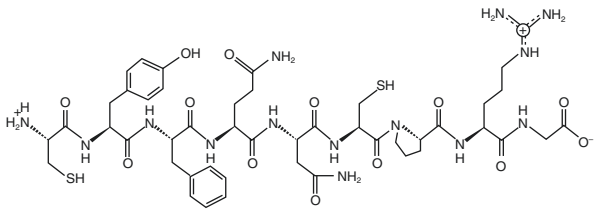

Fig. 11 Structural formula of vasopressin

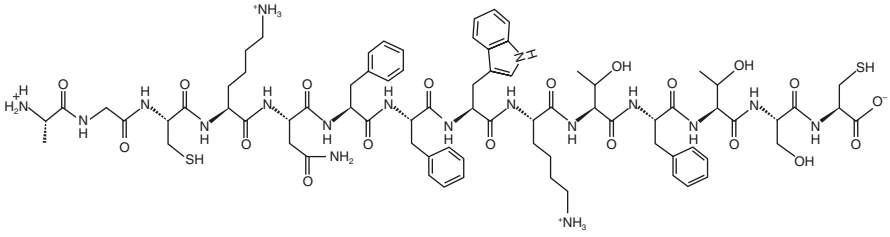

Fig. 12 Structural formula of somatostatin 14

5 Receptors for Neuropeptide

Neuropeptides are the type of neurochemicals that produce neuronal signals by acting on cell surface receptors. Like in the case of a neurotransmitter, neuropeptide release is not restricted to the synapse, but after discharge, it can spread over a certain distance to produce its action via a receptor that is regulated by G-protein (GPCR). Activation results in GDP switch to GTP and thus dissociation of the G-protein from its coupled receptor. Further peptide signals are then augmented by the induction of multiple intracellular secondary signal developing pathways like activation of adenylyl cyclase-cAMP and phosphatidylinositol pathway. Peptides are found to be exhibited not only at postsynaptic receptors but also on axon terminal, dendrites, and cell bodies [9].

6 Psychopharmaceuticals

The word psychopharmaceuticals is used to define any chemical substance that impacts mood, perception, or awareness due to modifications in the performance of brain neuronal network. Psychopharmaceuticals are therefore limited not only to the therapy of illnesses connected with the brain, but also to the therapy of cognitive modifications [50].

6.1 Neurodegenerative Disorder

Neurodegenerative diseases mean breaking down or death of the neuron. The features of these diseases include the following:

6.1.1 Parkinson's Disease

1. Slowness or loss of movement called bradykinesia or akinesia
2. Tremors of limbs
3. Stiffness of muscle and rigidity

This is seen because of the deterioration of neurons in substantia nigra. Since it forms dopaminergic nigrostriatal tract Parkinson's shows loss of striatal dopamine, which is a core feature of pathology. Thus, the psychopharmaceuticals used for treatment should focus on the following:

1. Increase the action of dopamine
2. Modify other neurotransmitter (NT) action that might oppose or boost dopamine (DA) functions

This can be achieved by increasing the action of remaining dopamine, replenishing DA by giving levodopa, mimicking the action of dopamine receptor agonists,

blocking the action of neurotransmitters that are blocked by the dopamine, and blocking the pathways that dopamine inhibits or stimulates.

1. *Increasing the action of remaining dopamine*

   It can be achieved by inhibiting the uptake of dopamine in presynaptic neuron, e.g., nomifensine which is a potent dopamine reuptake inhibitor, and also by selectively inhibiting the monoamine oxygenase B enzyme, e.g., selegiline, rasagiline, and safinamide.
2. *Replenishment of dopamine*

   This effect cannot be achieved by using intravenous administration of dopamine but can be gained by giving in the form of levodopa.

   The enzyme DOPA decarboxylase converts levodopa to dopamine in the periphery and by COMT to 3-methoxy tyrosine, which can be prevented by administrating extracerebral decarboxylase inhibitor carbidopa (alpha-methyldopa hydrazine) and benserazide. Catecholamine methyltransferase inhibitors include entacapone and tolcapone [51]. Chemical structure of drugs used to treat the diseases is shown in Figs. 13, 14, 15, and 16.

   Since there is no decrease in the amount of dopamine receptors postsynaptically dopa agonists can be used. Agonists for dopamine produce their antiparkinsonism activity by binding directly to dopamine receptors and thus restricting endogenous neurotransmitter. These subclasses are aimed at D_2-type receptors of the dopamine. Dopamine agonists are classified into two types ergo-

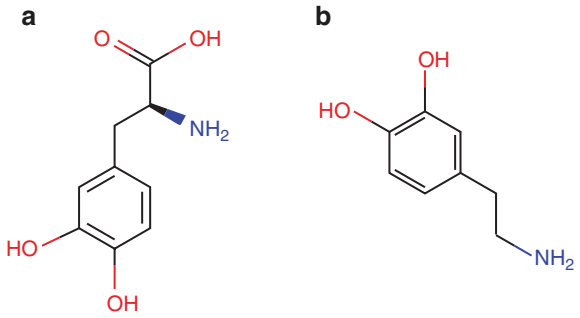

Fig. 13 Structural formula of (**a**) levodopa and (**b**) dopamine

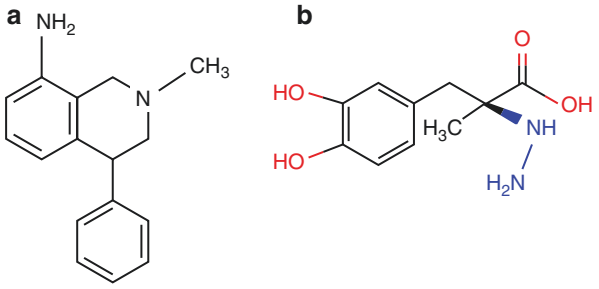

Fig. 14 Structural formula of (**a**) selegiline and (**b**) carbidopa

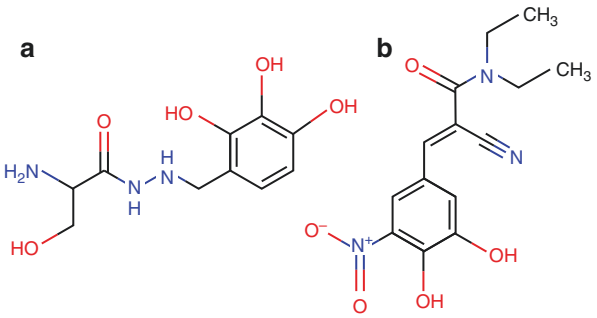

Fig. 15 Structural formula of (**a**) benserazide and (**b**) entacapone

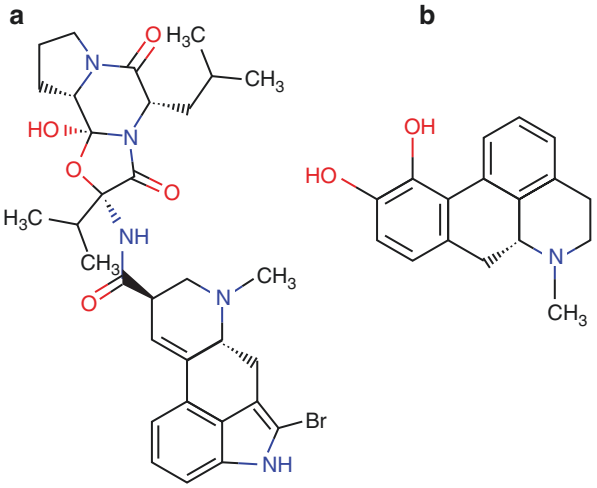

Fig. 16 Structural formula of (**a**) bromocriptine and (**b**) apomorphine

line and non-ergoline type. Agonists of ergoline dopamine include bromocriptine, pergolide, lisuride, and cabergoline, while ropinirole and pramipexole are non-ergoline agonists [51].

Apomorphine is a dopamine receptor agonist that is used subcutaneously [52]. Dopamine prevents firing of the cholinergic neuron and also acetylcholine (ACh) release through D_2 receptor. Drained ACh activates the neurons of GABA/Enk through M1 receptors that oppose dopamine's inhibitory action on them. Without dopamine, release of ACh is more and its exciting impact on GABA/Enk cells cannot be hindered. This allows the use of antimuscarinic drug atropine [53].

6.1.2 Alzheimer's Disease

Alzheimer's disease is a disease that grows gradually and causes brain cells to emaciate and die. It is the most prevalent cause of dementia that leads to a decrease in the strength of thinking, cognitive, and social abilities that interrupt the capacity of a person to operate separately.

Alzheimer's disease is recognized in the cerebral cortex and subcortical areas by degenerating neurons and synapses. Cholinesterase inhibitors and memantine are the drugs approved for Alzheimer's therapy.

Treatment of Alzheimer's disease includes the following:

1. The manipulation of neurotransmitter that is lost or reduced by the neurodegeneration
2. Reduction and reversal of factors leading to amyloid formation

Acetylcholine (Ach) activity can be enhanced by:

Synthesis promotion by giving choline precursor, stopping degradation by cholinesterase, and reproducing action using muscarinic and nicotinic agonist. The disease is marked by a decrease in the role of the cholinergic neuron. The use of cholinergic acetylcholinesterase inhibitors decreases the rate of decomposition of acetylcholine (ACh), thereby elevating Ach concentration in CNS and resisting the ACh loss caused by the degeneration of cholinergic neurons.

Tacrine, velnacrine, and aminoacridine are centrally active reversible cholinesterase inhibitors [54]. Donepezil is also a piperidine derivative specifically intended with reversible acetylcholinesterase inhibitor activity [55]. Also known as pseudo-irreversible rivastigmine, an acetyl cholinesterase inhibitor, produces the same action as ACh by binding to the enzyme acetylcholinesterases (AChe) leading to carbamylated complex, thus stopping ACh binding [56].

Metrifonate is an irreversible organophosphate acetylcholinesterase inhibitor [57]. Galantamine has shown to increase the amount of acetylcholine at the synaptic level by decreasing its enzymatic degradation through acetylcholinesterases [58].

6.2 Muscarinic Agonists

Amyloid plaque formation reduces the potential of muscarinic receptors to transmit signals, causing decreased cholinergic activity. However muscarinic receptors last permanently and thus have become an active therapeutic target to upgrade cognitive function in patients with diseases. Drugs such as methacholine, carbachol, and bethanechol are resistant to cholinesterase but structurally comparable to Ach.

Nicotine also stimulates presynaptic receptors on cholinergic nerve terminal that produces increased ACh release.

Glutamatergic mechanism plays a major role in rapid synaptic transmission and learning and memory procedures that are significantly disrupted in Alzheimer's disease due to increased oxidative stress associated with amyloid beta peptide [59].

Structural formula of drugs used in the treatment of Alzheimer's diseases is revealed in Figs. 17, 18, 19, and 20.

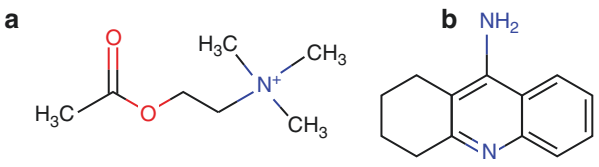

Fig. 17 Structural formula of (**a**) acetyl choline and (**b**) tacrine

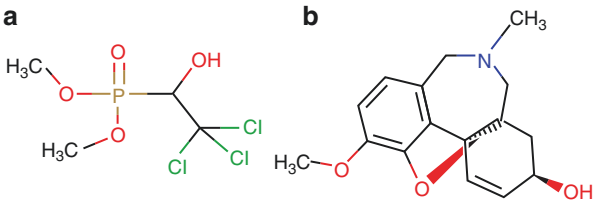

Fig. 18 Structural formula of (**a**) galantamine and (**b**) metrifonate

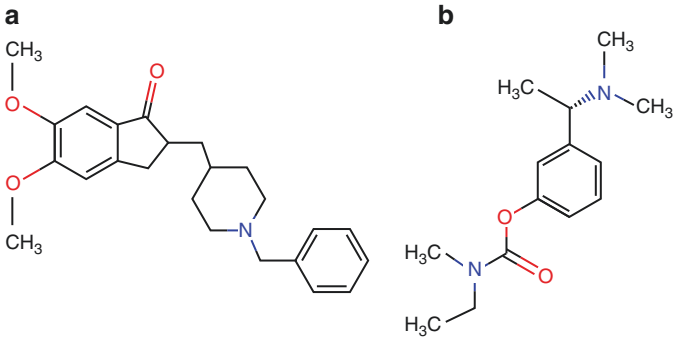

Fig. 19 Structural formula of (**a**) donepezil and (**b**) rivastigmine

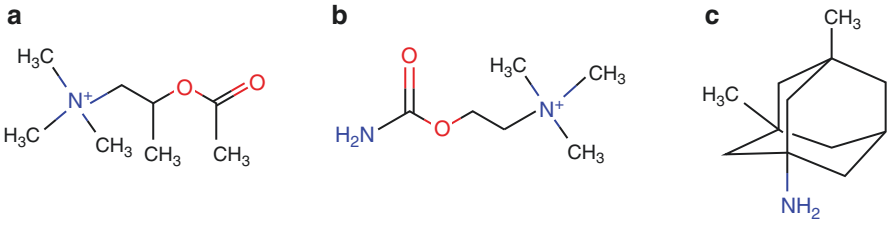

Fig. 20 Structural formula of (**a**) methacholine, (**b**) carbachol, and (**c**) memantine

6.2.1 Epilepsy

This is an episodic nervous system disorder resulting from a group of neurons showing excessive synchronous and sustained discharge. Seizures are prevented by either reducing the excitation or enhancing neuron inhibition.

This is attained by:

1. Growing the amount of gamma-aminobutyric acid (GABA), by preventing its uptake or metabolism or activating GABA receptor
2. Blocking excitatory voltage-gated sodium channel or calcium channel
3. Opening of the inhibitory chloride channel
4. Decreasing the glutamate release or its N-methyl-D-aspartate (NMDA) receptors

Phenytoin indicates no impact on the resting potential of the membrane but reduces the discharge caused by depolarizing the neuron while leaving the first action potential integral.

It generates action by blocking voltage-gated sodium channel; that is, it turns out voltage-gated sodium channel to be inactivated and thus keeps it in an inactivated and unresponsive state.

6.3 Ethosuximide

The transient T-type calcium streams in thalamic neurons, causing epileptic spike and wave release, seemed to be suppressed [60].

6.4 Barbiturates and Benzodiazepines

These drugs produce action through GABA-A-type-mediated activation of chloride ion channel. Phenobarbitone functions directly to extend the opening time while benzodiazepines allosterically change the receptor and enhance the Cl^- channel opening frequency [61, 62].

6.5 Valproic Acid/Sodium Valproate

Gamma-aminobutyric acid (GABA) transaminase is reported to be inhibited, thereby increasing concentrations and inhibition of GABA. But the impact of anti-seizure is generated more quickly than this impact.

6.6 Lamotrigine

Lamotrigine is a new-generation antiepileptic drug [63]. Experimentally, glutamate release and thus its exciting impact have been shown to be reduced.

6.7 Vigabatrin (Gamma-Vinyl GABA)

It is chemically similar to GABA and thus binds to GABA transaminase and produces an irreversible impact on it, leading to an antiepileptic effect. It has also shown to lessen the amount of glutamate.s

6.8 Tiagabine

It is a lipophilic derivative of nipecotic acid that obstructs GABA's neuronal and glial ingestion leading to increased extracellular GABA and prolonged post-excitatory neuronal hyperpolarization.

6.9 Gabapentin

Gabapentin was considered as a cyclohexane analog of GABA, an agonist to its receptor, but has shown to increase GABA level by inhibiting the enzyme GABA transferase and potentiating glutamate decarboxylase (GAD). Structural formula of drugs used in the treatment of epilepsy is shown in Figs. 21 and 22.

6.9.1 Depression

There is a different hypothesis proposed as a cause of depression.

The oldest and widely accepted theory suggests that a functional deficit of monoamine neurotransmitter such as adrenaline and 5-hydroxytryptamine (5-HT) can trigger it. Chemical structure of adrenaline is depicted in Fig. 23.

In addition reduction in the level of brain-derived neurotropic factor or malfunction of its receptor TrkB is associated with depression.

Hypothalamic neurons which control the pituitary function also receive inputs from noradrenergic and 5-HT which control the release of molecules from this cell.

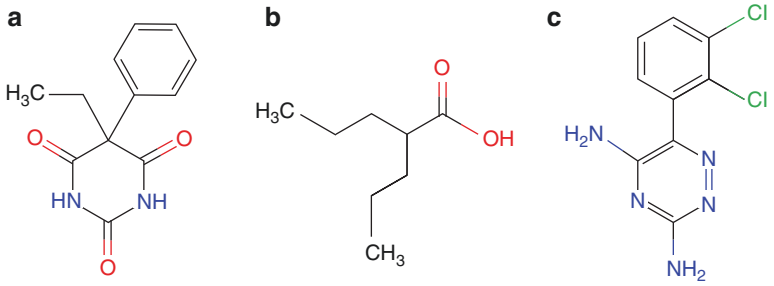

Fig. 21 Structural formula of (**a**) phenobarbitone, (**b**) valproic acid, and (**c**) lamotrigine

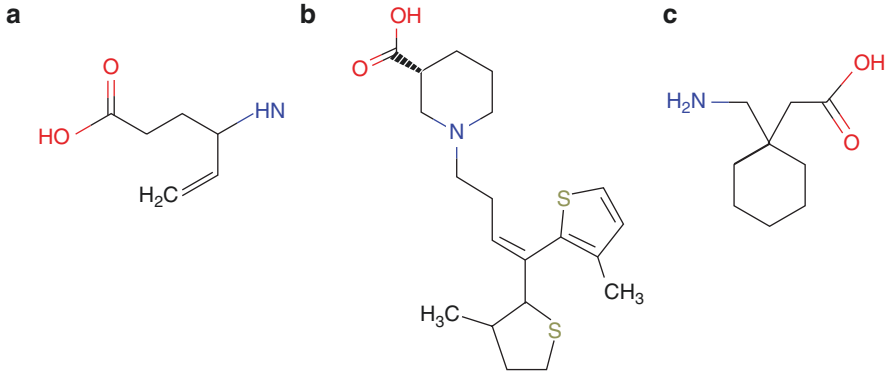

Fig. 22 Structural formula of (**a**) vigabatrin, (**b**) tiagabine, and (**c**) gabapentin

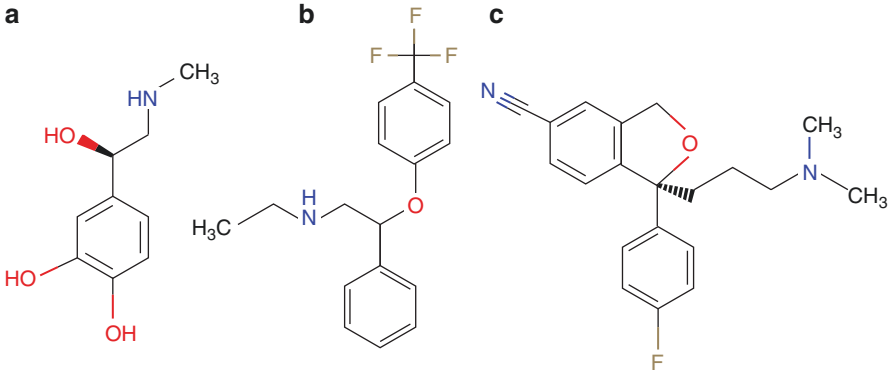

Fig. 23 Structural formula of (**a**) adrenaline, (**b**) fluoxetine, and (**c**) escitalopram

Hypothalamic cells release corticotrophin-releasing hormones that stimulate pituitary cells to secrete adrenocorticotropic hormones that lead to cortical secretion (high in depressed patients).

Antidepressants are medications prescribed for depression and mental health and are type of the medications often prescribed. They include inhibitors of selective serotonin reuptake (SSRIs), atypical antidepressants, tricyclic antidepressants (TCAs), and monoamine oxidase inhibitors (MAOIs). Thus antidepressants majorly act by increasing the concentration of monoamines 5-HT and noradrenaline in the synaptic cleft [64] and availability for binding.

7 Selective Serotonin Reuptake Inhibitors (SSRIs)

SSRIs are frequently prescribed antidepressants. Examples include fluoxetine, paroxetine, citalopram, escitalopram, and sertraline.

7.1 Fluoxetine and Paroxetine

It is used to treat depression, obsessive compulsive disorder [65], bulimia [66], panic disorder [67], premenstrual dysphoric disorder [68], and post-traumatic disorder [69].

Escitalopram is used for major depressive disorder or generalized anxiety disorder [70] and is shown to be more effective than citalopram.

Sertraline is often prescribed to cure the major depressive disorder, obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, dysphoric premenstrual disorder, and disorder of social anxiety. Among all the SSRIs type escitalopram is found to be more effective [71]. Structural formula for adrenaline, fluoxetine, and escitalopram is shown in Fig. 23.

8 Serotonin-Norepinephrine Reuptake Inhibitor (SNRI)

Serotonin and reuptake inhibitors of norepinephrine (SNRIs) are a class of drugs that are efficient in treating depression. These are also used to treat long-term (chronic) pain and anxiety disorders, particularly nerve pain. SNRIs block neurotransmitter serotonin and epinephrine reabsorption (reuptake) in the brain [72].

Examples: Duloxetine, venlafaxine [73, 74]. Structural formula of this is depicted in Fig. 24.

8.1 Duloxetine and Venlafaxine

They are used to treat the major depressive disorder, widespread anxiety, fibromyalgia, and neuropathic pain, while venlafaxine is specifically used to treat social phobia [75].

8.2 Mono-Amino Oxidase Inhibitor (MAO-I)

This acts by inhibiting enzymes MAO A and MAO B that leads to degradation of monoamine neurochemicals, for example isocarboxazid. It has been reported to treat mood and anxiety disorders, Parkinson's, and dementia [76].

8.2.1 Schizophrenia

Progressive disintegration between the individual and the world. Antipsychotics or neuroleptic are the agents used to treat symptoms caused by psychosis (delusions, hallucinations, paranoia, or disordered thought) or schizophrenia.

Antipsychotics are also known as neuroleptic drugs, i.e., reduce nervous tension, and are classified as shown in Table 2. Structural formula of drugs is shown in Fig. 25.

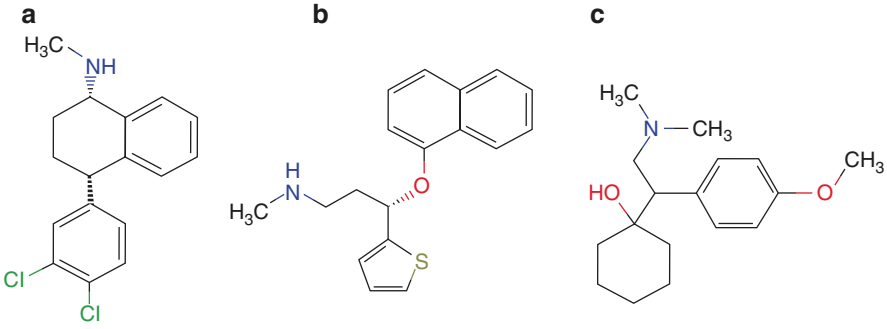

Fig. 24 Structural formula of (**a**) sertraline, (**b**) duloxetine, and (**c**) venlafaxine

Table 2 List of neuroleptic agents

Typical antipsychotics	Atypical antipsychotics
Thiothiazine	Risperidone
Haloperidol	Clozapine
Flupentixol	Ziprasidone
Trifluoperazine	Lurasidone
Chlormazapine	Zotepine
Perphenazine	Quetiapine

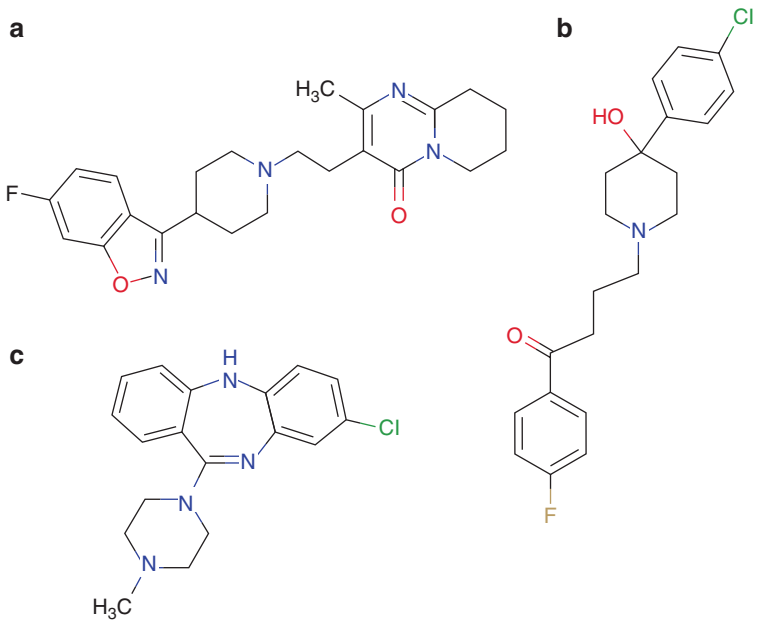

Fig. 25 Structural formula of (**a**) risperidone, (**b**) haloperidol, and (**c**) clozapine

They act by antagonizing the dopamine (DA) function.

Acute neuroleptic increases the DA neuron dismissal and hence release of dopamine. That is because of the antagonists of DA:

1. Obstruct the inhibitory effect of released dopamine on end autoreceptor
2. Prevent the action of DA on the DA neuron with similar inhibitory receptors
3. Block postsynaptic DA receptors on neuron inhibited by released DA which can initiate positive feedback to DA neurons

Thus, outright effects are through D_2 receptor binding.

Drugs like haloperidol and chlormazapine increase monoamine concentration by inhibiting MAO enzymes and thus are implicated for the chemotherapy of schizophrenia [77]. Drugs like risperidone act by blocking dopamine D_2 receptor postsynaptically without affecting dopamine concentration.

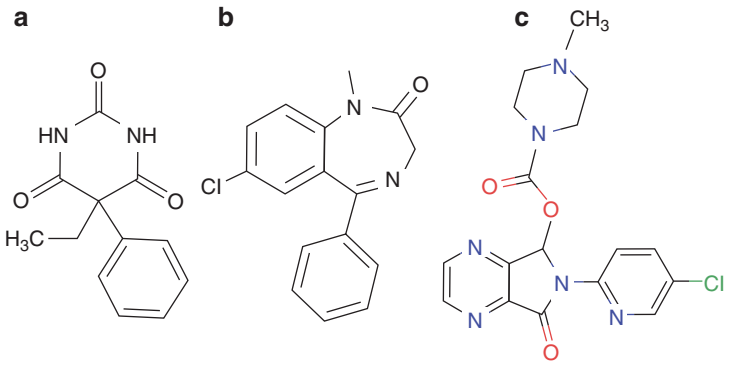

Fig. 26 Structural formula of (**a**) phenobarbitone, (**b**) diazepam, and (**c**) zolpidem

8.3 Anxiety and Hypnosis

Anxiety disorders are one of the conventional types of diseases. Neurochemicals such as serotonin, GABA, and norepinephrine are the major role players in anxiety. Alcohol is the widely used antipsychotic agent since the early days [78, 79]. However, barbiturates replaced this treatment (e.g., phenobarbitone, meprobamate) [80].

Barbiturates attach non-competitively to a different receptor domain which may be linked directly to the chloride channel. While showing an allosteric interaction with GABA, it also elevates Cl conductivity by raising the channel opening duration.

Diazepam connects in the brain to a particular site. Solubilized receptor studies have established that the binding site is a GABA-A-type receptor element which is involved in a Cl-channel opening. Allosteric communication among GABA-A-type receptor and diazepam leads to increased drug binding. This is thought to be an outcome of interaction between the GABA recognition site on a þ-subunit GABA receptor and an a-subunit benzodiazepine recognition site [81].

Benzodiazepine's overall effect involves boosting the increase in GABA-induced Cl ion conductance and thus facilitating its inhibitory actions. This is achieved by enhancing the likelihood and therefore the frequency of Cl ion opening of channels.

The imidazopyridine zolpidem (insomnia therapy), which was originally considered a ligand of BZ1 receptor, is marked as the high-efficiency ligand for the GABA-A receptor a1 subunit [82]. Chemical structure of some common drugs used in anxiety and hypnosis is shown in Fig. 26.

9 Conclusion

The study of neuropeptides, psychopharmaceuticals, and their receptors is one of the widely studied fields of research and the research data available is vast. Understanding these signaling pathways of neuropeptides and position of neuropeptide receptors in the brain nervous system, in the region of regulating significant tasks, offers a solid foundation for continued interest in ligands of neurochemical

receptors, i.e., agonists, antagonists, and modulators. Although huge clinical trials have been performed, the increasing amount of genetic research showing linkages between disease and neuropeptide signaling further highlights the view that we will see many neuropeptide ligands and receptors of neurotransmitters as drugs. Thus, a better knowledge of neurochemical functions and their signaling pathway will lead to significant future discovery and development.

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Role of Chemical Agents in Nervous System: A Paradigm

Guno Sindhu Chakraborthy

Abstract

Neurons serve as an important feature in the biological system where it controls the whole body via central and autonomous system. Both the systems have a defined role and function and looking into it various chemical agents are present which help in the function and regulation of the system. They are mainly responsible for mood elevation, signal transmission, binding properties, transportation, etc. for their regulation. These chemical agents include acetylcholine, dopamine, GABA receptors, glutamate, noradrenaline, and serotonin. These chemical agents follow their own pathway and possess the chemical function and synthesis either with chemical substances or with biological pathways to accelerate the system. Thus it is very clear that most of the neuromodulators and neurotransmitters are involved in controlling the major functions of the body. This chapter enlightens about the various aspects of it.

1 Introduction

In general the era behind the theoretical aspects of nerve and its physiology is mainly dependent on the chemical nature and behavior of the tissues of which they are composed and mainly the outline of their mechanism. It holds a justification that still we are lacking behind the biochemistry of nerves and its joining due to many exogenous factors when compared with other organs in our body. Hence owing to this many researchers are working nowadays to underline the phenomena behind the chemistry of human brains which controls everything [1].

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This thought process is mainly due to the chemicals and their transmission present in brain via impulses or signals. Hence due to these signals or transmission the neurons help in the metabolism and in enzymatic reactions. This was mainly a concern to researchers that the identification and their properties were directly related to the enzymes and in turn metabolism which hold equal importance in the determination of cells associated with it. So an importance of biochemistry holds its place and becomes rapid progress in understanding the spatial arrangement of enzyme system and regulating their metabolism. Subsequently the structure studies of the nervous tissues are not in detail as there are so many linkages associated with it in defining the process of cure [2].

In understanding the thoughts regarding this subject I have tried to explain the general structure of the system and its various components which will help in understanding the neurosecretion and chemicals responsible for secretion, function, and metabolism. Eventually a secure system is always preferred which is associated with formation and execution of the chemical agents present in nerves [3].

2 Cells of Nervous System

Neurons are composed of branched structures known as dendrites. Further the composition of the cell body comprises mitochondria, nucleus, endoplasmic reticulum, and Golgi apparatus. The later parts are axon, cell membrane, and glia cells. Neuron is considered the general part of the cell body with a nucleus which controls the whole activity of cell. The fluid cytoplasm present inside the cell extends to dendrons and each dendron contains fiber-like structures which are known as dendrites. These are that fibers which behave as optical and pass the electric impulses from one neuron to another neuron and further they are passed to the cell body for its function.

The axon considered as a thin section of neuron is formed by a single extension of the cytoplasm present in cell body. It helps in transmitting the impulses or signals away from the object and finally ends in a knob known as synaptic knob. The starting point of axon commences from the cell body in a tapered membrane type known as axon hillock. This axon hillock is generally devoid of ribosomes and endoplasmic reticulum. A number of microtubules and microfilaments constitute to form a transportation system for the axon which helps in the movement of the cell body.

The second part comprises glia cells which mainly focus on the biological behavior of neurons and their relative activities as they perform the housekeeping functions of brain. It acts as a glue and holds all the cells together and they are of two types: the larger ones (macroglia) and the smaller ones (microglia). Further microglia comprises astrocytes and oligodendrocytes [4].

Astrocytes are the major part of blood-brain barrier which protects the brain circulation as they provide the structural support. They mainly help in the regulation of ions and larger molecules in the region of the synapses. A diagrammatic representation structure of neuron is shown in Fig. 1.

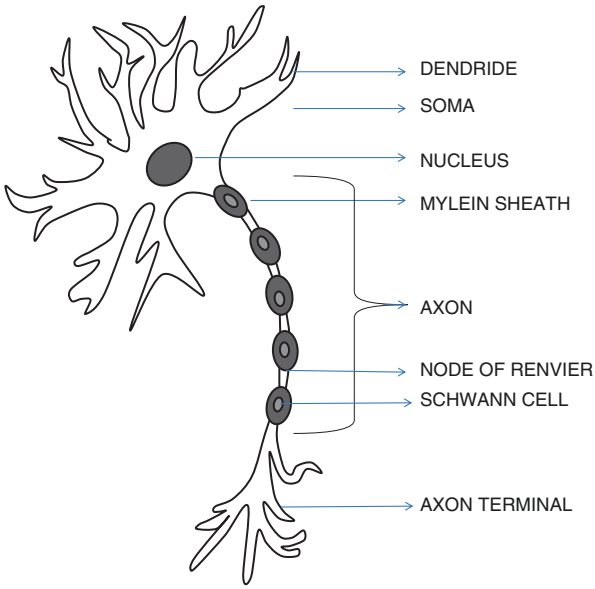

Fig. 1 Structure of neuron

Another part which is present is called as Schwann cells which are seen along the length of axon. These cells wrap around the axon part filling the gaps between each cell attached to it. When neurons are attached with Schwann cells they are called as myelinated neurons and they act as an electrical insulator which speeds up the transmission or nerve signals to a rapid one. Oligodendrocytes are small cells which act as spider in the process of astroglia. They are larger in size and consist of microtubules which are arranged parallel. They serve a functional role in maintaining the certainty of brain. In some cases unmyelinated sheaths are also present but they do not pass any type of signals to the neurons or are generally slower than the myelinated ones.

2.1 Nerve Impulses

It has been observed that whenever a reaction is seen it is due to pass of electric field surrounding the object. Similarly the impulses from brain which pass to the other parts of the body maintain the balance between inner side and outer side of the cell membrane for its activeness and this phenomena is called as membrane potential. During this phase the neurons have a negative charge as they are or in other words they are called as resting potential.

The resting potential mainly depends upon the concentration of ions responsible which are potassium, sodium, chloride, and carboxylate. Among these four ions the concentrations of potassium and carboxylates are higher inside the cell whereas the concentrations of sodium and chloride are higher outside the cell. But in case of resting phase the potassium ions are allowed to move free in the cell

mainly in the axon membrane to maintain the balance and function of the impulse. Whenever any ions are moving in the cell or its surroundings there is a change in the electrical potential and alteration is observed which is known as depolarization. It changes the permeability and thereby allows the sodium to bind easily to the site which causes a sudden influx in the axon part. So due to this shift of charges the charge inside the cell changes and gets converted to action potential. So there is a change of ions from one mode to another until it achieves the resting potential and gets restored. This is the period of repolarization and thus this is a way of the length of the impulses which are passed inside and outside the brain cells [5].

2.2 Parts of Nervous System

It is very clear that in nervous system two major controlling parts are present which are known as autonomous nervous system (ANS) and central nervous system (CNS) and in both these systems different agents are present which work differently in the physiological system. These chemical agents are known as neurotransmitters. They are generally the chemical messengers which are used to pass the information from one neuron to another and later to effector cells. These smaller triggering molecules influence in three major ways like excitatory, inhibitory, and modulation of the impulses. The excitatory transmitter helps in the generation of an electric field called as its action potential whereas the inhibitory prevents the damage or stops the high flow of signals and also helps in the binding sites of receptors. In case of neuromodulators they do not restrict the joint in cleft between the neurons and as a result a huge number of neurons get affected which leads to a great disturbance in the joining signals from one to another. Neuromodulators therefore regulate the behavior of neurons while conducting over a slow course of time than others like the stimulation and stopping of the transmitters [6].

These chemical agents are further a group of smaller amine molecules, attachment of amino acids, or group of neuropeptides. These agents and their interactions are involved in the process of countless functions of the nervous system and they are well in balanced structured form for controlling the body's function. The major neurotransmitter agents are described as follows:

2.2.1 Acetylcholine

The first neurotransmitter discovered was a small molecule called as acetylcholine (Ach). Is an ester of choline. It is an endogenous compound with a very short life and is rapidly destroyed by an enzyme known as acetylcholine esterase. It works well on muscarinic and nicotinic receptors. The major importance of system belonging to the peripheral nerves is released by the action of motor nerves and the nerves present in autonomic nervous system. Acetylcholine serves as a major neurotransmitter in the nervous system pertaining to CNS to maintain the cognitive function. It has been seen that if there is any damage in the cholinergic neurons present in CNS there is a positive effect on Alzheimer's disease.

Synthesis:

- Acetyl CoA when reacted with choline leads to the formation of ACh with the help of an enzyme called acetyl transferase and this is mainly inhibited by hemicholinium.
- Active uptake of choline by sodium-dependent carrier.
- Ach is transported into vesicles for storage (transport is inhibited by vesamicol).
- Release of Ach is done by exocytosis which depends on calcium (release is inhibited by botulinum toxin).

The release of Ach can also be blocked by an anesthesia and excess of magnesium which competes with calcium.

There are major six sites where the release of acetylcholine is observed and they are all preganglionic fibers of ANS, postganglionic parasympathetic nerve endings, postganglionic sympathetics of the sweat glands, neuromuscular junction (NMJ), adrenal medulla, and central nervous system.

2.2.2 Glutamate

Glutamate is the main excitatory transmitter present in the CNS. An inhibitor transmitter is known as GABA while another neurotransmitter is glycine, an amino acid which is present in spinal cord. The biosynthesis of glutamate is generally summarized as the presence of enzyme glutamate dehydrogenase (GDH) which initiates the process of glutamate, alpha-ketoglutarate (α-KG), and ammonia with the help of energy NAD+ or NADP+ acting as supportive coenzyme. This reaction proceeds in the brain as a part of oxidation of the amine which states that the oxidation of glutamate to αKG results as ammonia. But to the presence of glutamatergic neurons a higher amount of the presence of ammonia results in reductive amination and thereby the end product formed will be α-ketoglutarate (α-KG) and ammonia [7]. The enzyme glutaminase referred to as phosphate-activated glutaminase (PAG) is initiated by phosphate catalyze and thereby breaks down the group of amide resulting in the formation of glutamate and ammonia. The conversion of glutamate and ammonia from glutamine is purely dependent on the reverse reaction of glutamine synthetase which is an ATP-dependent reaction which is shown in Fig. 2 where there is a relation of astrocyte from glutamatergic and GABAergic neuron [8].

Certain types of glutamate receptors are present which have their specific pharmacological agonist and they are categorized as follows:

1. **AMPA receptors**
2. **NMDA receptors**
3. **Kainate receptors**
4. **Metabotropic receptors (mGluR1–8)**

AMPA Receptors (AMPARs)

They are known as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid and are mainly the family of ligand-gated ion channels, otherwise called as ionotropic

receptors. The up front of these possesses the flow of calcium and sodium ions and exit of the potassium ion and hence closes soon after opening.

These mediators are made up of GluA1–4 and GluA2 subunits and they are generally separated from the genes comprising N- and C-terminal which are at extracellular and intracellular binding sites of the ligand but more towards the N-terminal regions of S1 and S2 due to its acceptance and affinity. These subunits are of flip and flop type and are towards the C-terminal end loop of the transmembrane domain of TM III and IV which results in altered desensitization of the kinetic profile. The AMPA being impermeable is controlled by calcium ions by GluA2 subunits and thereby determines the posttranscriptional changes of amino acid to TMII generally known as QR ending sites.

The GluA2 is an expressed protein present in CNS which gives rise to AMPA receptors and hence interacts with the intracellular proteins which makes potent AMPA receptor subunits. The regulation of AMPA receptor is depicted below in Fig. 2.

Functions of AMPA receptors:

- Responsible for synaptic transmission
- Increase the postsynaptic responses
- Insertion of permeable calcium

NMDA Receptors (NMDARs)

These receptors increase the passage of ions like calcium, sodium, and potassium ions. It requires a conformational change for its opening, thereby blocking or

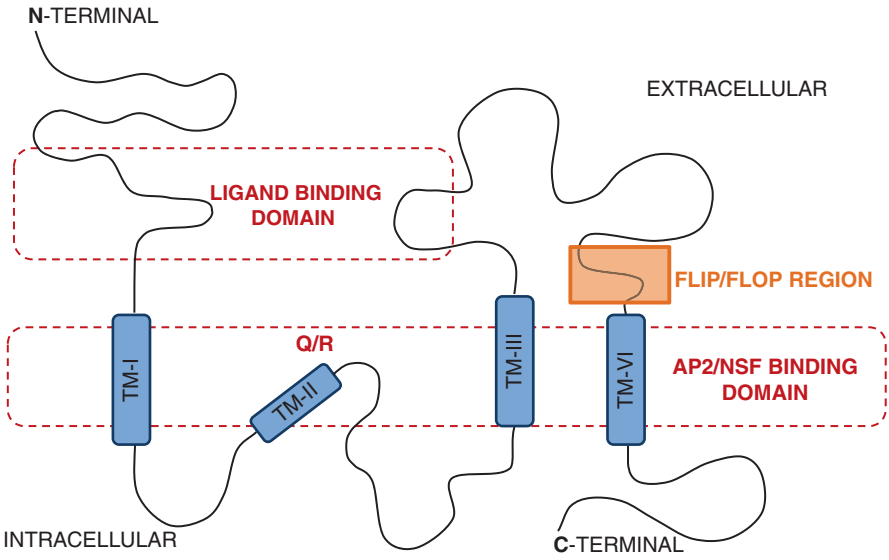

Fig. 2 Regulation of AMPA receptor

removing the magnesium ion to its site. The removal of magnesium is only possible when it depolarizes with an alteration in the electric field repulsion of the cation which is by AMPA receptors. This also allows the calcium influx for its activation and hence a calcium-dependent enzyme which regulates the postsynaptic and the receptor density which in turn regulates the plastic property of the synaptic.

Kainate Receptors

These types of receptors are generally ionotropic and have similar functions to those of AMPARs. They are made up of NMDA and AMPA receptors and share the same structural composition. They are made from multimeric assemblies obtained from GluK1–3 and GluK4,5 subunits. When GluK1–3 subunits combine with at least another subunit it leads to the formation of functional heteromeric and homomeric assemblies which when expressed in the cell lines and have low affinity to the kainite part. GluK5 subunits are retained in the endoplasmic reticulum unless assembled with GluK1–3. The regulation regarding the kainite receptor is explained as in Fig. 3.

In case of their functional part they have active role in epileptogenesis—intraperitoneal injection of kainate which has been used in the model of temporal lobe seizures. Further, more research for the development of new selective pharmacological aspects is looked upon for the improvement of the receptor-binding property. So due to this it has been observed that kainite receptors are activated by synaptic plasticity. They are used for the induction of NMDA receptor-independent long-term potentiation (LTP) and in mossy fiber synapse. Outside the hippocampus, the kainate receptors present in synaptic plasticity are found in the somatosensory cortex where the receptor-mediated transmission is reduced [9].

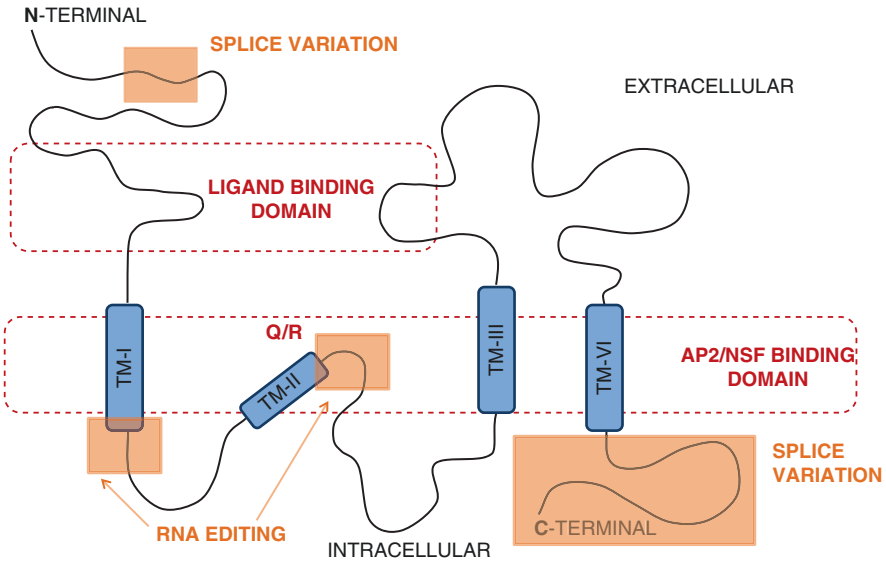

Fig. 3 Regulation of kainate receptor

Metabotropic Receptors

These receptors are of second class of neurotransmitter which affects the ion channel opening. It mainly depends upon the activation of molecules which are inside the cell and is involved in the second messenger pathway and they are much slower than the ligand-activated ion channels.

In this the ligand binds to the receptor, which triggers the signaling cascade inside the cell. And thereby it causes the ion channel to open and allows the flow of cations through gradient concentration techniques resulting in depolarization. A neurotransmitter which binds to a metabotropic receptor may have a change in the cell responding to a second neurotransmitter that acts through a ligand-activated channel. When signals pass through the metabotropic receptors they have positive effects on postsynaptic cell and they do not have any effects on ion channels. Hence in this way it has been seen that there are eight known types of metabotropic receptors labeled as mGluR1–8 and they are found in presynaptic neurons, where they show their increase in the phosphatidylinositol [10, 11]. The functions of metabotropic receptor are shown in Fig. 4.

3 GABA (Gamma-Aminobutyric Acid)

3.1 GABAergic System

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter present in the CNS and finds a similar distribution to glutamate with respect to diffusion and a distinct neurotransmitter system [12].

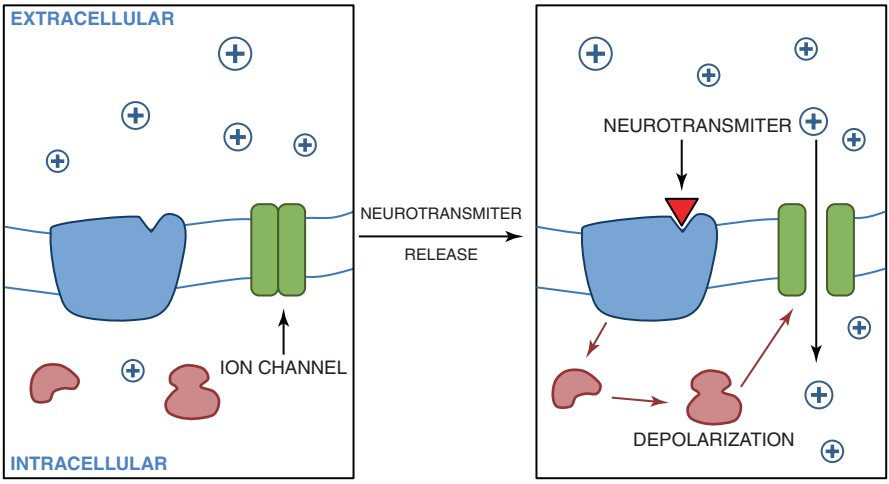

Fig. 4 Function of metabotropic receptor

3.2 Synthesis and Inactivation of GABA: Cycle Neuron-Astrocyte

The synthesis of GABA is done by decarboxylation of glutamate which is catalyzed by an enzyme known as glutamate decarboxylase. The precursor used is glutamine which is transported from astrocytes to form glutamate and further glutamine is converted inside the neuron leading to the formation of glutamate catalyzed by glutaminase, the enzyme responsible for conversion [13].

This process takes place in the synaptic cleft by astrocytes and is further converted back to glutamine. The mechanism followed is the transamination of GABA to aldehyde forming its succinate semialdehyde by GABA transaminase. Further the oxidation takes place and leads to succinate and this enters to TCA cycle and gives 2-oxoglutarate and is finally amidated to glutamine using ammonia and ATP [14]. Glutamine is then exported and the cycle closes. Commonly three subtypes of GABAergic receptors are mainly used for its clarification [15].

3.2.1 $GABA_A$

The $GABA_A$ receptors are considered as one of the major inhibitory neurotransmitter receptors present in mammalian brain. There are mainly five homologues which are surrounded by chloride ion-selective channel and they are gated by GABA [16]. The receptor located at postsynaptic membrane mediates the inhibition which is located at extrasynaptic membrane and they respond to the ambient GABA and confer a long-term inhibition [17]. These are mainly confined to drugs like benzodiazepines and are used often for their sedative, hypnotic, and anxiolytic effects [18].

3.2.2 $GABA_B$

They are mainly G-protein-coupled receptors and are the main inhibitory neurotransmitters present in CNS [19]. They play a role in the psychiatric disorders and mainly considered as attractive drug targets. They are metabotropic receptor and inhibit the adenylate cyclase. They majorly form subunits like GABA (B1a) and GABA (B1b) and result in the formation of heterodimeric forms GABA (B(1a,2)) and GABA (B(1b,2)) which are present in the extracellular domain known as venus flytrap (VFT) [20]. Due to this a decrease is found in the cAMP levels and this decrease changes the membrane protein phosphorylation status leading to an increase in the potassium permeability (membrane hyperpolarization) and a decreased activity of calcium channels which shows a reduced neurotransmitter released by neuron [21]. This receptor finds its implementation in the areas of cortex, thalamus, and cerebellum region of brain [22]. The structural setup of $GABA_B$ receptor is depicted in Fig. 5.

3.2.3 $GABA_C$

It is also known as GABAA-rho receptor. This type of receptor is generally Cl^--permeable ionotropic receptor based on native and recombinant type. In this type of receptor three rho-subunits are formed from various species which are generally cloned and their patters are expressed in retina and in some parts of the brain. They are molecularly determined and are specific to amino acid residues in the subunits

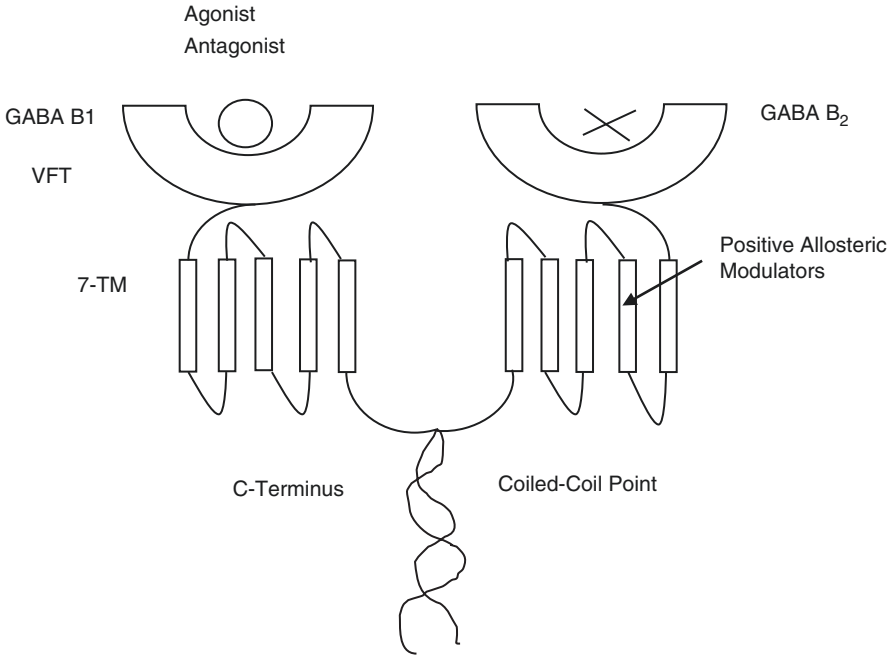

Fig. 5 Structural setup of $GABA_B$ receptor

[23]. With the opposite of the GABA receptor the opening is much slower and it remains for a longer time in the channel [24]. Due to this unique feature they play a significant role in retinal signal processing via mechanism like slower activation process leading to segregation from numerous inhibitory and contribution to multi-neuronal pathways [25]. The molecular structure and role of GABA $_C$ receptor are described in Fig. 6.

4 Serotonin

Chemically serotonin is 5-hydroxytryptamine or often called as 5-HT which is mainly found in brain, blood platelets, and bowel function. It is responsible for the regulation of mood, social behavior of the environment, and appetite; helps in digestion; and enables sexual desire in living organisms. As it is also a neurotransmitter it generally relies on the signals which pass between the nerve cells or the neurons and helps to maintain the intensity of the signals. The neurotransmitter plays its role in CNS and is found to be more effective in gastrointestinal tract. Certain facts of serotonin also hold its importance in bone metabolism, breast milk induction, and liver regeneration process and it helps in cell division for the formation of newer cells in the living system. Certain functions of serotonin are described below:

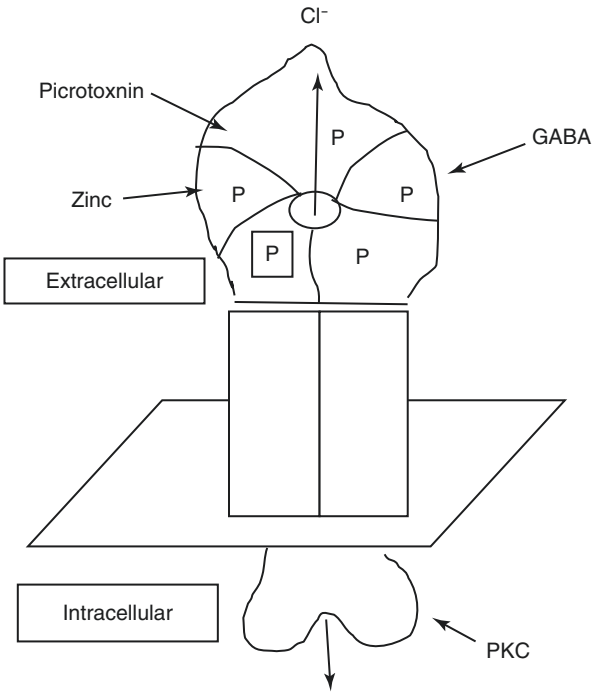

Fig. 6 Molecular structure of $GABA_C$ receptor

1. Bowel function: It regulates the bowel movement, thereby reducing the appetite while eating. This enhances the chemical component and helps in lesser ingestion of the material so it effectively induces the bowel movement.
2. Mood: It has a strong impact on the mood elevation of organisms and relates to various emotional factors like happiness, sadness, well-being, etc. It also alters the anxiety property and thereby has its own mechanism of alerting according to the situation [26].
3. Clotting: It helps in the formation of clots in blood. It is released by platelets during the process of wound either externally or internally due to which there is vasoconstriction in blood vessels which reduces the flow of blood in the circulation and results in the formation of clots.
4. Nausea: Due to unpleasant substances either by inhaling or by physical means there is an irritation produced in the gut which thereby increases the transit time for expulsion of the irritant either by anal route or by oral route and hence stimulates the nausea part responsible for the signal production in the brain and resulting part is nausea.
5. Bone density: The free molecules present in the gut derived from the serotonin pass the signals of osteoblast by binding through a receptor known as Htr1b. The receptor inhibits the phosphorylation of cAMP-responsive element-binding protein (CREB) by phosphokinase A (PKA) enzyme which leads to reduced expression of the cyclin genes and decreases the proliferation of osteoblast. In this process the Wnt signaling pathway helps in binding

to the frizzled receptors which induces the destabilization, leads to the accumulation of the unphosphorylated β-catenin, and regulates the transcription of osteoblast target genes. In differentiation to the serotonergic neurons the ventromedial hypothalamus neurons by the Ht2C receptor inhibit the synthesis of epinephrine and decrease the sympathetic tone which in turn controls the proliferation of osteoblast through molecular clock gene and regulates bone resorption. This inhibition results in the profound formation and negative resorption. This is mainly by the resorption of the PKA or by activating transcription factor (ATF4) pathway which leads to the combination of receptor activator of nuclear factor kappa-B ligand and finally which helps in osteoblast.

6. Sexual function: It inhibits the sexual desire or the motivation of sex performance which contributes to initiation and satiety. The behavior is generally impaired with 5HT agonists and certain amounts of agents which increase 5HT [27]. Though it inhibits the process the stimulations produced by 5-HT2C receptors increase the erections and later on inhibit the ejaculation but in case of 5HT1A the opposite effects are observed as it facilitates ejaculation due to the release of 5HT from the lateral hypothalamus at the time of G point or ejaculation. Figure 7 describes the correlation between noradrenaline, dopamine, and serotonin with respect to sexual behavior [28].

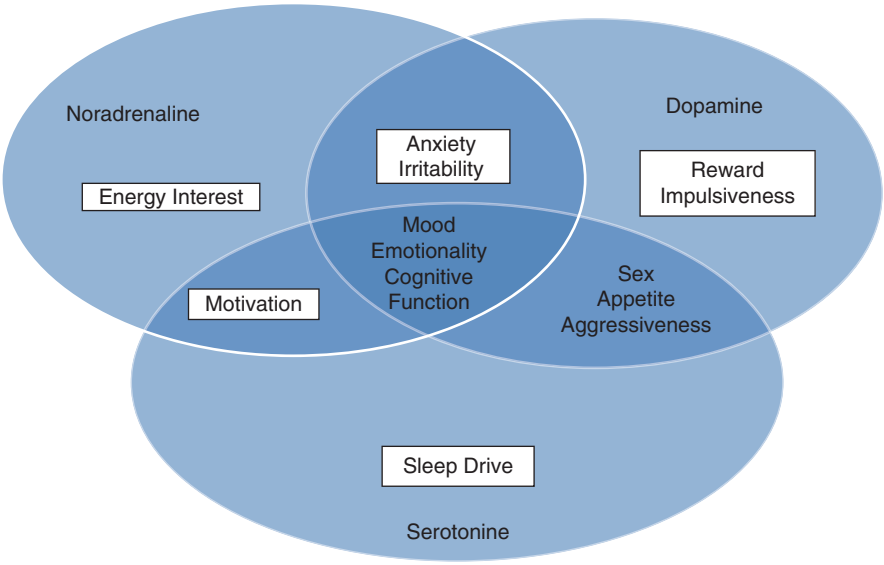

Fig. 7 Relation between serotonin, dopamine, and noradrenaline on sexual behavior

The presence of serotonergic neurons is seen in the raphe nuclei of the reticular formation and they are separated into two parts, namely rostral past with ascendent projections and a caudal part with descendent projections.

1. Ascendent serotonergic system (nc. raphe dorsalis, nc. raphe pontis centralis superior)

   This type of system mainly projects into the cortex region of the brain and also in limbic structures, namely hippocampus and amygdala. Apart from it other areas are basal ganglia, many hypothalamic nuclei and areas, and some thalamic nuclei. They are important for the regulation of the emotional prospectus and hypothalamic function and help in sleep cycle. The regulation is also seen in the sensory area like visual cortex region.
2. Descendent serotonergic system (nc. raphe pontis, nc. raphe magnus, nc. raphe obscurus)

   The second type is responsible for the structure pertaining to caudal parts of CNS like brainstem, cerebellum, and spinal cord. These neurons play an important role in the serotonergic system which potentiates the analgesic and opiate effects. The system also helps in the modulation of the preganglionic neurons of the ANS and stimulates the anterior part of the spinal cord.

4.1 Synthesis and Inactivation of Serotonin

Serotonin is synthesized in two different steps by the involvement of tryptophan, the precursor.

In the first step tryptophan is hydroxylated by an enzyme named tryptophan hydroxylase which later on forms 5-hydroxytryptamine which is a step preventing the enzyme involved in serotonin synthesis [29].

The second step comprises decarboxylation of 5-hydroxytryptophan which gives rise to 5-hydroxytryptamine, a biogenic amine formed aligned with catecholamines [30]. The process is catalyzed by the help of an aromatic L-amino acid decarboxylase called 5-hydroxytryptophan decarboxylase.

Another method of synthesis of serotonin is via the pathway to form melatonin hormone. The amino group present in serotonin is treated with acetic acid to undergo the process of acetylation to form the substance *N*-acetylserotonin. This is further methylated to the indole hydroxyl group which results in the formation of melatonin [31]. The synthesis is shown in Fig. 8.

These serotonergic neurotransmissions are generally discontinued by the reuptake of serotonin and its subsequent intracellular metabolism. The inactivation of serotonin is catalyzed by two enzymes namely monoamine oxidase (MAO) and aldehyde dehydrogenase (catecholamine inactivation) [32]. The inactivated form of 5-hydroxyindoleacetic acid is eliminated in urine conjugated with glucuronic acid which is generally a marker in neuroendocrine tumors developed from the secretion of serotonin [33].

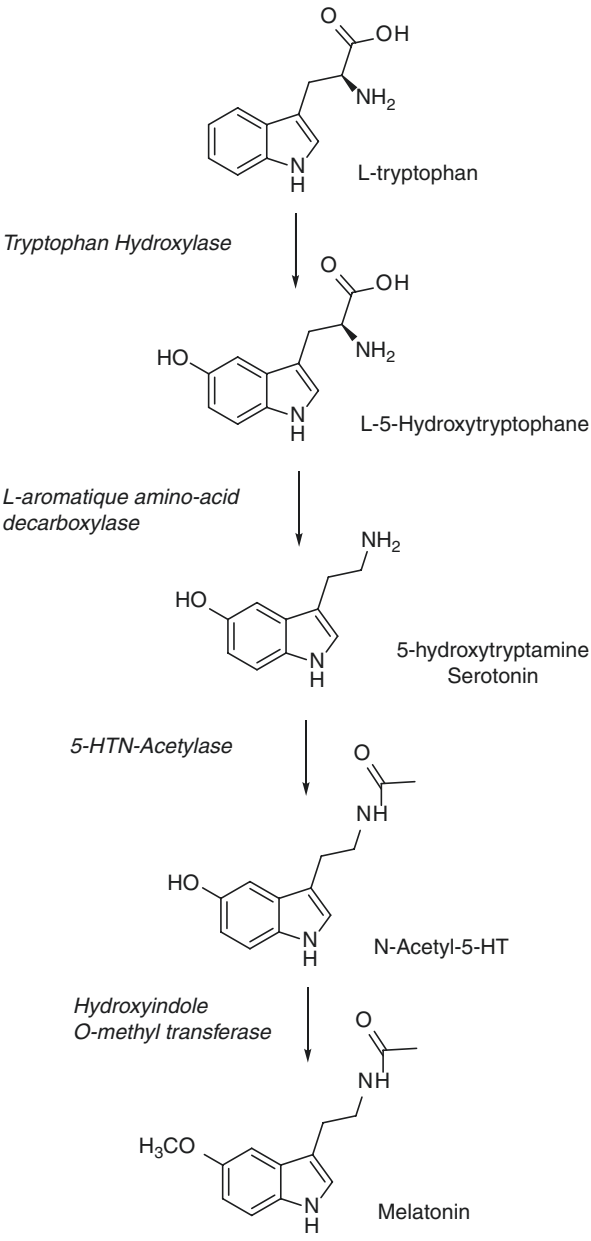

Fig. 8 Synthesis of serotonin and melatonin

5 Dopamine

Dopamine otherwise known as DA chemically is 3,4-dihydroxyphenethylamine belonging to the group of catecholamine and phenethylamine family. It is a monoamine compound which possesses positive inotropic activity. It generally functions

as a hormone and a neurotransmitter agent which takes part in the regulation of brain and body. It helps in the regulation of movements, attention, learning, and emotional changes which occur in human beings. It also binds with alpha-1 and beta-1 adrenergic receptors in higher doses. These are routed by myocardial beta-1 adrenergic receptors, while dopamine increases the heart rate and force, thereby increasing the heart rhythm. Alpha-1 adrenergic receptor helps in triggering the soft muscle present near the cardiac region, which initiates vasoconstriction and finally there is an upfold in the systemic vascular resistance. The trigger of dopaminergic receptors in kidney vasculature leads to the dilation of blood vessel in kidney which results in larger glomerular filtration rate, kidney blood flow, sodium excretion, and urine output.

Majority dopamine has a combination of five major receptors like D1, D2, D3, D4, and D5 which are the class of G-protein-coupled receptor. It has been observed that D1 and D5 belong to D1 like whereas D2, D3, and D5 are of D2 like. These receptors with the specific function and locations are described in a tabular form (Table 1).

Table 1 Dopamine rector with functions and locations

Receptors	Location	Functions
D1	They are present in bulk concentration mainly observed in the mesolimbic, nigrostriatal, and mesocortical areas	They are involved in the voluntary movements, regulation of growth factors, lifestyle and other behavioral changes of the physiological system
D2	They are expressed in high levels in substantia nigra, olfactory bulb, caudate, putamen, ventral tegmental area (VTA), nucleus accumbens and are found in lower level in hypothalamus, septum, kidney, cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia	They are basically involved in thought process by controlling the blood flow and the receptors involved with them which leads to the activation process
D3	They are expressed only in CNS which are found in olfactory bulb, nucleus accumbens	They are involved in hormonal secretions pertaining to instinct behavior and stimulation of regulations of locomotor functions
D4	They are seen in the areas of substantia nigra, hippocampus, amygdala, thalamus, hypothalamus, kidney, frontal cortex, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia, globus pallidus, lowest receptor found in CNS than all dopamine receptors	They are involved in the control of kidney functions, function related to stomach motility, blood factors and in upliftment of cognitive functions
D5	Substantia nigra, hypothalamus, hippocampus, dentate gyrus, kidney, heart, blood vessels, adrenal glands, gastrointestinal tract, sympathetic ganglia	Mainly observed in the process of pain which affects the endocrine functions related to dopamine

There are mainly four different pathways by which they are regulated and they are mentioned as nigrostriatal, mesolimbic, mesocortical, and tuberoinfundibular.

1. Nigrostriatal pathway: In this type of pathway the fibers originate from the substantia nigra, slowly project rostrally, and get distributed to the basal ganglia part. Dopamine in this pathway is effective in cases of movement and learning skills. The degeneration of the system generally causes Parkinson's disease. They pass through the ascending projections to the dorsal striatum and modulate the motor control.
2. Mesolimbic pathway: They originate from the ventral tegmental area spreading up to amygdala, piriform cortex, lateral septal nuclei, and nucleus accumbens. They are involved in emotion and reward system by mediating the pleasure part in brain which controls the functions of food, sex, healthy being, etc.
3. Mesocortical pathway: Here in this particular pathway the dopaminergic fibers are generally observed from the A10 region present in the ventral tegmental area of the brain and are projected to frontal cortex and septohippocampal regions. They are involved in cognitive and emotional behavior. They have shown the effectiveness in the prefrontal cortex of the brain which is involved in working memory and attention gainers and have positive effects on levels when they are increased or decreased.
4. Tuberoinfundibular pathway: This particular cycle finds its occurrence from the arcuate nucleus of the hypothalamus present in the brain and gradually projects to the pituitary gland. It inhibits the release of the prolactin hormone responsible for lactation and due to this it causes galactorrhea. So due to this phenomenon dopamine is also coined as prolactin-inhibiting factor (PIF), prolactin-inhibiting hormone (PIH), or prolactostatin.

5.1 Synthesis of Dopamine

Dopamine is synthesized from an amino acid named as tyrosine and its levo form is used as a precursor. Further it is converted to L-Dopa with the help of an enzyme known as tyrosine hydroxylase (TH) and L-amino acid decarboxylase which is called as dihydroxyphenylalanine (DOPA) and decarboxylase (DDC). Further conversion takes place from L-Dopa to dopamine with the help of pyridoxal phosphate. It is observed that TH is a limiting factor which is observed in the biosynthesis of dopamine [34]. The reaction can be of two methods which are described in Fig. 9 and the reaction is also described below.

5.2 Chemical Synthesis of Dopamine

L-Tyrosine + THFA + O_2 + Fe^{2+} → L-DOPA + DHFA + H_2O + Fe^{2+}

L-DOPA + pyridoxal phosphate → dopamine + pyridoxal phosphate + CO_2

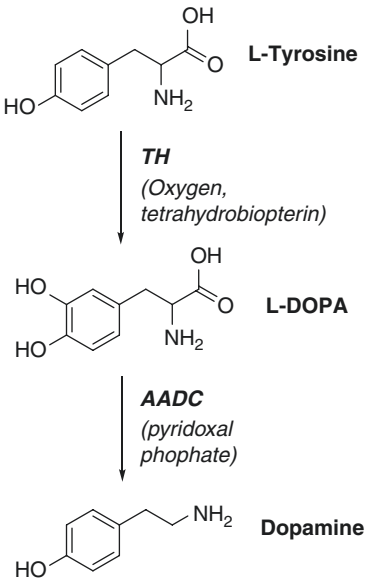

Fig. 9 Synthesis of dopamine

5.3 Noradrenaline (Norepinephrine)

It is also called as norepinephrine which acts as a hormone and a neurotransmitter. This particular agent is released when there is a change in the physiological system due to stress or other effects which are caused in CNS by the activation of brainstem called as locus coeruleus, the part which sends signals to both the sides of brain. The occurrence of neurotransmitter is from the postganglionic part of the sympathetic nervous system which transmits signals from one part to another part. The part adrenal medullar is seen to be counted by the nerve cells of postganglionic and releases norepinephrine into the blood.

It is a naturally occurring sympathomimetic agent and is agonist to receptors like alpha1, alpba2, and beta1. It has been observed that very little effects are seen in beta2 or dopamine receptor. The major function of noradrenaline is to raise the systolic and diastolic blood pressure by creating vasoconstriction and thereby reduce the blood flow to organs and tissue like kidney, liver, and skeletal muscle. This is mainly due to positive inotrope and chronotrope and is metabolized by catechol-*o*-methyltransferase (COMT) and monoamine oxide (MAO) enzymes. They generally regulate the excitatory function of glutamate and also inhibit the functions of GABA. The binding to the specific receptors helps in targeting cell membrane and thereby causes specific signals for proper function as per the location.

It is synthesized from a nonessential amino acid called as tyrosine or from an essential amino acid called as phenylalanine which serves as a precursor and seen in synaptic vesicles and performs the function by releasing into the synaptic cleft and thereby acting on adrenergic receptors either by the process of degradation or by the uptake of cells. The process deals with the formation of phenylalanine to tyrosine

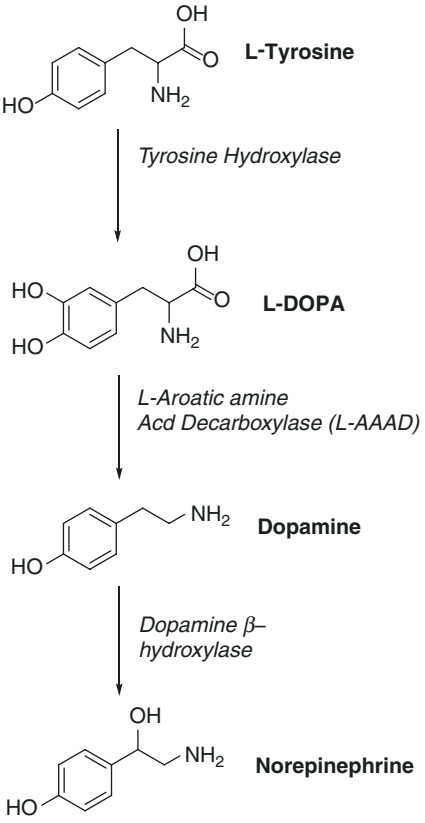

Fig. 10 Synthesis of noradrenaline (norepinephrine)

with the help of phenylalanine hydroxylase, the enzyme responsible for the conversion which yields tetrahydrobiopterin as a cofactor, and further the conversion of tyrosine to L-Dopa by tyrosine hydroxylase with tetrahydrobiopterin and with the initiation of ferrous [35]. Further the process gets decarboxylated to dopamine and later it is converted to norepinephrine with the help of enzyme called dopamine β-monooxygenase (Fig. 10).

5.4 Degradation of Noradrenaline

The breakdown of noradrenaline is by COMT or by monoamine oxidase which leads to the individual components like aldehyde dehydrogenase and aldehyde reductase further broken down to give vanillylmandelic acid, 3,4-dihydroxymandelic acid, and 3,4 dihydroxyphenylglycol biologically inactive in nature and they are the waste product found in urine (Fig. 11) [36].

The binding property of noradrenaline is more specific to target site which is classified into four categories of subtypes present in CNS. They are as follows:

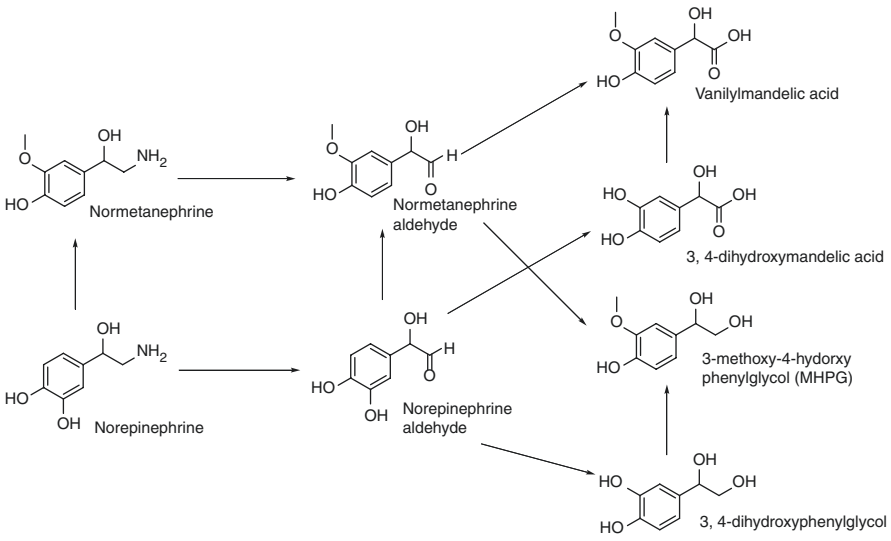

Fig. 11 Degradation of noradrenaline (norepinephrine)

1. Alpha1 receptor: They are seen in the postsynaptic part of neurons and regulate the excitatory properties.
2. Alpha2 receptor: It is found in the terminals of presynaptic and regulates the stopping effects by a feedback inhibition system.
3. Beta1 receptor: They are those receptors which focus only on the adjoining effects.
4. Beta2 receptor: It is present in CNS which is highly regulated in glial cells. They have control in the bonding between the nerves and immune system and possess the physiological role.

Norepinephrine is generally present in brainstem, more precisely in the locus coeruleus (group of A6), tegmentum, and reticular formation of the medulla and pons (groups of A1, A2, A5, A7).

1. Locus coeruleus

   These are the axons present in the neuron of locus coeruleus which projects out virtually to all CNS regions. They are mainly responsible for the excitability of other projection systems and regulate the process of attention, arousal, sleep cycle, and response to stress. These are mainly found in the systems of emotional behavior.
2. Neuronal groups of the tegmentum and reticular formation: They mainly project to the cord of spine, brains, hypothalamus, and limbic system which are responsible for the functioning and behavioral changes in the visceral part. In the spinal cord they regulate the excitability of anterior horn motor neurons. The reticular formations are the groups of small neurons which release the adrenaline to the locus coeruleus which is responsible for stress-related factors.

However in spite of these criticisms the value in bringing up the components involved in voluntary functions of our body holds a major role. And it can be hoped that further investigations will be carried out to study in depth about them with clinical manifestations [37].

6 Conclusion

The main objective of this chapter is to examine the various theories of the chemical transmitters of the nerve impulses and their neurosecretions with a broad text of the metabolism and degradation.

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Pathophysiology of Neurodegenerative Diseases: Basics to Advanced

Sathish Kumar Manoharan
and Poonguzhali Sathish Kumar

Abstract

Neurodegenerative diseases are heterogeneous group of diseases characterized by the progressive damage to the structure and functions of the components of central nervous system (CNS) and/or the peripheral nervous system (PNS). Millions of people are affected worldwide by various types of neurodegenerative diseases, among which Alzheimer's disease (AD) and Parkinson's disease (PD) are the most common types. Other neurodegenerative diseases are Huntington's disease (HD), motor neuron disease (MND), spinocerebellar ataxia (SCA), spinal muscular atrophy (SMA), and prion disease. The etiopathogenesis of most of these diseases is unknown. However, extensive research on neurochemistry and neurotransmitters has contributed significantly to the exploration of pathophysiological mechanisms of NDs. In this chapter, the underlying pathological mechanism behind the most common neurodegenerative disease, i.e., Alzheimer's disease, has been discussed based on the recent scientific data.

1 Introduction

Neurodegenerative diseases are a heterogeneous group of diseases characterized by the progressive damage to the structure and functions of the components of central nervous system (CNS) and/or the peripheral nervous system (PNS). Millions of

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people are affected worldwide by various types of neurodegenerative diseases, among which Alzheimer's disease (AD) [1] and Parkinson's disease (PD) [2] are the most common types. Other neurodegenerative diseases are Huntington's disease (HD) [3], motor neuron disease (MND) [4, 5], spinocerebellar ataxia (SCA) [6, 7], spinal muscular atrophy (SMA) [8], and prion disease [9]. The etiopathogenesis of most of these diseases is unknown. However, extensive research on neurochemistry and neurotransmitters has contributed significantly to the exploration of pathophysiological mechanisms of NDs. In this chapter, the underlying pathological mechanism behind the most common neurodegenerative disease, i.e., Alzheimer's disease, has been discussed based on the recent scientific data [10].

2 Etiopathogenesis of Alzheimer's Disease

2.1 Definition

Alzheimer's disease (AD), also known as senile dementia, is a progressive neurodegenerative disease that destroys memory, learning, and mental functions [1].

2.2 Types of Alzheimer's Disease

There are three types of Alzheimer's disease, namely:

1. Late-onset/sporadic Alzheimer's: Most common variant in 90% of total Alzheimer's disease cases. Environmental factors and genetic variations are the main underlying causes for this type.
2. Early onset: Less common variant found in 5–10% of total Alzheimer's disease cases. Genetic mutations in genes such as PSEN 1, PSEN 2, and APP in chromosome 14 are found to be the major causes for this variant.
3. Familial Alzheimer's: Rarest variant found in less than 1% of total Alzheimer's disease cases. A genetic mutation in chromosomes 21, 1, or 2 is found to be the underlying cause for the disease type.

2.3 Epidemiology

1. Alzheimer's disease is considered to be the most common variant of dementia (affecting more than 25 million people throughout the globe). Alzheimer's disease accounts for 60–75% of total dementia cases.
2. As developing nations contribute more number of elderly people (above 65 years), the prevalence of Alzheimer's disease in such population will increase.

3. Prevalence rate of Alzheimer's disease: In 65 years and above elderly population: 4.4%; global prevalence: 3.9% in 60 years + people; regional prevalence: Africa—1.6%, China and Western Pacific—4.0%, Latin America—4.6%, Western Europe—5.4%, North America—6.4%.
4. Age-specific Alzheimer's disease prevalence rate doubles every 5 years after 65 years.

2.4 Etiology

Alzheimer's disease is considered to be a multifactorial disease. The etiologic hypothesis of Alzheimer's disease is as follows:

1. Genetic susceptibility: (a) Genetic mutations in genes such as PSEN 1, PSEN 2, and APP in chromosome 14; (b) genetic mutations in chromosomes 21, 1, or 2; (c) APOE ε4 gene; (d) familial aggregation, etc.: there is a strong epidemiological evidence for this etiologic factor.
2. Vascular pathway: (a) hypertension, (b) obesity, (c) diabetes, (d) high levels of total cholesterol, (e) silent infarcts, and (f) leukoaraiosis. Moderate to sufficient evidence is available for this etiological factor.
3. Psychosocial: (a) psychosocial factors, (b) inactive lifestyle, (c) low education, (d) low economic status, (e) social disengagement/weak social networking, (f) lack of physical activity, and (g) lack of mentally challenging activity. Moderate to sufficient evidence is available for this etiological factor.
4. Nutritional or dietary: (a) folate deficiency, (b) vitamin B12 deficiency, (c) antioxidant deficiency, (d) vitamin A deficiency, (e) vitamin E deficiency, and (f) vitamin C deficiency. Insufficient to limited or mixed evidence is available for this etiological factor.
5. Toxic exposures, inflammation, or others: (a) high levels of CRP, (b) high levels of IL-6, (c) heavy metals such as mercury or aluminum (through occupational exposure), (d) high consumption of drinking water with higher levels of aluminum, (e) ELF-EMF (through occupational exposure), (f) craniocerebral trauma, (g) estrogen therapy, and (h) depression.

2.5 Risk Factors

1. Modifiable: (a) smoking, (b) sedentary or inactive lifestyle, (c) poor social networking, (d) socioeconomic status, (e) heavy alcohol consumption, (f) lack of physical activity, (g) improper diet, (h) education, etc.
2. Unmodifiable: (a) increasing age, (b) gender (women at higher risk than men), (c) family history, (d) racial and ethnic differences, etc.

2.6 Pathogenesis

Microscopic changes begin in brain long before the clinical manifestations (i.e., appearance of first signs and symptoms) of memory loss.

Brain possesses more than 100 billion neurons or nerve cells. All these nerve cells connect with others to form a communication network. Groups of neurons or nerve cells have specific or special functions. Some of these nerve cells are involved in learning, memory, thinking, and functioning of special senses (hearing, smelling, and seeing). These nerve cells or neurons perform their specific or special functions through coordination and consumption of large supplies of oxygen and other fuels. These nerve cells also process, store, and communicate the received information to perform their functions.

Scientists believe that etiological agents and risk factors alter/damage the functioning of the nerve cells. As the damage progresses, the nerve cells lose their functional ability and eventually die, sometimes leading to irreversible damage to the brain.

Plaques and tangles (abnormal structures) are believed to be the primary suspects in the pathogenesis of Alzheimer's disease. Plaques (protein fragments—beta-amyloid) accumulate in the spaces or areas between neurons. Tangles (protein fragments—tau) accumulate within the nerve cells.

The appearance or onset of these plaques and tangles in the pathogenesis of Alzheimer's disease is not clearly elucidated till date by the scientists. But it is generally believed that these plaques and tangles cause damage to the communication networks of nerve cells leading to loss of thinking, reasoning, learning, and memory.

The pathophysiologic role of other etiological agents (genetic mutations, vascular factors, psychosocial factors, nutritional or dietary factors, toxic exposures, inflammation, etc.) remains largely unclear.

Seven stages of Alzheimer's disease: (a) stage 1: no cognitive decline (no dementia); (b) stage 2: very mild cognitive decline (no dementia); (c) stage 3: mild cognitive decline (no dementia); (d) stage 4: moderate cognitive decline (early stage); (e) stage 5: moderately severe cognitive decline (mid stage); (f) stage 6: severe cognitive decline or middle dementia (mid stage); (g) stage 7: very severe cognitive decline or late dementia (late stage).

2.7 Signs and Symptoms

1. Difficulty in remembering newly learnt information (early symptom of Alzheimer's disease because plaques and tangles mainly cause damage to the part of brain that is related to learning).
2. Worsening confusion (about place, events, and time), mood changes, behavior changes, disorientation, and unfounded suspicions (on family, professional caregivers, health professionals, friends, and society) occur as the disease progresses.

3. As the disease state further worsens, difficulty in speaking, walking, writing, and swallowing occurs. Further serious learning and memory loss and behavioral changes occur.

2.8 Pathology

(a) Atrophy, (b) mitochondrial dysfunction, (c) inflammation, (d) vascular damage, (e) production of free radicals, (f) presence of beta-amyloid plaques and tau proteins, etc.

2.9 Complications

(a) Bladder problems, (b) restlessness/anxiousness, (c) agitation, (d) bowel problems, (e) depression, (f) loss of balance or coordination (falls), (g) infections (pneumonia), (h) malnutrition, (i) dehydration, (j) bed sores, (k) wandering, etc.

2.10 Biomarkers for Diagnosis of Alzheimer's Disease

(a) Medical history of the patient, (b) family history of the patient, (c) psychiatric history, (d) cognitive history, (e) behavioral history, (f) neurological tests, (g) physical tests, (h) cognitive tests, (i) quantity of beta-amyloid (through PET imaging), (j) abnormal brain tau levels (through PET imaging), (k) beta-amyloid and tau levels in CSF, (l) glucose metabolism (through PET imaging of the brain), (m) blood tests (thyroid and vitamin levels), (n) MRI/CT (to determine atrophy or rule out TBI/cerebral stroke/tumor).

2.11 Treatment

(a) Cholinesterase inhibitors (donepezil, galantamine, rivastigmine), (b) memantine, (c) memantine + donepezil.

3 Conclusion

In recent times considerable attention has been given to understand the etiopathogenesis of various neurodegenerative diseases. Also the high prevalence rate of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease throughout the globe has triggered the comprehensive study on the etiology, underlying pathophysiological mechanisms, and complications involved in such diseases, so that the cost-effective diagnostic process and pharmacological therapy can be developed [11].

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Part II

Revisiting Neurodegenerative Diseases

Current Perspectives in the Management of Neurodegenerative Alzheimer's Disease: Preclinical and Clinical Status

Arunachalam Muthuraman, Muthusamy Ramesh, and Thiagarajan Venkata Rathina Kumar

Abstract

Alzheimer's disease (AD) is a chronic progressive organic brain disorder. It mainly accelerates the abnormal neurochemical functions of acetylcholinesterase (AChE), acetylcholine, and amyloid and tau proteins. The net effects are neurodegeneration, neuroinflammation, and neuronal death. All these effects are observed in the later stage of AD patients with brain atrophy. The early stage of AD shows the changes of free radical, antioxidant defense enzyme, and metal ion concentration in neuronal system, which lead to development of the oxidative stress, imbalance of cell signal (communication), and activation of the cellular organelle (mitochondria, nuclear, and ribonucleic acids) dysfunction. Furthermore, multiple drug targets are explored to prevent AD. Clinically some of the medicines like donepezil and memantine are used in the management of AD. Currently, numerous preclinical research works are targeted and they include acetylcholine modulators, β-amyloid pathways and related enzymes (α, β, and γ-secretase), amyloid-β aggregation inhibitor, immunotherapy (active and passive), neurotrophin, mitochondria, and nuclear receptor (PPAR-γ). All these targets are interlinked with the regulation of neurochemical alteration and restoration of neuronal structure and functions for the amelioration of AD. This

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book chapter guides the possible neurochemical research targets for the management of AD along with current perspectives of preclinical and clinical trials of specialized AD-targeted drugs.

Abbreviations

1T1C	One-target-one-compound
3APS	3-Amino-1-propane sulfonic acid
a7-nAChR	α7-Nicotinic acetylcholine receptor
Ab	Amyloid-β peptide
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChR	ACh receptor
AD	Alzheimer's disease
ADAS-Cog	Alzheimer's disease assessment scale-cognitive subscale
ADCS	AD co-operative study
ADCS	Alzheimer's disease co-operative study
APP	Amyloid precursor protein
ATP	Adenosine-triphosphate
BACE1	Beta-secretase 1
BBB	Blood-brain barrier
BCL_2	B-cell lymphoma-2
BDNF	Brain-derived neurotrophic factor
cGMP	Cyclic guanosine monophosphate
ChAT	Choline acetyl transferase
CIBIC+	Clinician's Interview-Based Impression of Change Plus Caregiver Input
CSF	Cerebrospinal fluid
EGCG	Epigallocatechin-3-gallate
EOAD	Early-onset familial Alzheimer's disease
GSK-3	Glycogen-synthase-kinase-3
HA	Huperzine-A
LMTX	Leuco-methylthioninium
LOAD	Late-onset sporadic Alzheimer's disease
MAP 2c	Microtubule-associated protein-c
MMSE	Mini-mental state examination
MPTP	Mitochondrial permeability transition pore
NFTs	Neurofibrillary tangles
NGF	Nerve growth factor
p70S6K	70 kDa Ribosomal protein S6 kinase
PDE	Phosphodiesterases
PPAR-γ	Peroxisome proliferator-activated receptor-gamma
PSEN1	Presenilin 1

PSEN2	Presenilin 2
RAGE	Receptor for advanced glycation end products
RCTs	Randomized controlled trials
RNS	Reactive nitrogen species
ROS	Reactive oxygen species
SP	Senile plaques
$VEGFR_2$	Vascular endothelial growth factor receptor-2

1 Introduction

AD is a progressive neurodegenerative disorder. The management of AD is complicated with multifactorial conditions. It is the most common irreversible types of dementia [1–3]. The major causative factor of AD is age-related neurochemical changes and neuronal proteins [1]. Worldwide, the progress rate of AD and deaths are higher. The hallmark of AD is an accumulation of beta-amyloid (β-amyloid) protein in the brain which leads to gradual rising of neuronal cell death in the brain. It produces various clinical symptoms like loss of intellectual property and social skills. Certain genetic factors make the complexity of AD [4, 5]. In addition, various toxic proteins like tau (τ) proteins and neurofibrillary tangles (NFTs) also play a key role in the progression of neurodegenerative disorders like Alzheimer's disease [6, 7]. The major symptoms of AD are changes in day-to-day activity and quality of life [8]. The major molecular mechanism of AD progression is too complicated due to the involvement of multiple cellular proteins, enzymes, ion channels, and genetic factors [2]. The major types of AD are (i) late onset of AD and (ii) sporadic form of AD. Both the types of AD are regulated by genetic factors and it is altered during the aging process of cerebral neurovascular system [4]. In addition, early-onset familial Alzheimer's disease (EOFAD) is a rare type of autosomal dominant type of AD and it is commonly aggregated within the family members [9].

The progression of AD is a very common type of dementia in the elder population. The devastating process of the neurological system causes progressive cognitive impairments, functional alteration, and loss of independence in day-to-day life. AD affects 5% of individuals over the age of 65; 25% over the age of 80; and one by the third percentage over the age of 90 years [10, 11]. Worldwide, about 35 million people suffer from AD. Furthermore, it is recognized as one of the most challengeable medical problems of the geriatric population due to the rising of social and economic costs [12]. The expected AD progress is more than 115 million people with dementia by 2050 [11, 13]. Moreover, the AD is reaching epidemic proportions with the large human, social, and economic burden. Therefore, there is an urgent need to develop more efficient treatment and to delay the onset of AD progression [14, 15]. Frequency of new AD progression is rapid and larger in the global geriatric population by rising changes of global lifestyle pattern and accumulation of unavoidable environmental toxicants [4, 16]. Now, around 5.3 million US citizens are affected by AD and victims of AD are sequentially increased to five million

every year and it will reach ~13 million by 2050. And worldwide, the level of AD population will reach around 100 million by 2050 [17].

The pathogenesis of AD is too complex and it involves multiple cellular molecules. The major hallmarks of AD progression are accumulations of amyloid-beta proteins (Aβ), NFTs, and microtubule-associated protein, i.e., tau proteins. The initial event of AD progression starts with an excessive biosynthesis of Aβ proteins and it turns to accelerate the NFTs and it correlates with significant cognitive impairments [18]. Subsequently, Aβ and NFTs trigger the tau proteins leading to impairment of the neuronal function and enhancement of the neuronal cell death (neurodegeneration). In EOAD, the autosomal dominant AD progression is enhanced by neuronal Aβ proteins with mutations of specialized genes, whereas late-onset sporadic Alzheimer's disease (LOAD) progression is not clear. LOAD progression is most likely to impair the Aβ clearance than overproduction [19, 20]. In addition, an e4 allele of apolipoprotein E has been identified as a major genetic factor for the progression of LOAD. The EOAD is mainly due to the variability of three major genes, i.e., amyloid precursor protein (APP), presenilin 1 ($PSEN_1$), and presenilin 2 ($PSEN_2$) [21, 22]. Several mechanisms have been proposed and explored in the pathogenesis of AD [2]. The Aβ cascade, hyper-phosphorylation of tau protein, oxidative stress, deficiency of acetylcholinergic function, neuroinflammation, and heavy metal ions were explored in the pathogenesis of AD [23, 24]. However, the precise cellular and molecular mechanism to treat the AD is still unclear. The explored targets based on some medicines are used for the mitigation of AD. The aggregation of Aβ fibrils is employed in the progression of AD. And soluble Aβ oligomers are identified as a key player in the pathogenic process of AD. The helical filaments of tau proteins also make the NFTs to modify the posttranslational functions via hyper-phosphorylation of tau proteins [25]. Both neuronal proteins, i.e., Aβ and tau proteins, accelerate the neuroinflammation and neurodegeneration. These factors are more selectively vulnerable to cortical and hippocampal neurons, which lead to the development of AD [26].

2 Pathophysiology

2.1 Amyloid Cascade Hypothesis

Amyloid cascade hypothesis is one of the key processes of AD with Aβ deposition and formation of senile plaques [27]. The soluble form of Aβ peptides is produced by cleavage of amyloid precursor protein (APP) via activation of α-secretase, β-secretase, and γ-secretase [28]. The abnormal activation of secretase creates the imbalance of biosynthesis of Aβ protein and clearance of Aβ protein. It has multiple oligomeric forms. Some of the oligomeric forms are toxic in nature in AD progress. The reason for the formation of toxic Aβ oligomeric protein is still unclear. The properties of toxic Aβ oligomeric proteins, i.e., sequence length, concentration, and conditions of stability of Aβ oligomer, are the major contributing factors in AD

progress [29]. The assembly of Aβ oligomer causes neuroinflammation and neurodegeneration. It is also known as amyloid toxicity. Alteration of vascular endothelial growth factor receptor-2 (VEGFR2) function is also associated with amyloid toxicity [30]. The multiple changes of cerebral vascular function cause the abnormalities of neurovascular functions via amyloid dyshomeostasis process [31]. The administration of amyloid-β-targeted medicines and immunotherapies are not effective in the early AD patients, because the extracellular accumulation of amyloid-β fibrils does not have intrinsic cytotoxic action and does not enhance the tau protein accumulation. The major limitations of amyloid cascade hypothesis-targeted drugs are as follows: (a) extracellular accumulation of amyloid-β fibrils; (b) sometimes distribution of senile plaques is extensive in non-demented patients than AD (hence no direct correlation with the onset of AD); (c) senile plaques and neurofibrillary tangles develop independently; and (d) genetically driven synaptic failure independent of amyloid cascade hypothesis. The consideration of these points in the amyloid hypothesis is necessary to treat AD conditions [28, 32, 33].

2.2 Hyper-phosphorylation of Tau Protein

The formation of NFTs occurs mainly due to the hyper-phosphorylation of tau protein in AD progress. Tau protein belongs to the family of microtubule-associated proteins and it provides stability to the microtubules of axon [34, 35]. In addition, tau proteins have several phosphorylation sites and it is important for the maturation of nerve cells via phosphorylation of tau protein. In healthy neuronal cells, phosphorylation and dephosphorylation of tau protein are a dynamic cyclic process. When hyper-phosphorylation of tau protein accelerates the formation of double-helix tau fiber, it enhances the destabilizing microtubules and neuronal death [36, 37]. Further, the relationships between Aβ oligomer and tau protein phosphorylation play a key role in neurodegeneration and AD progress [37].

2.3 Oxidative Stress Hypothesis

The free radicals like reactive oxygen species (ROS) and reactive nitrogen species (RNS) are rapidly generated in neuronal tissues with multiple toxic stimuli because the neuron is a highly sensitive and energy-utilizing tissue. Hence, it is a more vulnerable tissue. Therefore, the slight changes in the normal neuronal functions alter the normal physiological beneficial actions and cellular signaling pathways. The rapid and chronic accumulation of radicals and ion channels alters the nuclear and mitochondrial function, and pre- and posttranscriptional proteins lead to deleterious effect in neuronal system [38]. The highly reactive oxygen species of brain tissue is formed by the utilization of 20% more oxygen than the needs of mitochondrial respiratory chain reactions leading to oxidative stress [39]. The neuron is a major functional unit of the brain. And it is composed of a large number of

polyunsaturated fatty acids and is ready to react with various bio-radicals leading to enhancement of lipid peroxidation. The chronic peroxidation of membrane lipids induces cellular and molecular apoptotic reactions. At the same time, the natural neuronal antioxidant molecule, i.e., reduced glutathione, fails to scavenge the free radicals leading to oxidative stress-associated neuronal injury [40, 41].

2.4 Cholinergic Hypothesis

Acetylcholine (ACh) is one of the major neurotransmitters for the parasympathetic neuron. It plays a key role in multiple physiological and body functional actions. Chen and Mobley's research work has explored the function of the cholinergic system in AD progress. The dysfunction of cholinergic activity contributes to producing the loss of memory whereas the reconstruction of the cholinergic neuron and their neurotransmitters help in the reduction of lack of cognitive function [42]. The levels of ACh in the neuron system are maintained by choline acetyltransferase (ChAT) and acetylcholinesterase (AChE) activity. In AD, the levels of ACh, ChAT, and AChE activity are altered in brain tissue. ACh is widely distributed in different parts of the brain and helps to maintain the cognitive performance, i.e., learning and memory process [43]. It is synthesized by acetyl-CoA and choline with the catalytic reaction of ChAT activity. ACh and its ACh receptor (AChR) actions support the transfer of nerve impulses to various cholinergic pathways of the brain. Further, AChE is subjected to hydrolyzation of ACh and it produces the acetic acid and choline. Moreover, the ACh level induces the neuronal plasticity with the help of synaptic transmission of neuronal networks of brain cells and regulates the neuronal functions [44].

2.5 Inflammatory Hypothesis

The inflammatory process is one of the common processes of various disorders. Free radicals and ion channels are interlinked to inflammatory reactions. Together, all three factors enhance the multiple cellular and biomolecular signaling pathways leading to inflammation. The inflammatory process of the neuronal system slightly differs because the specialized protein, i.e., microtubule and glial cells, contributes to the progress of neuroinflammation. In AD, the posttranslational proteins, i.e., Aβ oligomer, tau protein, and NFTs, contribute to the neuroinflammatory process. In addition, AD-associated chronic neuroinflammation is also characterized by an accumulation of a large number of mononuclear leukocytes and macrophages. Similarly, overexpression of pro-inflammatory cytokines is also observed in brain tissue of AD patients [44, 45]. Neuron-specific glial cells, i.e., microglia and astrocytes, contribute to the inflammatory reactions and it accelerates the production of pro-inflammatory mediators (interleukin-1β, interleukin-6, tumor necrosis factor-α, interleukin-8, macrophage inflammatory protein-1, prostaglandins, leukotrienes, coagulation factor, and protease activity). All these factors are known to induce the neuronal death via autocrine and paracrine actions [46, 47].

2.6 Metal Ion Hypothesis

Metal ions like aluminum, copper, iron, manganese, and zinc contribute to the various physiological functions. However, these heavy metals commonly help in the neurological function and also are important to maintain the homeostasis process. However, the abundant accumulation of heavy metals in the neurological system causes neurodegeneration. Because the heavy metals catalyze the reaction of various cellular enzymes, they also serve as cofactors for multiple cellular signaling and metabolic process. The major heavy metal-reactive protein is metalloprotein and it is employed in the process of neuronal metabolism [48, 49]. Furthermore, it also regulates the blood-brain barrier (BBB) function of the brain. Metal ions contribute to the induction of the neurodegenerative process via induction of oxidative stress, mitochondrial dysfunction, misfolding of cellular proteins, and alteration of metal ion transport function [50, 51]. Various studies have reported that aluminum, zinc, copper, and iron are involved in the production of Aβ protein [52, 53]. Aluminum is one of the major heavy metals and it is responsible for the accumulation of Aβ and tau protein. In addition, copper is also involved in the process of the development of neuroinflammation [54, 55]. Accumulation of iron, aluminum, and copper is observed in aged human brain and AD patient's brain [56, 57]. Summary of the pathophysiology of AD has been depicted in Fig. 1.

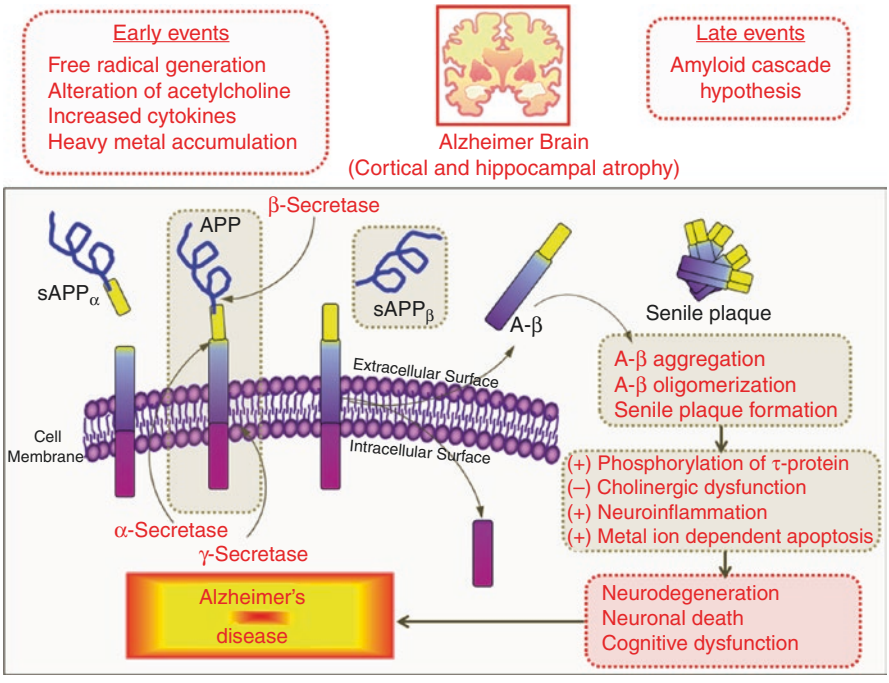

Fig. 1 Illustrated pathophysiological mechanism of AD. The net (early and late) effects enhance the neurodegeneration and neuronal death which is reflected in memory (cognitive) dysfunction

3 Drug Targets for AD

Based on the pathogenesis of AD, several targets have been identified from various documents. However, some of the targets are explored in AD patients, i.e., AChE and N-methyl D-aspartate (NMDA) receptor. These targeted medicines ameliorate the various cognitive disorders in experimental animals as well as in humans. However, it is proven to produce the symptomatic relief of cognitive disorders. Thus, the identification of newer targets for the treatment of AD is required [58, 59]. However, some of the drug targets are clinically approved such as cholinesterase inhibitors (i.e., donepezil) and *N*-methyl-D-aspartate inhibitors (i.e., memantine). In addition, various newer drug targets for AD are explored in preclinical research and clinical trials. Such targets are metabolic modulators of Aβ oligomer, inhibitors of Aβ aggregation, accelerators of Aβ and tau protein degradation, activators of α-secretase, inhibitors of γ-secretase, immune modulators, neuromodulators, mitochondrial regulators, and agonists of peroxisome proliferator-activated receptor-gamma (PPAR-γ) [60].

3.1 Cholinergic Neurotransmitter-Targeted Drugs

Cholinergic neurotransmitter-targeted drugs are the first approved medicines for cognitive disorders. Wang et al.'s research report explored that memory functions are interlinked with cholinergic neurotransmitter and multiple neuronal cell signaling systems. The cholinergic hypothesis is widely proposed in AD. Administrations of cholinergic inhibitors ameliorated the cognitive disorders especially in AD [61]. In addition to that, cholinergic inhibitors and acetylcholinesterase (AChE) inhibitors attenuated the cognitive dysfunction. Furthermore, a modulator of cholinergic receptors like muscarinic and nicotinic ACh receptors also produces the nootropic action. In 1993, FDA has approved nootropic agent, i.e., tacrine (muscarinic and nicotinic ACh receptor modulators), for the management of mild-to-moderate AD. However, the usage of tacrine in the United States was stopped in 2013. Because it has a low safety margin and it causes the potential hepatotoxicity due to the first-pass metabolism and forms a toxic intermediate. Further, other cholinesterase inhibitors, i.e., donepezil, rivastigmine, and galantamine, were also approved for the various cognitive disorders [62–64]. Newer nootropic agents, i.e., velnacrine, physostigmine, eptastigmine, and metrifonate, produced the ameliorative effect with the inhibition of AChE activity [62, 65]. Moreover, NMDA receptor antagonist, i.e., memantine, has also been approved for the management of AD. Furthermore, it alters the glutamatergic system to treat the moderate-to-severe AD [66]. Besides the approved drugs, various newer lead compounds are still under investigation for the treatment of AD. The details of lead compounds for the management of AD are illustrated in Fig. 2.

Huperzine-A (HA) is an alkaloid derivative of Chinese herbal medicine *Huperzia serrata*. It is identified as a selective inhibitor of acetylcholinesterase activity. Further, the action of HA is similar to a commercial synthetic compound, i.e.,

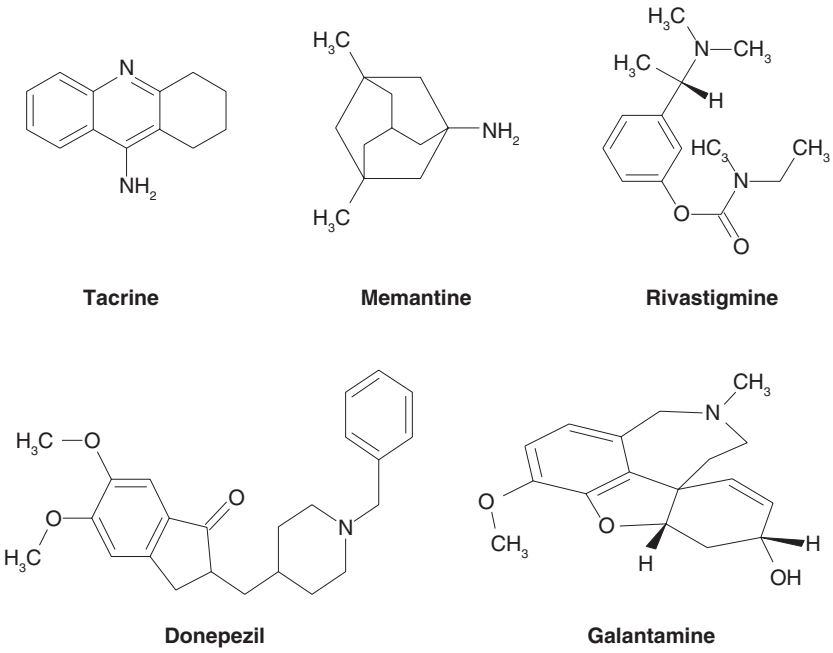

Fig. 2 FDA-approved drugs for the treatment of AD

donepezil. HA and donepezil have a promising role in the treatment of AD and have shown an improvement in daily living activity [67]. Some trials reported that HA does not have significant influence in cognitive impairment as per AD Assessment Scale-Cognitive Subscale (ADAS-Cog). The clinical data comprised of poor methodological quality [68]. Prodrug of HA, i.e., ZT-1, is derived from a natural resource and it has a potent and selective AChE inhibition. The phase I clinical trials reported that ZT-1 has rapid absorption and distribution properties in human [69]. Another AChE inhibitor, i.e., physostigmine, was extracted from Calabar beans for the treatment of AD; it has serious side effects [70]. (-)Phenserine is another derivative of physostigmine. It also inhibits AChE activity and improves cognitive impairment. The major mechanism of (-)phenserine is that it reduces the translation process of APP leading to a reduction in the concentration of Aβ. Hence it is considered as a multi-targeted drug for AD treatment [65, 71]. Memogain (Gln-1062) is an inactive prodrug of galantamine and it enhances the cleavage of galantamine via brain carboxylesterase activity. The bioavailability of memogain is greater than 15-fold of galantamine due to its hydrophobic nature. It is considered as a valuable drug for the management of AD due to its higher potency, reduction of lower plaque density, maximal induction of cognition function, and least side effects in gastrointestinal system [72].

Another newer multi-targeted drug, i.e., ladostigil, is effective in AD with a combination of acetylcholine-butyrylcholinesterase inhibitor and brain-selective

monoamine oxidase A and B inhibitor. Experimentally, it ameliorated the scopolamine-induced impairment of spatial memory with the reduction of cholinergic activity [73]. In addition, it also has anti-apoptotic and neuroprotective action via regulation of APP, activation of protein kinase C, and mitogen-activated protein kinase signaling process [74, 75]. NGX267 (AF267B) is an M_1-selective muscarinic receptor agonist and it enhances the cognitive functions. In the AD of transgenic mice, it also reduced the levels of $A\beta_{1-42}$ and tau hyper-phosphorylation levels in the transgenic mice of AD [76]. Moreover, a newer α7 nicotinic acetylcholine receptor (a7-nAChR) agonist, i.e., EVP-6124, crosses the BBB and enhances the cognitive functions in AD patients. Further, EVP-6124 also evidenced that it ameliorates the AD patients and moved to phase III clinical trials [77]. In addition, the selective agonist of α7 nicotinic receptor, i.e., GTS-21, showed beneficial effects for AD in phase II clinical trial [78]. The details of newer compounds for the management of AD are illustrated in Fig. 3.

The pathophysiology of AD has mainly expressed the loss of cholinergic neurons in the basal forebrain and cerebral cortex which leads to reduction of the cholinergic transmission. Acetylcholinesterase-targeted medicines improve cognitive functions. However, newer molecules also modulate the muscarinic and nicotinic acetylcholine receptors of the cholinergic neuron and enhance the cognitive functions [79, 80]. The enantiomer of (–)-phenserine inhibits the acetylcholinesterase activity and reduces the APP and Aβ concentrations via reduction of the translation process of

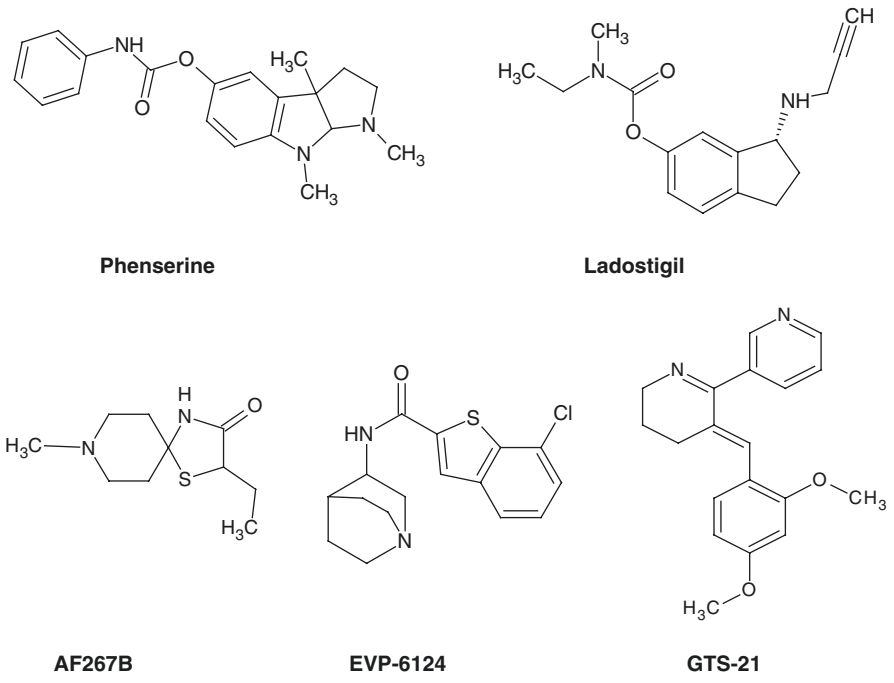

Fig. 3 The newer cholinergic inhibitors in clinical trials

APP mRNA sequence. Furthermore, the newer (+)-phenserine enantiomer, i.e., posiphen, showed poor acetylcholinesterase inhibitory action along with the reduction of APP production via decreasing the APP mRNA translation process [81, 82]. The randomized controlled trials (RCTs) of phenserine have shown beneficial effects on cognitive functions in mild-to-moderate AD patients. Moreover, Assessment Scale-Cognitive subscale (ADAS-Cog) and the Clinician's Interview-Based Impression of Change Plus Caregiver Input (CIBIC+) trial were not initiated for AD [83].

Furthermore, the muscarinic receptor agonists based on AD therapy have limited success and produce fewer adverse effects. Talsaclidine, AF-102B, and AF-267B (NGX-267) are the major M_1-muscarinic receptor agonists and it affects the Aβ production [19, 79]. Talsaclidine and AF-102B potentially reduce the Aβ concentrations in cerebrospinal fluid (CSF) of AD patients. It also produces undesirable cholinergic receptor-mediated adverse effects like rising the salivary flow and xerostomia [84]. Ispronicline (AZD-3480) is a selective agonist of nicotinic receptor ($\alpha_4\beta_2$) and it has positive effects on cognition improvements in healthy and age-associated mild-to-moderate AD patients [85]. Phase II RCT of ispronicline or donepezil expressed a significant memory-enhancing effect on AD after 12 weeks whereas ispronicline (20 mg dose) has shown limited effects of cognitive function in AD patients [85]. The partial agonist of nicotinic ($\alpha_4\beta_2$ and $\alpha_6\beta_2$) receptors, i.e., ABT-089, reverses the scopolamine-associated cognitive deficits in healthy volunteers. However, phase II RCT of ABT-089 has been documented to produce the stable cognitive function in mild-to-moderate AD patients [86]. EVP-6124 is another nicotinic (α_7) receptor agonist; it showed safe and well-tolerated action of cognitive function in AD patients [87]. It has entered phase II RCT (NCT01073228) testing for mild-to-moderate AD patients. Further, various cholinergic neurotransmitter-targeted drugs with multifunctional compounds have entered various phases of the preclinical screening process.

3.2 Amyloid Peptide-Targeted Drugs for the AD Management

Amyloid peptides contributed to various cellular signaling processes for the pathogenesis of AD. The alteration of amyloid peptide biosynthesis and metabolism are the responsible factors for the progress of cognitive dysfunction. The rate of amyloid biosynthesis is faster and higher in AD, and at the same time metabolism rate is too slow. Therefore, excessive amyloid peptides enhance the formation of tau proteins and NFTs. Altogether, it plays a key role in the progress of neurodegeneration, brain atrophy, and AD. Numerous, anti-AD drugs are driven based on the amyloid hypothesis. Most of the RCTs are carried out to target the Aβ peptides. Furthermore, it is derived from proteolytic cleavage (β-secretase and γ-secretase) reaction of APP via the amyloidogenic pathway [88, 89]. $Aβ_{1–40}$ and $Aβ_{1–42}$ are by-products of an amyloidogenic pathway. $Aβ_{1–40}$ is the most frequent and common form of Aβ peptides whereas $Aβ_{1–42}$ form is in higher proposition in the aggregation process of Aβ and enrichment of amyloid depositions. Currently, amyloid hypothesis follows the

changes of both Aβ peptide concentrations in CSF including the assessment of $A\beta_{1-42}$ and $A\beta_{1-40}$ ratios in AD patients [89, 90]. The RCT results expressed that the removal of Aβ peptides from the circulation is not sufficient to reverse the damage of neuron and to stop the AD type of dementia [91]. However, the amyloid hypothesis with the efficient anti-amyloid drugs in RCT has not been translated yet.

3.2.1 Decreasing Aβ Production by β-Secretase Inhibitors

Various β-secretase-1 ($BACE_1$) inhibitors are discovered by in silico techniques. However, potential preclinical testing and RCTs of those inhibitors are limited. LY2811376 is one of the first non-peptide types of $BACE_1$ inhibitor. It showed satisfactory pharmacokinetic and pharmacodynamic actions in animals and in humans. Furthermore, it is easy to cross the BBB and produced long-lasting effect on the reduction of Aβ peptides in healthy volunteers. Moreover, RCT was stopped due to excessive chronic non-targeted toxicological reactions. The next generation of orally active $BACE_1$ inhibitor, i.e., LY2886721, reduces the concentrations of $A\beta_{40}$, $A\beta_{42}$, and sAPP-β in CSF along with higher safety and good tolerable actions [92]. This molecule was also terminated due to potential abnormal liver function tests. In addition, newer $BACE_1$ inhibitor, i.e., MK-8931, was tested in phase I clinical trial and AD patients. It significantly reduces the levels of CSF-Aβ concentration in a dose-dependent manner in mild-to-moderate AD patients [93, 94]. However, it also elicits fewer adverse effects with different doses and is well tolerated in healthy human subjects as well as in AD patients [95]. Further, the orally active $BACE_1$ inhibitor, i.e., E2609, reduced the Aβ concentrations in CSF and plasma with single and multiple oral ascending doses [96, 97]. Therefore, the reduction of Aβ production with β-secretase inhibitors can play a key role in the management of AD patients. The chemical structure of β-secretase inhibitors in clinical trials is illustrated in Fig. 4.

3.2.2 Decreasing Aβ Production by γ-Secretase Inhibitors

γ-Secretase inhibitors are also one of the key targets for the reduction of Aβ concentrations in AD patients. The newer γ-secretase inhibitor, i.e., semagacestat (LY-450139), is identified as a potential newer molecule for the treatment of AD patients. It reduces the plasma and CSF concentrations of Aβ peptides in a dose-dependent manner. It also disturbs the Notch signaling proteins and cell surface receptors via inhibition of γ-secretase activity [98]. Moreover, another γ-secretase inhibitor, i.e., avagacestat (BMS-708163), also produced the additional Notch-sparing effect and it did not produce the efficacy in mild cognitive impairments in phase II trials [99, 100]. However, thiophene sulfonamide derivative of selective γ-secretase inhibitor, i.e., begacestat (GSI-953), inhibits the cleavage of APP over Notch signaling process. Phase I clinical trial showed a promising effect on the reduction of Aβ concentration [101]. The natural compound of Notch-sparing secretase inhibitor and insulin sensitizer, i.e., NIC5-15, has shown the improvement in cognitive function with the reduction of Aβ production and multiple cellular mechanisms. In addition, it showed safe and good tolerable action in AD patients [2, 102]. The newer microglial modulator, i.e., CHF5074, also reduces

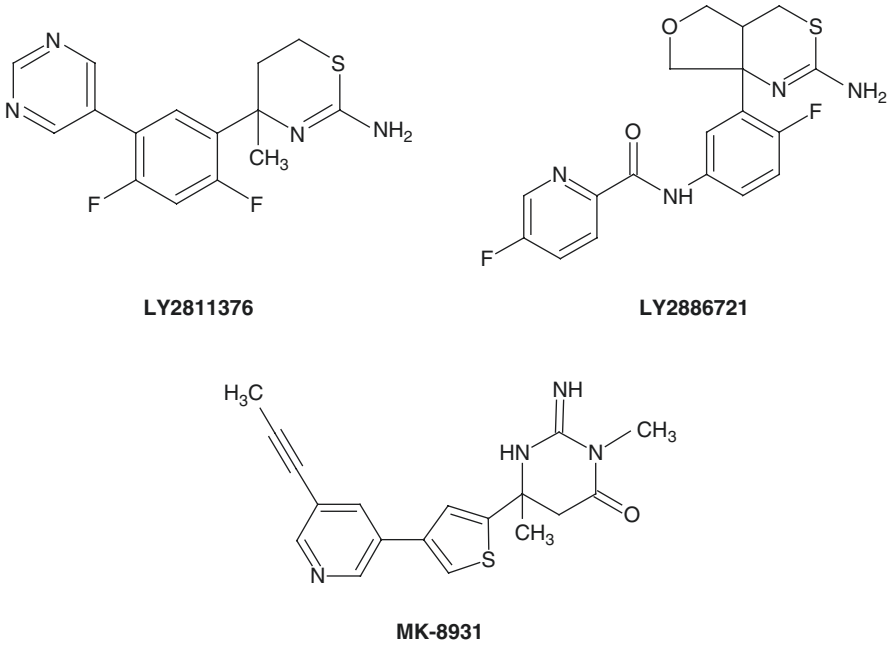

Fig. 4 β-Secretase inhibitors in clinical trials

the brain Aβ biosynthesis and enhances the spatial memory function in transgenic mice model of AD. Further, it shows the well-tolerated and safer dose-dependent effects in mild-to-moderate AD patients [19]. Currently, novel γ-secretase modulator, i.e., E2012, reduces the levels of $A\beta_{40}$ and $A\beta_{42}$ concentrations in a dose-dependent manner without affecting the Notch cleavage process [103]. The chemical structure of γ-secretase inhibitors in clinical trials is illustrated in Fig. 5.

3.2.3 Decreasing Aβ Production by α-Secretase Activators

The upregulation of α-secretase activity contributes to the non-amyloidogenic cleavage process of APP and it decreases the level of Aβ concentration and raises the production of the soluble domain of APP-alpha (sAPPα). sAPPα is one of the key molecules of neuroprotective action in AD [104]. Hence, the stimulator/activator of α-secretase activity is very essential in the management of AD patients. Such agents are muscarinic receptor agonist, glutamate modulators, serotonin receptor regulators, statins, estrogens, testosterone, and protein kinase C activators. These agents are tested in various phases of clinical trials. However, the evidence of these molecules' efficacy in AD patients remains to be explored [105, 106]. The selective $GABA_A$ receptor modulator, i.e., etazolate (EHT-0202), enhances the actions of neuronal α-secretase activity and increases sAPPα production [107]. In addition to that, RCT (NCT00880412) has shown that it produces the good oral bioavailability in mild-to-moderate AD [22]. Further,

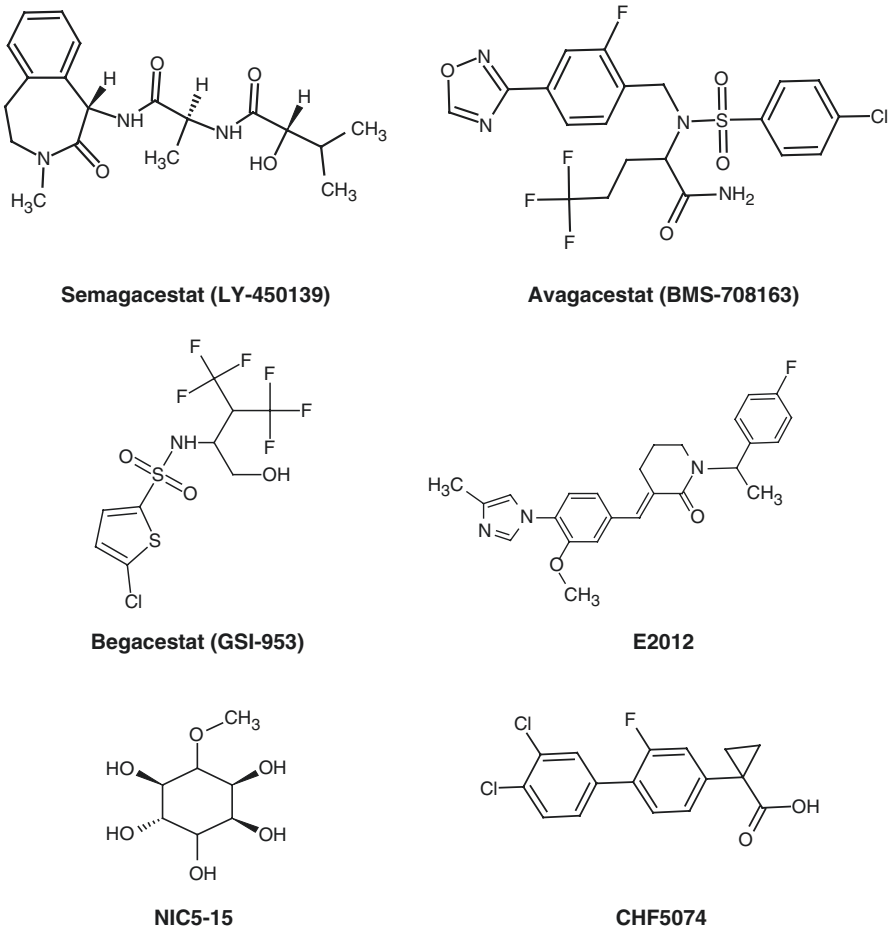

Fig. 5 Chemical structure of γ-secretase modulators in clinical trials

macrocyclic lactone-derived antineoplastic agent, i.e., bryostatin-1, and its synthetic analog have shown potential α-secretase stimulatory action via activation of protein kinase C and promotion of sAPPα secretion in AD patients [105, 108]. Moreover, bryostatin-1 also reduces the levels of $A\beta_{1–40}$ and $A\beta_{1–42}$ concentration in mouse brain with AD and improves the cognitive behavior [108]. The phase II clinical study (NCT00606164) documented that bryostatin-1 is safer in mild-to-moderate AD patients. Currently, exebryl-1 also modulates the β-secretase as well as α-secretase activity leading to reduction of Aβ peptide formation in the mouse brain and it also attenuates memory impairments. Further, in 2008, this molecule crossed the phase I RCT for the management of AD [22]. Hence, the reduction of Aβ production with α-secretase activators can play a key role in the management of AD patients.

3.2.4 Prevention of Aβ Aggregation for AD Management

The major step of AD management with the amyloid hypothesis is the prevention of Aβ aggregation. Orally active Aβ aggregation inhibitor, i.e., tramiprosate, binds to Aβ oligomer leading to reduction of Aβ aggregation and prevention of fibril formation. Chemically it is named as 3-amino-1-propane sulfonic acid (3APS) [109]. Further, it produces a cytoprotective effect against the Aβ-associated neurotoxicity with the reduction of soluble and insoluble Aβ peptide concentration in transgenic mice [110, 111]. Clinical trials expressed that tramiprosate slows the process of hippocampal atrophy and the beneficial effect of cognition, and phase III trial has been stopped owing to an unsuccessful demonstration of therapeutic efficacy [112, 113]. The endogenous stereoisomer of inositol, i.e., scyllo-inositol, shows anti-aggregation effect in AD patients. Moreover, it is stabilized with small conformer of $A\beta_{42}$ and is neutralized with cell-derived Aβ oligomers which lead to decrease in the neuronal excitability, and neuroinflammation, and worsen the cognitive deficits in mice [114]. However, the safety and clinical efficacy of scyllo-inositol in phase II RCT were not significant [115, 116]. The natural flavonol of green tea leaf, i.e., epigallocatechin-3-gallate (EGCG), also shows the neuroprotective action and prevents the aggregation of Aβ oligomers [117]. Further, it also modulates the cell signaling process and reverses superoxide dismutase activity that leads to improvement of the neuronal mitochondrial and cholinergic receptor functions [118].

In addition, metal chelator, i.e., PBT_1 (clioquinol), enhances the solubilization of Aβ oligomers in the mice model of AD. Phase II clinical study has suggested that PBT_1 was not showing the significant clinical effects in AD patients; thus, the phase III trials were unrestricted [119, 120]. Moreover, second-generation metal chelator PBT_2 reduced heavy metal-induced Aβ oligomerization [121]. It has a greater effect on BBB permeability; obstruction of Aβ oligomerization decreases soluble and insoluble Aβ and enhances the Aβ oligomer clearance. Phase II trial showed that PBT_2 reduces the concentrations of CSF-$A\beta_{42}$ and improves the cognitive function in AD [121, 122]. In addition, advanced glycation end-product modulators, i.e., TTP488, show beneficial effects in phase II study comprising mild-to-moderate AD patients [37, 123]. Currently, various lead molecules are identified with the chemical structure for the inhibition of Aβ aggregation [103]. Even, anticancer drug, i.e., bexarotene, is also reported to reduce $A\beta_{42}$ peptide deposition via inhibition of $A\beta_{42}$ aggregation and it also delays the formation of toxic peptides in neuroblastoma cells [124]. The chemical structure of Aβ aggregation inhibitors in clinical trials is illustrated in Fig. 6.

3.2.5 Active Immunotherapy for AD Management

The progression of neurodegenerative disease like AD is not only due to the oxidative stress and neuroinflammation; immunological reaction also contributes to the pathogenesis of AD, because the specialized neuroimmune cells like glial cells (astrocytes and oligodendrocytes) are employed in neuroimmune reactions. Thus, the area of immunotherapies is the major target for the management of AD. Currently, the vaccine approach supports better therapy for AD management. The major vaccine, i.e., AN-1792, was used for the RCT to reduce the levels of

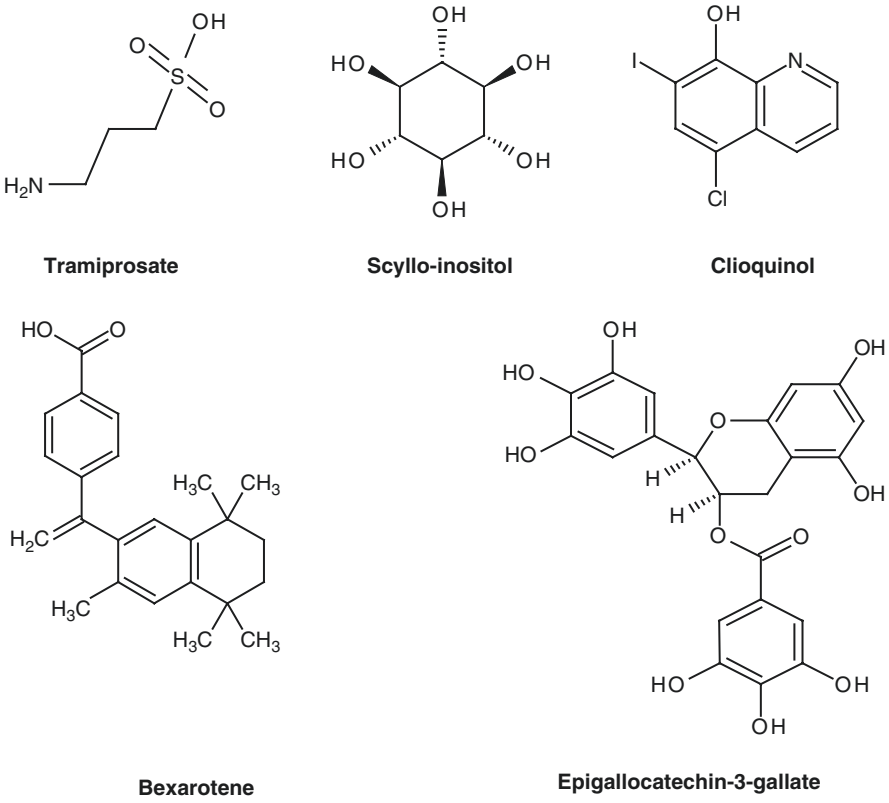

Fig. 6 Chemical structure of Aβ aggregation inhibitors in clinical trials

$A\beta_{1–42}$ in AD patients. However, this trial was terminated due to their severe side effects. In these trials, 6% of the participants showed these unwanted effects. However, it provided the newer idea to improve the successful therapy for AD patients [103]. The second-generation active immunotherapy vaccine, i.e., CAD106, comprises $A\beta_{1–6}$ peptides, and it reduces the level of Aβ concentration with the acceptable antibody response. Moreover, it also showed safer and better tolerance effects in phase II trials [113, 125]. The newer liposome-based vaccine, i.e., ACI-24, reduces the levels of amyloid plaque concentration and restores the cognitive functions in transgenic mice. It consists of $A\beta_{1–15}$ peptides and produces better efficacy in ongoing phase I/II clinical trial in mild-to-moderate AD patients [95]. In addition, the synthetic peptide i.e., UB-311 also entered in phase-I clinical trials. It consists of UBITh helper T-cell epitopes coupled with $A\beta_{1–14}$ peptides. The results of the phase I clinical trial of UB-311 revealed that it has significant safety and tolerability actions [103, 126]. Thus, it has entered phase II clinical trials. The newer lead molecules are entering into the clinical trials as active immunotherapy agents for AD patients. Such agents are ACC-001, V950, Lu AF20513, and AD02. ACC-001 and Ab1–7/Qs21 are under phase IIa clinical trials as an adjuvant

immunotherapeutic vaccine for mild-to-moderate AD patients [127]. Currently, multivalent Aβ peptide/ISCOMATRIX™ adjuvant, i.e., V950, has been developed to alter the Aβ antibodies with the recognition of pyroglutamate modification and N-terminal truncated Aβ fragment modification. This molecule is under phase I clinical trials [128]. Moreover, another vaccine was developed with modification of T-helper epitopes of tetanus toxoid with the replacement of $A\beta_{1–12}$ peptides, i.e., Lu-AF20513. Currently, this molecule is under phase I trial [129, 130]. In addition to that, amyloid-beta (Aβ)-targeted vaccine, i.e., AD02, elicits the Aβ antibodies. This molecule has entered phase III study and it has produced DNA amyloid-beta protein modulatory action in experimental animals [131]. Crucially, tau protein-targeted active immunotherapy vaccines, i.e., AADvac1 and ACI-35, are also developed and these molecules are under investigation in preclinical studies with the transgenic model of AD [132].

3.2.6 Passive Immunotherapy for AD Management

Vaccine therapy is one of the newer techniques for the prevention of neurodegenerative disease progression like AD and it alters the neuroimmune function. The first humanized monoclonal antibody, i.e., bapineuzumab (AAB-001), is targeted to N-terminus segment of Aβ peptides, especially $A\beta_{1–5}$. It is strongly bound to the amyloid plaques in the deposited location of neuron [133]. And it reduces further aggregation of Aβ and plaque burden via activation of Fc-associated microglial phagocytosis process for Aβ plaques in mice. The result of RCT failed to enhance the cognitive function in mild-to-moderate AD [133]. In addition, solanezumab (LY-2062430) is also obtained by humanized monoclonal antibody methods and it has been targeted to mid-domain of $A\beta_{16–24}$ peptides which reduce the aggregation of soluble Aβ peptides. The clinical reports documented that it showed potential and significant improvement of cognition function in mild-to-moderate AD patients [134]. According to the ADAS-Cog and Mini-Mental State Examination (MMSE) reports, solanezumab delays 34% of cognitive impairments in phase III clinical trial [135]. Moreover, ponezumab (PF-04360365) has also been prepared by humanized IgG2dA monoclonal antibody and it shows safer immune effector action and reduces the AD progression without antibody-associated side effects [110, 111]. Another molecule, i.e., GSK-933776, is a humanized Fc-attenuated/inactivated anti-Aβ monoclonal antibody and it shows various pharmacological actions without affecting the amyloid-related abnormalities of brain edema in mild AD patients [136, 137]. Aβ peptide-targeted humanized $A\beta_{1–15}$ monoclonal antibody with IgG4 isotype molecule, i.e., MABT5102A, inhibits the Aβ aggregation without the generation of microglial cell hyper-activation associated with vasogenic edema and cerebral microhemorrhage events [138]. The selective Aβ peptide-targeted human monoclonal antibody, i.e., aducanumab (BIIB037), changes the action of the misfolding process of Aβ peptides. Furthermore, it also restores the calcium homeostasis actions in Tg2576 mice along with the reduction of soluble and insoluble Aβ peptides in a dose-dependent manner [139]. Current clinical reports reveal that it is beneficial to improve the cognitive status in mild AD patients. The phase Ib clinical trial of aducanumab revitalized the "*amyloid cascade hypothesis*" and brought

effective improvements by activating mononuclear mediated phagocytosis process [140]. Both active and passive immunizations are reported to inhibit the generation of toxic Aβ aggregation and contribute to the removal of soluble and aggregated Aβ peptides. The mechanism of immunotherapy undergoes three different immunological reactions to promote the Aβ removal in AD patients, i.e., (i) solubilization of Aβ via antibody-binding action to Aβ peptides, (ii) phagocytosis of opsonized Aβ peptides via activation of microglial cells, and (iii) extraction of Aβ peptides from the brain of AD patients via effective plasma antibodies. The third mechanism is also known as "sink" hypothesis. Both immunization (active and passive) therapies enhance the clearance of Aβ proteins [127].

3.3 Tau Protein-Targeted Drugs for AD Management

Tau is a cytoplasmatic protein; it binds to microtubular proteins during the process of polymerization and stabilizes the microtubular (cytoskeletal) proteins. After the initiation of abnormal activation of amyloid signaling process, a subsequential chain reaction starts with the formation of tau and NFT proteins. In AD patients, tau proteins are hyper-phosphorylated and enhance the aggregation of neurofibrillary tangles. Hence, tau proteins are the major competitors of the amyloid peptide hypothesis in the pathogenesis of AD [141, 142]. The selective tau protein aggregation inhibitor, i.e., leuco-methylthioninium (LMTX), prevents the formation and spreading of NFT in a transgenic mouse model of LMTX. The metabolites of LMTX, i.e., methylthioninium, degrade the tau proteins in AD patients. It is the first molecule identified for the reduction of tau protein accumulation in AD [143]. The phase II study results revealed that LMTX has safety and effectiveness in mild and moderate AD [144]. The modulators of serine/threonine kinase have potential regulatory action on tau protein phosphorylation. The glycogen synthase kinase-3β (GSK-3β) is one of the serine/threonine kinase enzymes and it reduces the production of Aβ peptides in AD. Clinically, a small molecule of non-ATP competitive GSK-3 inhibitor, i.e., tideglusib (NP-031112), reduces the symptoms of cognitive impairment in AD patients via lowering of tau protein hyper-phosphorylation, reduction of tissue amyloid plaque levels, and prevention of neuronal loss in experimental animal models of AD as well as in AD patients [145].

Moreover, tau-directed compound, i.e., valproate, has only reached phase III RCT. However, the results have shown an insignificant effect on the reduction of cognitive function in AD patients [146]. The major therapeutic approaches of tau-targeted medicine are (1) modulation of tau hyper-phosphorylation with inhibitors of tau-phosphorylating kinase enzymes, (2) inhibition of tau aggregation, and (3) acceleration of disassembly of aggregated tau proteins. The first approach was altered by the acceleration of glycogen-synthase-kinase-3 (GSK-3), 70 kDa ribosomal protein S6 kinase (p70S6K), and serine/threonine-protein phosphatase subunits A (PP2A) activities leading to induction of the tau hyper-phosphorylation and reduction of the neurofibrillary tangle formation [142, 147]. The deregulation of

GSK-3 activity plays a key role in the pathogenesis of AD via interference of tau and amyloid processing, cellular signaling, and gene transcription process. Lithium and valproate are known to treat neuropsychological disorders via inhibition of GSK-3 and reduce the tau phosphorylation process in experimental animals. In addition, it has neuroprotective action via upregulation of anti-apoptotic proteins, i.e., B-cell lymphoma-2 (BCL_2), inducing the production of neurotrophic factors (i.e., nerve growth factor, NGF) [142, 148]. Moreover, RCT results revealed that the 10-week treatment of lithium in mild AD patients did not show any significant effect on improving the cognitive function [149]. In addition, AD co-operative study (ADCS) report also revealed that the treatment of valproate in AD did not produce any significant memory-boosting effects in the mild-to-moderate type of AD patients, whereas it reduced the incidence of agitation and psychosis in AD patients [136].

Currently, numerous GSK-3 inhibitors are under clinical trials. Thiadiazolidinone derivative, i.e., NP-031112 (NP-12), is known to inhibit the GSK-3 (non-ATP competitive) activity and it reduces the cognitive dysfunction via prevention of tau phosphorylation, amyloid deposition of Aβ peptides, and prevention of neuronal death in experimental animals [103, 150]. The histological dye, i.e., methylthioninium chloride (methylene blue), also acts on tau proteins and prevents the aggregation of tau peptides. In addition, it also produces the antioxidant action via enhancement of mitochondrial function [151, 152]. Further, it showed more efficient action with a combination of rivastigmine for reversing the hyoscine-associated cognitive dysfunction in laboratory animals [153]. Clinically, treatment of 60 mg of methylthioninium chloride to a moderate stage of AD patients has shown beneficial effects with the reduction of AD disease progression [154]. Furthermore, a new formulation, i.e., leuco-methylthioninium, is under investigation in phase III RCTs. However, the confirmation of its safety and efficacy is needed to explore in a different stage of AD patients [130, 155].

Davunetide (AL-108, NAP) is an eight-amino-acid peptide fragment and is evidenced to produce neuroprotective actions. The AL-208 protein is recommended to administer through the intravenous route to AD patients. Another molecule, i.e., NAP, has been recommended to administer in nasal route. Both the molecules produce an activity-dependent neuroprotective protein, regulate the ion movements in microtubular proteins, inhibit the tau hyper-phosphorylation, and reduce the Aβ-associated neurotoxicity [156, 157]. Moreover, davunetide also ameliorated the cognitive impairment in amnestic patients (phase II RCT) with higher safety and tolerability [156]. Vitamin, especially nicotinamide (vitamin B_3), prevents cognitive impairments in a mouse model of AD via enhancing the precursor action of coenzyme NAD^+ and it reduces the tau (Thr_{231}) phosphorylation and inhibits the microtubule polymerization [158]. In addition, it enhances the microtubule stabilization via inhibition of neuronal sirtuin deacetylase activity and upregulation of acetyl-α-tubulin, protein p25, and 70-kilodalton microtubule-associated protein-c (MAP 2c) [158]. Multiple clinical studies have shown that nicotinamide reduces the neurodegeneration and improves the cognitive function in mild-to-moderate AD patients (NCT00580931) [159].

3.4 Neurotrophin-Based Drugs for AD Management

Neurotrophins have multiple pharmacological actions including neuroprotective actions. Neurotrophins are dimeric peptide hormones and it contributes to various neurophysiological actions like neuronal growth, neuronal tissue survival, and differentiation of neurons. Nerve growth factor (NGF) is one of the major neurotrophins to regulate the multiple neurological functions [160, 161]. In addition, brain-derived neurotrophic factor (BDNF) also has substantial neuroprotective action and preventive action of AD progression. Hence, neurotrophin has been viewed as an attractive target for the management of cognitive dysfunction in AD [162]. The genomic delivery of NGF, i.e., AAV2-NGF (CERE-110), readily crosses the BBB and enhances the production of ACh levels in cholinergic neurons of basal forebrain [163, 164]. A newer neurotrophin, i.e., T-817MA (chemically 1-{3-[2-(1-benzothiophen-5-yl)ethoxy]propyl}azetidin-3-olmaleate), has neuroprotective action and it also improves the cognitive function in transgenic mice [165]. Further, it showed safety and tolerability in phase II trial study of AD patients [166]. The primary action of neurotrophin is the induction of neurogenesis, especially in damaged brain tissue of AD patients. Neurogenesis of cholinergic neuron in basal forebrain depends upon the NGF actions on damaged neuron for neuronal survival and induction of nerve fiber outgrowth ability. In AD, NGF and Aβ balance is important for the management of neurodegeneration. Hence, amyloidogenic pathway regulation based on NGF plays a key role in the regulation of cognitive function in AD patients [160, 167]. The basal forebrain cholinergic neuron-targeted delivery of NGF prevented the cholinergic neuronal death, stimulated synaptic plasticity, and promoted cognitive function in animals as well as in AD patients [168]. Furthermore, these positive results of intracerebroventricular administration of NGF were counterbalanced with the adverse effects like pain and weight loss [167, 169]. Hence, alternative method, i.e., gene therapy, was developed to deliver the human NGF and it was tested in early stage of AD patients [170, 171]. Further, ongoing phase I and phase II RCT studies are focused to deliver the NGF via adeno-virus-vector system (CERE-110, NCT00876863, NCT00087789) to explore the safety and efficacy in AD patients [172].

In addition, encapsulated cell-based bio-delivery of NGF in specific brain location (cholinergic basal forebrain neurons) for enhancing the nootropic action without adverse effects is under investigation in phase I stage [173, 174]. The major focus of this study is safety, tolerability, and efficacy of encapsulated delivery of NGF on cognition function and behavior changes in mild-to-moderate AD patients. Preliminary results have shown good safety, good tolerability, no serious adverse effects like severe pain and weight loss, no expression of cortical nicotinic receptors, and better improvement of cognitive functions [175]. Various clinical reports have revealed the potential action of intranasal delivery of NGF and topical application of NGF. It was found as noninvasive and less risky and it reduces the expenditure in healthcare system [176, 177]. Hence, the novel method of NGF therapy may be useful to improve the cognitive function in AD patients.

3.5 Mitochondrial Targeted Drugs for AD Management

Mitochondrial dysfunction is one of the key functions in the progression of neurodegenerative disorders including AD. Mitochondrial dysfunctions are interconnected with various cellular processes like free radical generation (oxidative stress), calcium dyshomeostasis (calpain activation), release of apoptotic factors, and activation of Aβ and tau pathology in AD. Hence, mitochondrial targeted drugs possess a great potential to ameliorate the AD progression [178]. Latrepirdine is the oldest antihistamine drug and it also has mitochondrial function-enhancing potential. Experimentally, it has been proven to treat the AD-associated cognitive dysfunction [179]. It modifies the APP and Aβ peptide levels in hippocampal tissue to regulate the mitochondrial membrane potential (ψ) and induce the adenosine-triphosphate (ATP) production [180]. Mitochondrial targeted drug actions in AD are focused on multiple cell signaling proteins including Aβ and tau peptides. At the early stage of AD, mitochondrial dysfunction accelerates the synaptic damage, apoptosis process, and neurodegeneration [180]. The generation of APP and Aβ and interaction with mitochondria occur in both ways via secondary cell messengers like ATP and free radical production and movement of cytosolic free calcium (Ca^{2+}) ions. A nonselective antihistamine (also mitochondrial function booster), i.e., latrepirdine, showed a safe, tolerated, and potential ameliorative action in mild-to-moderate AD patients in phase II trials [179–181]. Moreover, latrepirdine with a combination of donepezil- and memantine-based RCTs is under investigational stage (NCT00829374 and NCT00912288) [166]. In addition to that, it also inhibits the acetylcholinesterase and butyrylcholinesterase, NMDA receptors, and voltage-gated calcium channels. It has 200 times lesser potency than NMDA receptor blockers (memantine). Latrepirdine still has ample scope to be explored in AD therapy due to its multitargeted action and preservation of mitochondrial structure and function in neurons. Moreover, latrepirdine also closes the mitochondrial permeability transition pore (MPTP), which is an important event in the activation of Aβ-associated apoptosis [180]. Therefore, the detailed study of the structure-activity relationship of latrepirdine and derivatives can treat the AD via mitochondrial mediated actions [182].

3.6 PPAR-γ-Targeted Drugs for AD Management

Peroxisome-proliferator-activated receptor-γ (PPAR-γ) is one of the primary targets for the management of type 2 diabetic mellitus. PPAR-γ is one of the nuclear receptors and it alters nucleic acid functions [183, 184]. Thiazolidinedione derivative, i.e., pioglitazone, enhances the insulin sensitivity of islets of Langerhans of beta cells, heart, kidney, and skeletal muscle including brain tissues [185]. The alterations of insulin sensitivity in neurovascular tissue contribute to a variety of neurological problems like stroke and parkinsonism including AD. The administration of PPAR-γ agonist enhances the cognition function in a transgenic animal model of AD as well as in humans [186, 187]. Furthermore, pioglitazone has ameliorated the risk of mild cognitive impairment progress in AD [188–191]. Moreover, other

nuclear receptor targets like RXR and PPAR are also tested in the animal model of AD. The results revealed the significant effect on diabetic-associated AD and Aβ-induced AD [192]. Therefore, PPAR-γ agonist has a promising role in the management of AD.

3.7 Multi-Targeted Drugs for AD Management

Some of the newer molecules are identified in the management of AD. Docosahexaenoic acid derivatives, i.e., omega-3 polyunsaturated fatty acids, were tested in AD patients. It is reported that it has potential free radical scavenging action like vitamin E action in RCTs of AD patients. In addition, the early prescription of docosahexaenoic acid supplementation in elderly people showed beneficial effects on the improvement of cognitive function and delayed the progression of AD [193]. Some clinical trials revealed that docosahexaenoic acid did not produce beneficial effects on the attenuation of cognitive function and behavioral disturbances in mild-to-moderate AD patients [194]. Moreover, the treatment of polyunsaturated fatty acids produced moderate ameliorative action on AD patients and it did not alter the biomarkers of neuroinflammation and Aβ levels in CSF and/or plasma. Moreover, the detailed evidence with antioxidant supplementation in AD patients has not been studied. The supplement of healthy nutrients and minerals still has value to claim their effect in AD patients. Though high doses of vitamin E showed the risk of mortality, no therapeutic effects were observed in AD. However, the administration of vitamin E with a combination of micronutrients showed more effective neuroprotective action in AD patients [193, 195].

The specialized neuro-lipids, i.e., sphingolipids and sphingosine pathway, are identified in the progression of AD. The cholesterol-lowering drugs like statins also reduce the neuro-lipids via interaction with sphingosine pathway. In AD patients, statins produce a beneficial action and detailed results are awaited from the ongoing trial [196]. In addition, statins reduce the levels of Aβ production and prevent the Aβ-associated neurotoxicity due to its pleiotropic actions like antioxidant, anti-inflammatory, and anti-apoptotic actions. Moreover, phase III RCT revealed that atorvastatin did not show any beneficial action in mild-to-moderate AD patients [197, 198]. Clinical data revealed that the brain of AD patients has less content of serotonin neurotransmitter. Hence, the sensitizations of various serotonin receptors are altered by multiple ways in different parts of the brain. The serotonergic receptor system is very closely linked with learning and memory function. The primary role of the serotonergic system in memory function is achieved with modulation of cholinergic neurons in the hippocampus of the brain. Some of the serotonin receptors, i.e., 5-hydroxytryptamine-1A (5-HT_{1A}), 5-HT_4, and 5-HT_6 modulators, entered into clinical trials [199]. Serotoninergic receptor-6 (5-HT_6) antagonist, i.e., SB-742457, has ameliorated the cognitive function in mild-to-moderate AD (NCT00710684) [200, 201]. Another RCT report revealed that 5-HT_4 agonist, i.e., PRX-03140, showed some unwanted effects (NCT00693004 and NCT00672945) and it was terminated [202].

Phosphodiesterases (PDE) are widely expressed in various parts of the brain including cortex and hippocampus. The selective PDE-9A inhibitors, i.e., PF-04447943, regulated the cyclic guanosine monophosphate (cGMP) signaling pathways and also accelerated the synaptic plasticity [203, 204]. In addition, the administration of PF-04447943 has enhanced the level of cGMP concentrations in CSF of healthy volunteers. Therefore, this molecule entered phase II RCT (NCT00930059) for the management of mild-to-moderate AD patients [203, 205]. Furthermore, the receptor for advanced glycation end products (RAGE) is present in various tissues like cell membrane of neurons, glia, and endothelial cells. And it has multi-ligand-binding site including for Aβ peptides. Hence, RAGE promoted the influx of Aβ into the CNS via BBB. In AD, especially diabetic-associated AD conditions, this receptor is highly active and accelerates the AD progression via synthesis of autacoids and cytokines (neuroinflammation), procoagulant activity within the endothelium (thrombus), the free radical synthesis (oxidative stress), and induction of apoptosis [206]. Moreover, the soluble form of RAGE (sRAGE) is competing with Aβ-binding site of membrane-linked RAGE and promotes the clearance of soluble circulating Aβ. The RAGE inhibitors, i.e., PF-04494700 and TTP-488, are under investigation in a phase II clinical trial (NCT00566397) [207–209]. The summary of different drug targets for AD has been illustrated in Fig. 7.

Drug targets for Alzheimer's disease

Cholinergic modulators
Donepezil, rivastigmine, galantamine, tacrine, velnacrine, physostigmine, eptastigmine, metrifonate, huperzine-a, (-)phenserine, posiphen, memogain, ladostigil, NGX267, EVP-6124, GTS-21, talsaclidine, AF-102B, ispronicline and ABT-089.

Amyloid targeted drugs

Inhibitor of β-Secretase inhibitor
LY2811376 and LY2886721 and MK-893

Inhibitor of γ-secretase
Semagacestat, avagacestat, begacestat, NIC5-15, E2012 and CHF5074.

Activator of α-secretase
Etazolate and bryostatin-1.

Inhibitor of amylmd-β aggregation
Tramiprosate, scylloinositol, epigallocatechin-3-gallate, clioquinol and bexarotene.

τ-protein targeted drugs
Leuco-methylthioninium, tideglusib, valproate, NP-031112, davunetide and nicotinamide.

Active immunotherapy
AN-1792, CAD106, ACI-24, UB-311, V950, Lu AF20513, AD02 and ACC-001

Passive immunotherapy
Bapineuzumab, solanezumab, ponezumab, GSK-933776 and aducanumab.

Neurotrophins
Brain-derived neurotrophic factor, AAV2, NGF and T-817MA.

Mitochondrial targeted agents
Latrepirdine.

PPAR-γ targeted drugs
Pioglitazone.

Multi-targeted agents
Omega-3 polyunsaturated fatty acids, vitamin-E, SB-742457, PF-04447943, PF-04494700 and TTP-488.

Fig. 7 Summary of different drugs targeting Alzheimer's disease (including amyloid-targeted drugs for the treatment of AD)

4 Relationship of Neurochemical Alteration and Restoration Strategy of Neuron in AD

The cellular and molecular changes in AD brain are a too complex network process. Therefore, single targeted medicines are not effective in all kind of patients and conditions. Hence, the identification of exact neurochemical pathways and their molecular targets (enzymes, ion channels, ion flux mechanism, mitochondrial proteins, and nucleic acids) is necessary [2]. Furthermore, identification of neuron-specific modulators is essential for achieving the potential ameliorative effect in neurovascular disorders and neurodegenerative organic brain disorders [1, 2]. Understanding the previous section of this book chapter supports the development of AD-targeted medicines. In addition, with a combination of newer agents like immunotherapy (vaccine), neurotrophin and mitochondria- and nuclear receptor-targeted medicines are expected in the restoration of neurodegeneration via prevention of early and late events of AD pathology. Current clinical trials encourage to use the multi-targeted rationalized drugs. Therefore, this book chapter highlights the possible relationship of neurochemical targets for the treatment of AD and possible ways of restoration effect of neuronal system in AD.

5 Advantages and Disadvantages of AD Drug Therapy

An immunization strategy is one of the novel strategies for AD therapy. It has pros and cons in the effective management of cognitive function in AD. The pros of active immunization are promising the action in high Aβ antibody concentrations, requirement of only a few follow-up visits, and reduced cost of therapy. Though the rapid reduction of Aβ antibody levels produces multiple adverse effects, the controlling of these harmful effects is too difficult. Passive immunotherapy has specific Aβ epitopes and it is an easy target and is possible to control Aβ antibody immediately. Hence, it is more effective in aged AD population [132]. Moreover, administration of Aβ antibodies by passive immunotherapy mechanism is time consuming and costly and also raises the risk of vasogenic edema and cerebral amyloid angiopathy [137, 210]. Rest of the medication has its own advantages as well as limitations. The major advantages of these medicines are that it controls the cognitive impairment, is easily available and cheap, and improves the quality of life. However, it has some side effects, like lack of safety and efficacy in certain conditions and stages of AD.

6 Conclusion

This chapter covers the multiple aspects of AD progression, pathophysiological associated neurochemical changes, possible drug targets, and current status of (pre)-clinical trials. It gives clear perspectives of current research progress for the attenuation of AD and opens the Pandora's box for the finding of newer lead molecules. In

addition, it also covers the limitation of existing drugs. Therefore, this chapter may aid in the newer drug discovery process by reducing the challenges of AD treatment and financial burden of AD therapy.

7 Future Perspective

This book chapter makes an account on the current status of anti-Alzheimer's drugs that are in preclinical and clinical trials. Some of the medicines are available for the treatment of AD. However, the minimization of adverse effects of these medicines remains challengeable in the healthcare system. The understanding of the preclinical and clinical status of novel molecules may ease the new direction and may provide better management of AD therapy. Hence, the modification and development of selected category of molecular derivatives make the next generation of molecules in the drug discovery process of AD therapy. Multi-targeted approaches are still a valid approach to treat AD. However, the application of multi-targeted molecules in the specific condition of AD has a certain limitation due to its poor efficacy and safety. Thus, a one-target-one-compound (1T1C) approach is essential for the management of AD. Moreover, scientifically proven 1T1C molecules can help to make multi-targeted compounds and some of the molecules are already designed like dual inhibitors of AChE and $BACE_1$. Herbal medicines like Kai-Xin-San consist of *Ginseng radix*, *Polygalae radix,* and *Acori tatarinowii rhizoma* and they function based on multi-targeted actions in AD patients. The current novel methods like chemogenomics, metabolomics, and chinmedomics are also under investigation against AD via *in vitro*, *in silico*, and *in situ* studies.

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Revisiting Alzheimer's Disease

Salwa and Lalit Kumar

1 Introduction

Alzheimer's disease (AD) is regarded to be the most prevalent cause of dementia among geriatric population. It is regarded as a multifaceted, neurodegenerative disorder with characteristic features of patchy memory, disorientation and progressive diminution in cognition influencing a person's physical and mental status [1]. As the world's population grows older, AD will grow as an enormous severe public health concern. Eventually, neuronal injury and destruction affect multiple other components of the brain and thus prevent an individual from performing fundamental voluntary tasks such as walking and swallowing. The two main pathological hallmarks of AD are:

(a) External accumulation of Aβ protein (known as beta-amyloid plaques)
(b) Internal accumulation of hyperphosphorylated tau protein (known as tau tangles)

As the disease progresses, the transfer of information at synapses begins to fail owing to the interference of accumulated beta-amyloid, the amount of synapses reduces, and neurons ultimately die resulting in declining cognitive and functional abilities. Tau tangles are thought to contribute to neuronal death by preventing nutrient transportation and other vital molecules within neurons. Oxidative stress, inflammation, drastic cell loss shrinkage and widespread neuronal debris are few other characteristic features shown by human brains with advanced AD.

An estimated 40 million patients over the globe are suffering from AD. An approximately 5.2 million Americans aged above 65 suffered from AD in 2012 and a total care cost of $200 billion was recorded [2]. Due to many variables

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contributing to the complexity of creating efficient medicines for Alzheimer's, the therapeutic field of AD has remained barren. These variables include elevated drug development costs, comparatively long time required to observe the impacts of research therapy on disease progression, and drug permeability across blood-brain barrier, which allows the passage of only very specific tiny drug molecules [3].

2 Classification of Alzheimer's Disease

Alzheimer's disease has been broadly classified into the following categories (Fig. 1) based on aetiology and severity of the disease:

2.1 Based on Aetiology

2.1.1 Familial AD (fAD)/Autosomal Dominant AD (ADAD)/ Early Onset

It is caused by genetic mutations which directly lead to the overproduction of Aβ due to APP and/or presenillin (PSEN) 1 and 2 gene mutations.

2.1.2 Sporadic AD (sAD)/Late Onset

It is caused by genetic and/or environmental factors that make the brain susceptible to an increased production or reduced rate of clearance of Aβ. While genetic factor includes the inheritance of apolipoprotein ε4 (APOE ε4) allele, environmental factor includes cardiovascular diseases, stroke, obesity, smoking, sedentary lifestyle, diabetes, etc. that contribute to the progression of disease.

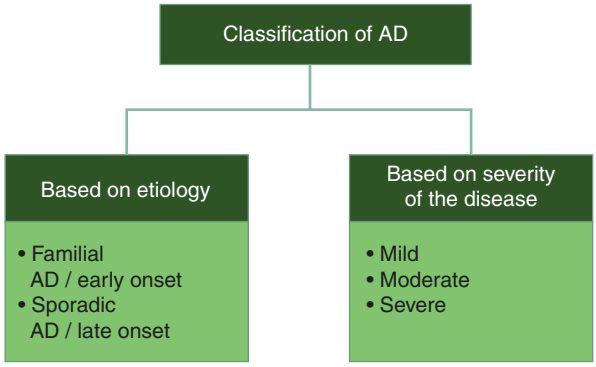

Fig. 1 Classification of Alzheimer's disease

2.2 Based on Severity of the Disease

2.2.1 Mild

It is an initial stage of AD. Patients experience substantial memory loss and other cognitive difficulties. Walking aimlessly, being lost, difficulty in handling calculations and money, taking long time for the completion of daily activities, and personality and behavioural changes are some of the problems faced by the patient. Diagnosis gives positive results for AD at this stage.

2.2.2 Moderate

Brain regions that control language, sensory processing, reasoning and consciousness are harmed at this stage. Patient fails to recognize their kith and kin. Loss of memory and confusion grow worse. They will not be able to learn new stuff or deal with new circumstances. Additionally, people may experience hallucinations, paranoia or delusions.

2.2.3 Severe

It is the more advanced stage of AD where amyloid plaques and neurofibrillary tangles (NFTs) spread considerably all over the brain and the brain starts shrinking. Patients lose their ability to communicate. Towards the end, the body may shut down leading the person to be bed bound and rely for care around the clock.

3 Revisiting AD Hypotheses

The field of AD has been desperately searching for its aetiology for well over a century. Many scientists have scrabbled into all the aspects of this complicated, multifactorial disorder since early 1980s where molecular studies of AD began with intense conviction to help the current patients and stop others from developing in the future. Following are the three major hypotheses proposed to explain AD pathology:

3.1 Cholinergic Hypothesis

Acetylcholine (ACh) is a predominant neurotransmitter that functions in all autonomic ganglia and is the one and only neurochemical triggering motor division of somatic nervous system. Figure 2 depicts cholinergic activity in ordinary and abnormal conditions. Cholinergic hypothesis is one of the oldest hypotheses of AD based on the cholinergic dysfunction due to decrease in the ACh synthesis/reduced acetylcholinesterase (AChE) activity or excess hydrolysis of ACh by AChE in both cortical and hippocampal regions. *In vitro* research showed that Aβ peptide inhibits cholinergic neurotransmission [4] and decrease in the amount of nicotinic and muscarinic acetylcholine receptors in the presynaptic cholinergic terminals results in the reduction of cognitive function [5]. Currently available drug therapy includes three

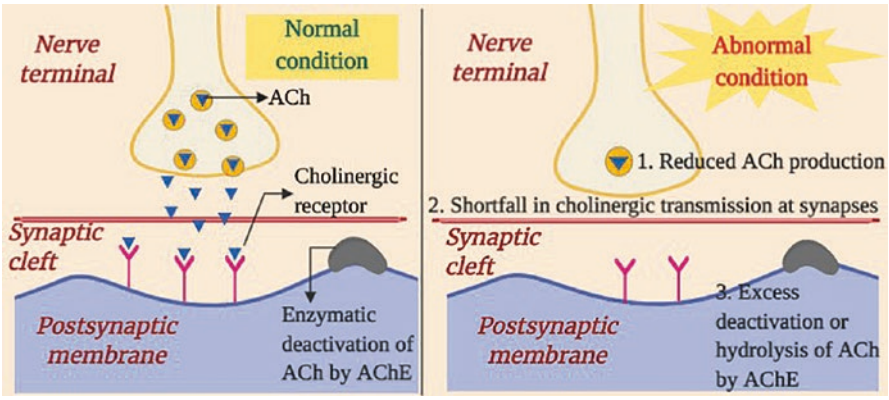

Fig. 2 Cholinergic activity of neurons in normal and abnormal conditions (ACh-acetylcholine)

drugs based on this hypothesis, i.e. rivastigmine, donepezil and galantamine. These are mainly for symptomatic treatment of AD. Gastrointestinal disturbances, mild efficacy, high price and short half-life are the major drawbacks of synthetic AChE inhibitors [6]. Development of molecules targeting distinct locations has been explored over the past two decades. However, cholinesterase inhibitors depicted positive impacts on cognitive, functional and behavioural symptoms in AD.

3.2 Tau Hypothesis

Alois Alzheimer in 1907 first described this hypothesis, but correlation between NFTs, Aβ and tangle structural composition was characterized later. Tau is defined as a soluble microtubule-associated protein found in neurons, which by binding and stabilizing microtubules plays a prominent role in the axonal growth and neuronal development. Under pathological conditions, tau protein hyperphosphorylation produces insoluble double-helical filaments and tangled clusters called NFTs, resulting in synaptic dysfunction and neuronal degeneration [7] (Fig. 3). Tau mutations leading to neurodegenerative disease follow distinct molecular mechanisms such as:

(a) Changes in tau splicing resulting in tau-isoform expression in abnormal patterns [8]
(b) Compromising tau's ability to bind and stabilize microtubules [9, 10]
(c) Increased tau fibrillization [11]

3.3 Amyloid Cascade Hypothesis

The community has accepted the amyloid cascade hypothesis as the only possible explanation for the disease's pathogenesis. The concept that amyloid deposits were

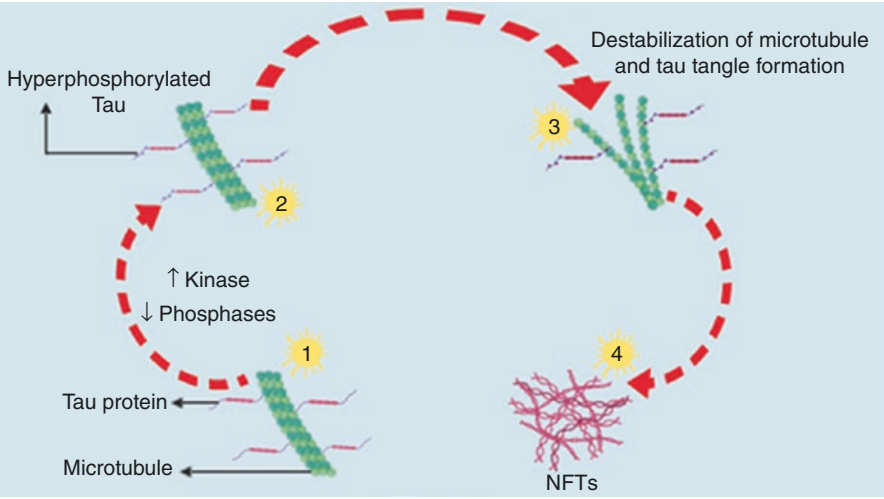

Fig. 3 Process involved in the formation of NFTs (NFTs—neurofibrillary tangles)

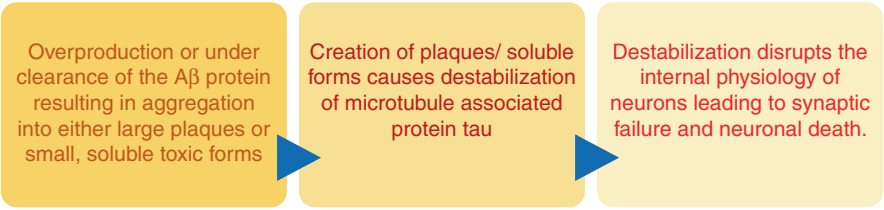

Fig. 4 Amyloid cascade hypothesis

the driving force in both familial and sporadic AD was suggested in the early 1990s. In brief, the hypothesis goes like this (Fig. 4):

The theory of amyloid cascade hypothesis suggests that amyloid beta (Aβ) accumulation is the beginning step for a sequence of occurrences that eventually lead to Alzheimer's. Aβ is generated by a serial abnormal proteolytic bifurcation of amyloid precursor protein (APP) by beta-site APP cleaving enzyme-1 (BACE1) and γ-secretase. $A\beta_{1–40}$ and $A\beta_{1–42}$ are the most predominately formed fragments. $A\beta_{1–40}$ is found in the healthy brain which is soluble and less neurotoxic. $A\beta_{1–42}$ is discovered predominantly in AD pathology brains and is extremely neurotoxic with higher tendency to aggregate. Recently, a newer proteolytic cleaved product, $A\beta_{1–43}$, has been revealed to possibly contribute to the formation of Aβ [12]. $A\beta_{1–43}$ is extremely neurotoxic and amyloidogenic, and deposits sooner than the two other cleaved products. Furthermore, amyloid peptide deposit has been reported to communicate with the membrane of the neurons, leading to formation of pore and increased ion influx resulting in neuronal loss and AD progression. Unfortunately, this hypothesis has not delivered on

providing a sufficient explanation for the onset of disease nor a target against which therapeutic intervention can be implemented because shutting down of this cascade with drugs has completely failed.

4 Bioflocculant Hypothesis: An Implication for Amyloid Hypothesis

Fortunately, one often overlooked theory seems to be making a comeback, although the name by which it goes is not well known. In 2002, Stephen Robinson and Brenda Bishop proposed the bioflocculant hypothesis to explain the role of Aβ in AD pathogenesis. It is a simple, broad hypothesis with testable questions. It postulated that secreted Aβ aggregates act like a spider web and capture any foreign or domestic pathogenic material. Of the little nasties one would expect this web to trap bacteria or other microbes that are high on the list (as well as unwanted proteins, blood products, and metals). Once this pathogenic material is immobilized, microglial cells, known as garbage men of the brain, can engulf and dispose it. The beauty of this theory is really twofold. The first, and most intriguing, is that it gives a function to the Aβ protein. It is likely that the mammalian brain, especially one as long-lived as a human's, evolved a system to protect itself from a lifetime of invading environmental detritus. Second, it can explain why the amyloid-beta protein aggregates are found in most of the elderly with and without cognitive decline [13]. The evidence presented by Robinson and bishop in their two papers is striking and there has been no shortage of evidence published since, corroborating their theory.

5 Current Treatment Modality

Till date, AD treatment has been completely supportive to provide a prosthetic environment, educate and assist family caregivers, help with day-to-day activities and manage behavioural issues using non-pharmacological interventions and psychoactive drugs [14]. Despite decades of intense research, pharmacological intervention for AD is only palliative and provides modest short-term relief. A variety of drugs have been briskly promoted by manufacturers and wishfully prescribed by the physicians. Clinically, they exist only in two established treatment options in the current market:

1. Acetylcholinesterase inhibitors: *donepezil* (1983), *rivastigmine* (1997) and *galantamine* (2000)
2. *N*-methyl-D-aspartate (NMDA) receptor antagonist: *memantine* (1968)

These provide modest symptomatic outcomes at best, but they have not been concretely demonstrated to significantly slow cognitive worsening [15]. Delaying the onset of disease even in small increments would significantly reduce the economic and social burden of the disease. While the prevailing therapy approaches

stay vital in today's AD management, drugs are used not only to set back the disease progression, but increasingly for behavioural problem also. Other pharmacological treatment involves:

1. Brain injury accompanied by inflammatory response reduction by using NSAIDs such as aspirin or ibuprofen
2. Increasing global/regional cerebral blood flow (CBF)
3. Lowering circulating cholesterol level using statins and HMG-CoA reductase inhibitors
4. Reducing oxidation by using antioxidants (vitamin E, *Ginkgo biloba*, ubiquinone)

6 Potential Therapeutic Interventions

Both AChE inhibitors and NMDA receptor antagonist have well-proven efficacy levels, although clinical outcome is rather limited to just symptomatic relief. In this context, there is an absolute need to come up with new therapeutic strategies as researchers are aware of microscopic alterations present in AD. Certain disease-modifying strategies explored in the last few years are discussed in the preceding section.

6.1 Anti-Tau Strategies

Neuronal cells usually synthesize tau protein to stabilize microtubules for accurate functioning of axonal morphology, development and polarity of neurons [16]. Consequently, targeting tau protein may therefore prove to be a major key for unlocking this disease in future.

6.1.1 Microtubule-Stabilizing Drugs

As failure to appropriately stabilize microtubules by tau may lead to tauopathies, drugs that stabilize microtubules may be pharmacologically useful for AD. A microtubule-stabilizing drug (i.e. paclitaxel) when administered to transgenic mice with tau overexpression showed improvements in microtubule density, rapid axonal transport and motor skills, thereby providing *in vivo* proof that the drugs capable of stabilizing microtubules can have a therapeutic benefit to human tauopathies. A significant amelioration in microtubule stability has been shown by epothilone D that is known for its blood-brain barrier clearance activity [17].

6.1.2 Tau Filament Formation and Tau Phosphorylation Inhibitors

Designing of tau filament formation inhibitors has been emphasized in order to boost the pathology of tau in AD. Rational design strategies and libraries of small-molecule screening have led to the enlistment of several distinct categories of inhibitors, even though preclinical information is not accessible yet. Inhibition of phosphorylation of tau protein has been shown to be a feasible goal for therapeutic

development, with many attempts concentrated on suppressing glycogen synthase kinase 3 (GSK3β). The most studied compound for inhibiting GSK-3 is lithium. Other compounds under exploration include sodium valproate, pyrazolopyridines, pyrazolopyrazines and amino-thiazole AR-A014418. However, this approach is complicated due to difficulties in generating inhibitors with appropriate specificity for GSK3β and target-mediated toxicity issues.

6.1.3 Tau Aggregation Blockers

Certain drugs such as lansoprazole possess stronger affinity towards tau protein and reduce tau-tau interaction indirectly [18]. It is known that methylene blue dye prevents tau interactions, inhibits Aβ accumulation, improves electron transport, decreases oxidative stress, regulates autophagy and inhibits AChEs.

6.1.4 Tau Degradation Enhancers

Heat-shock protein 90 (Hsp 90), which is a molecular chaperone protein engaged in folding of denatured proteins, has been well documented to play a crucial part in preventing tau degradation. Obstruction of Hsp 90 by curcumin has been investigated [19]. It also supresses tangle formation and dissolves already formed tangles.

6.2 Anti-amyloid Strategies

6.2.1 β-Secretase Inhibitors

Beta-secretase 1 (BACE1) enzyme which cleaves amyloid precursor protein (APP) to produce Aβ provides few of the most tempting aims for the development of new drugs because:

1. BACE knockout in mice has shown to eliminate Aβ production without side effects [20].
2. BACE belongs to a very-well-established class of proteases (aspartic proteases) against which suppressors (HIV protease inhibitors and renin) have been effectively established for human use [21].
3. Already the BACE X-ray crystal structure has been reported [22].
4. BACE peptidomimetic inhibitors with nanomolar activity have been produced [23].

The development of BACE1 inhibition treatment remains troublesome as this enzyme is found to play a vital physiological role and enzyme inhibition could end up in toxic effects. Also, the BACE1 active site is comparatively huge and it is unlikely that the bulky molecules required to inhibit the activity of BACE1 will permeate across blood-brain barrier [24].

6.2.2 γ-Secretase Inhibitors

Semagacestat is the only compound to reach phase III trials among the Aβ-lowering "hits", but due to adverse events the trial was prematurely terminated of dosing [25].

In 2004, at the International Conference on Alzheimer's Disease and Related Disorders researchers from Eli Lilly presented semagacestat (LY450139) phase I information. They stated that semagacestat lowered Aβ levels in blood but did not change its levels in cerebrospinal fluid (CSF). Unfortunately, owing to consideration of adverse impacts on cognitive and functional skills in patients who are receiving the drug relative to those who are receiving placebo, two massive phase III clinical trials of this drug in mild-to-moderate AD patients initiated in March 2008 were interrupted in August 2008. For Notch cleavage, the IC_{50} was only two-fold to threefold higher than for APP cleavage leading to low therapeutic index of semagacestat. However, toxicity distress induced by certain γ-secretase-cleaved substrates through interaction with γ-secretase facilitated Notch signalling or restriction of signalling modulating the zeal for using γ-secretase inhibitors [26]. Alternatively, another way to avoid this issue may be indirect inhibition of γ-secretase. Hepatic, splenic and cutaneous adverse effects were also found to be associated with γ-secretase inhibitors. Various molecules are under development, but their ability to cross blood-brain barrier and its efficacy levels needed to lower Aβ persistently remain questionable.

6.2.3 Aβ Vaccination

Active immunotherapy relies on the administration of an immunogen, often in combination with an adjuvant, to stimulate endogenous antibody production in the recipient, whereas passive immunotherapy employs pregenerated antibodies. Aβ vaccination is being studied by most of the pharmaceutical companies as it has proven to be one of the most electrifying strategies for clearing amyloid plaques from the brain. Three general mechanisms proposed to explain Aβ's clearance from the brain are (*a*) antibody penetration across the blood-brain barrier and opsonization of Aβ, followed by phagocytosis and activation of complement; (*b*) popularly subscribed peripheral sink mechanism, whereby the antibody-mediated clearance of Aβ in the periphery stimulates an equilibrating efflux of Aβ from the brain; and (*c*) catalytic modification mechanism, whereby antibody binding to monomers induces a conformational change that lowers the oligomerization and/or fibrillization propensity [27]. A drastic clearance of plaques was observed when transgenic mice were immunized with Aβ peptides (active immunization) or with monoclonal antibodies aimed against Aβ (passive immunization) along with improved cognitive performance [28]. After promising preclinical results, trials were begun using a synthetic human $Aβ_{1–42}$ in synchronicity with a T-helper cell adjuvant [29]. Unfortunately, human studies of active Aβ immunization were brought to a standstill because of the occurrence of meningoencephalitis in treated patients [30]. Occurrence of cerebral microhaemorrhages probably due to amyloid deposition in the vasculature of the brain of nearly all AD patients has emerged as a significant point of concern in immunotherapy. Therefore, during Aβ immunotherapy the requirement for repair and regeneration of vasculature is another dispute over premature therapy [31]. Innovative immunotherapeutic strategies like antibodies to APP's β-secretase cleavage site, DNA epitope vaccine and mucosal vaccination could be secure and efficient strategies for AD treatment as suggested by the preclinical data on mice.

Active immunotherapy approach distinctly deserves further research as a reaction of polyclonal antibody can prove more favourable. Yearly distribution cost and logistics of passive immunization several times to the AD population of the world when taken into consideration are daunting.

6.2.4 NSAIDs

Several nonsteroidal anti-inflammatory drugs (NSAIDs) have demonstrated selective lowering of Aβ42 through a mechanism likely involving the modulation of γ-secretase [32]. The epidemiological evidence suggests that the therapeutic strategy using NSAIDs for the treatment of AD bolsters the risk of the disease.

6.2.5 Statins

Epidemiological studies show a connection between high levels of plasma cholesterol and development of Alzheimer's disease. Aβ deposits, NFTs, cell death, activation of microglia and enhanced ventricular volume were observed in rabbits when fed with high-cholesterol diet. Retrospective studies convey that statins exhibit protection against AD. In few cases, the relative risk of AD was lowered by more than 70% [33]. The processes by which hypolipidemic drugs influence Aβ deposition in brain continue to remain an active field of research. There is rising proof, however, that elevated level of cholesterol increases the production of Aβ and deposition of plaques, and statins seem to compensate or reverse these impacts.

6.2.6 Prevention of Amyloid Aggregation

Clioquinol (iodochlorhydroxyquin), a metal protein attenuating compound (MPAC), successfully demonstrated the detachment of amyloid plaques in human brain samples after post-mortem by a process involving chelation of Cu^{2+} and Zn^{2+}. In addition, preliminary information from the phase II trial of clioquinol in AD individuals has reported reduction in plasma level of $A\beta_{42}$ along with cognitive deterioration [34]. Transgenic mouse model of AD when treated with clioquinol showed striking reduction in brain Aβ deposition. Colostrinin, a polypeptide rich in proline that is extracted from the ovine colostrum, absolutely blocks $A\beta_{42}$ aggregation. Clinical trial of colostrinin in AD individuals showed an abrupt halt in cognitive decline or even increase in cognitive skills. Further studies are still imperative to prove its efficacy for AD treatment [35].

7 Revisiting Rodent Models

Although rodents have been productive workhorses for research on Alzheimer's disease, the problems encountered by scientists in translating promising results from rodents into successful patient trials drive the field to explore other options for animal models. Most murine AD models are designed to convey transgenes of human that contain *APP*, *PSEN1* or both mutants. An attempt was made to promote the development of tau aggregations that are not seen by transgenic expression of *APP* or *PSEN1* alone by integrating several models with a human tau transgene [36]

Table 1 Towards advancement of complete modelling of AD pathogenesis

Animal models	Achievement	Year
APP transgenic mouse	Plaque pathology	1995
MAPT mutant transgenic mouse	Tangle pathology	2000
APP X MAPT transgenic mice	Plaque and tangle pathology	2001
Down's syndrome-derived stem cells	Pathology of diffuse plaque; proof for pre-tangles	2012
Complex APP mutation knocking into mouse genome	Plaque pathology; no overexpression	2014
Overexpression of APP mutations in human neuronal lines in gel system	Convincing plaque pathology; tangle pathology	2014
APP and PSEN mutant stem cell lines	Pathology of diffuse plaque; tau pathology	2015

(Table 1). Early APP mouse models were dependent on elevated transgenic expression to stimulate plaque formation and it suffered from absence of cytopathology and neuronal mortality [37]. Augmentation of tau pathology was succeeded by crossing familial AD (fAD) mutant APP mice with mutant MAPT (tau) transgenic mice suggesting tangle-like modifications occurring downstream of Aβ aggregation, but it faced a drawback of transgenic overexpression and numerous AD mutations [38]. Stem cells were initially cultured from skin biopsies of fAD patients, and human neurons derived from it have shown Aβ aggregation first and then alteration of tau without any overexpression [39] indicating that absence of NFT formation in prior mouse models was due to lack of human tau. Transgenic mouse models have been a great boon for neurodegenerative disorders, but they are a mixed blessing and should be used cautiously. As rodent models do not catch up many important elements of the disease process, these models were asserted to be helpful in studying AD initiation, but not the whole disease process [40]. Researchers have chosen the option of using 3D brain tissue models for use in preclinical studies over the previous 5 years. These tiny organoids are cultivated from stem cells over a period of a few weeks, and they allow numerous drugs to be assessed in a shorter duration of time.

8 Clinical Diagnosis of AD

Early diagnosis of AD seems to be a significant objective, as future medications are probably aiming at slowing the pace of AD progression or prevention instead of reversal of disease-induced neuronal harm. Thus, clinical treatments in the early and preclinical phases of the disease may likely be maximally fruitful. In 2007, a new conceptual framework for the diagnosis of AD was contributed by International Working Group (IWG) and US National Institute on Aging-Alzheimer's Association so that clinical phenotypes and diagnostic process integrated with biomarkers are better defined including complete stages of the disease. The diagnostic process kick-starts with the patient's history of illness and ends with test for biomarkers.

8.1 History of Current Illness and Relevant Review of Symptoms

- It enables us to determine the initial changes and present difficulties of the patient.
- Patient's appetite, mood and behaviour, sleeping habits, ability to perform daily activities, gait and balance are explored.
- Review of medications.

8.2 Physical Examination

- It includes detailed neurological examination.

8.3 Cognitive Screening

- Pivotal part of the diagnostic screening.
- Screening procedure assesses memory; attention; language; visual, spatial and perceptual function; and executive function.
- Validated tests include Montreal Cognitive Assessment (MCA) and Mini-Mental State Examination (MMSE).

8.4 Laboratory Studies

- Hypothyroidism, hypercalcaemia, high cholesterol levels, anaemia, vitamin D deficiency, hypocobalaminaemia, low folate levels, infections, etc. are some of the curable conditions that may aggravate cognition. Hence, screening of these conditions by laboratory studies is recommended.

8.5 Biomarkers

- A biomarker can be defined as a characteristic measurement of biological molecule(s) that indicates the normal condition and pathologic condition. Biomarkers of AD are found in CSF and blood.
- There exists a clear need of tangible biomarkers in order to productively monitor and predict disease progression, and to provide information for accurate diagnosis in the prodromal stages of AD. Additionally, clinical trials require biomarkers to monitor the consequences of new therapeutic interventions.
- Often used biomarkers in AD research include AD-related protein levels (e.g. Aβ40, Aβ42, tau, phosphorylated tau) in CSF [41, 42]. The concentration of

Table 2 Potential biomarkers supporting the clinical diagnosis of AD [43]

Methods	Measures
Thorough neurologic and neuropsychological examination of the subject	Emphasize mental status, memory storage and retrieval, focal signs
Neuroimaging (structural, magnetic resonance imaging)	Ventricular enlargement (ventriculomegaly) Thinning of the cortical ribbon Hippocampal atrophy/enlargement of the temporal horn of the lateral ventricle Brian microbleeds (for cerebral amyloid angiopathy)
Neuroimaging (metabolic)	Pittsburgh compound B (PiB) labelled with ^{18}F or ^{11}C ^{18}F-fluoroethyl-methyl-amino-2-naphthyl-ethylidene malononitrile (FDDNP) ^{18}F-fluoro-deoxyglucose PET Tau markers
Cerebrospinal fluid testing	$A\beta_{1-42}$ Total tau and phospho-tau 14–3-3 protein (to rule out spongiform encephalopathy)
Blood test	Apolipoprotein E isoforms (polymerase chain reaction-based assay) Neuron-specific enolase, S100B (as a measure of brain injury)

these proteins can be measured either by antibody-based technique (enzyme-linked immunosorbent assay) or by antibody-independent technique (mass spectrometry) (Table 2). The procedure involved in the removal of CSF from the patients is an invasive technique and is more painful due to lumbar puncture.

- As AD takes 10–20 years from onset to symptomatic stage, identification of AD-specific biomarkers at early stage is challenging and chances of misinterpretation are high.

9 Neuroimaging Biomarkers

Measurement of *in vivo* brain atrophy and AD pathophysiology can be best provided by neuroimaging with an excellent non-invasive set of method. It can also show the information on anticipating development of disease, even in patients with cognitive impairments that are comparatively lower or absent [41, 44, 45]. Regularly used AD biomarkers include two kinds of neuroimaging:

1. Magnetic resonance imaging (MRI)
2. Positron emission tomography (PET)

9.1 Magnetic Resonance Imaging (MRI)

Structural MRI (sMRI) is a neuroimaging method that investigates *in vivo* structural changes and assesses atrophy (or volumes) and neurodegeneration associated with AD. **Functional MRI (fMRI)** is used to measure the functional integrity of brain's network system. It measures blood oxygen levels, blood volume and blood flow in order to assess the activity of the brain during a sensory (longitudinal fMRI), cognitive or motor task (task fMRI) or at rest (resting-state fMRI) [46].

***Limitations of sMRI*:** It lacks molecular specificity and hence cannot directly detect amyloid plaques and neurofibrillary tangles (NFTs); it cannot assess brain function.

***Limitations of fMRI*:** It is problematic to conduct longitudinal fMRI in patients with severe cognitive impairment as this method is very susceptible to head movement; task fMRI results will remain invalid if the patient is unable to perform cognitive task adequately [47].

The following methods are used to extract or visualize data obtained from 3D MRI scans from cross-sectional and longitudinal studies:

1. *Cross-sectional methods*
   (a) *Visual assessment*: Quick, simple and effective way to evaluate MRI scans
   (b) *Quantitative region of interest-based technique or volumetry*
   - *Manual tracing*: Historically, manual measurement was used to extract volumetric (global and local brain volume) and morphometric (brain tissue morphology) characteristics, including medial temporal atrophy scores and tracing the regions of interest manually. *Limitations:* tedious and time-consuming technique.
   - *Automated and semi-automated techniques*: It has been developed to extract volumes of interest and cortical thickness values for numerous neocortical regions [48]. These techniques are useful for large-scale studies where manual intervention is not required.

   (c) *Quantitative voxel based*
   - *Voxel-based morphometry (VBM)*: It is useful for groupwise comparison of MRI scans of diseased against normal group. *Limitations*: Not applicable to individual diagnosis as it cannot summarize the measure of each subject.
   - *Automated individual subject diagnosis*: Multivariate analysis and machine-based algorithms are used to form a model of disease that is compared to an individual.

2. *Longitudinal methods*
   (a) *Global atrophy quantification*: Percentage change in global brain volume between two scans is quantified by this method. One of the methods developed for this quantification was boundary shift integral (BSI) which determines complete volume by which the brain surface has shifted at two time points between the scan.

(b) *Tensor-based morphometry (TBM)*: It gives a complete profile of voxel level-based degeneration and hence is employed to observe disease progression based on pathological changes.

9.2 Positron Emission Tomography (PET)

Radiolabelled ligands are used in PET for *in vivo* measurement of metabolic and neurochemical processes. Two kinds of PET ligands that are especially used in AD research are:

(a) ^{18}F-fluorodeoxyglucose (FDG)—measures metabolism of the brain primarily indicating synaptic activity [49].
(b) Amyloid tracers—bind to fibrillar amyloid plaques, e.g. ^{11}C-Pittsburgh compound B (PiB), ^{18}F-florbetapir (amyvid), ^{18}F-flutemetamol (Vizamyl), ^{18}F-florbetaben (Neuraceq) [50, 51]. As ^{11}C usage outside research centres was hindered by its short half-life, ^{18}F-labelled probes were developed that have a half-life of about 110 min.

10 AD Clinical Trials: A Look at Recent Progress

Since past three decades, the role of pathological hallmarks of AD has been well understood. However, attempts have stumbled to transform this insight into clinical gains. Major clinical trials have failed to stabilize or enhance cognition in Alzheimer's patients [52, 53]. Clinicaltrials.gov, a National Institutes of Health registry of publicly and privately funded clinical studies, had 244 drug molecules for Alzheimer's registered for testing in the decade of 2002–2012. Only one among the 244 drugs successfully completed clinical trials and made its way to confer approval from the FDA. Pre-specified clinical endpoints have not shown any statistically significant benefit in the clinical trials. However, several of these studies were not well designed in terms of agent selection, subject selection and drug dose, or they were subjected to termination because of the adverse effects [52, 54].

10.1 A Presumed Wave in Mild AD: Solanezumab

Antibody testing has taken the lead among putative disease-modifying therapies for AD since the conception of active and passive immunotherapy to lower beta-amyloid protein [28, 55]. Solanezumab is the most sophisticated antibody in present human trials (Eli Lilly). It mainly binds to soluble monomers targeting the middle region of Aβ and may also bind to low-n oligomers but not plaques. There was failure in achievement of clinical endpoints in two big phase III trials in mild and moderate AD patients. The moderate AD patients showed no advantage, demonstrating

that anti-Aβ drugs should be initiated in mild AD or even sooner which is the commonly held assumption. The findings in the mild AD patients led to a third phase III study as it indicated a little but statistically substantial benefit on cognition by this agent, in only mild subjects. Crenezumab, another antibody of interest, produced comparable indications of modest decline in cognition in patients with mild AD in a phase II trial [56].

10.2 A Major Gesture in a Tiny Trial for the Proof of Concept: Aducanumab

One of the powerful hints till date of an amyloid-targeting agent's prospective clinical and biomarker benefits lately appeared in a phase 1b trial of a human monoclonal antibody (BIIB-037 or aducanumab) that arose from a big screen of B-cell clones collected from healthy older individuals. It apparently attaches to plaques and oligomers but not monomers. Both the cautious design of the study and the human antibody nature may have led to the beneficial clinical and biomarker outcomes. In 2015, aducanumab stepped into obligatory phase III trials.

10.3 "Secondary Prevention" Trials

Some of the anti-amyloid drugs that emerged to meet their objectives failed to attain clinical benefits in mild-to-moderate AD patients. These agents have shifted their area to try "secondary prevention" or pre-symptomatic studies in subjects who are found to be at higher risk of AD development as shown by PET amyloid imaging and/or CSF Aβ42/tau assays. At the moment such prevention studies are being performed, in the world's biggest kindred carrying presenilin-1/presenilin-2 or APP mutations.

11 Conclusion

As the world's population ages, count on AD patients will continue to increase which will bring up the challenge for development of targeted and effective drug delivery. In the future, our capacity to acknowledge early signs and stop development of disease will grow more critical. Being a multifactorial disease, single-target ligands were not able to demonstrate pharmacodynamic impacts during clinical trials on AD patients conducted in large scale. Therefore, development of new drug design ought to draw attention in the direction of multi-targeted ligands. In conclusion, novel strategies are being focused on examining the prospects of disease-modifying drugs in the infancy stage of AD, along with the aid of biomarkers that predict a clear picture of disease progression before this haunting disorder develops. Some trials have obtained promising results whereas others are inconclusive.

Nevertheless, given the unmet need, we anticipate that the therapeutics aimed at targeting the downstream mechanisms will ultimately play a part in tearing down this disastrous disorder. Rather than questioning one hypothesis against the other, we should chase numerous approaches, resulting in a range of therapies that may together stop the emerging tragedy that AD has become. Further, the question whether the removal of accumulated abnormal proteins in the AD brain will contribute to clinical advancement in patients is looking for an answer. Based on the current state-of-the-art research, it is being hoped that new disease-modifying treatment may sooner enter the market and significantly help the suffering patients to breathe a sigh of relief.

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Advancement and Challenges in Parkinson's Disease: A Recent Outlook

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Abstract

Parkinson's disease (PD) is a multifactorial neurodegenerative disease that disturbs the dopamine neural circuit by affecting the basal nuclei. It is symptomized as motor and cognitive disturbances. Standard therapeutic regimen exhibits improvement in motor symptoms but is ineffectual in reversing the condition and delaying the progression of the disease. Thus, alternative approaches have been pursued in various areas. This perspective analyzes the various strategies studied and researched for treatment of PD along with contributions in the treatment of PD.

Keywords

Parkinson's disease (PD) · Cell therapy · Immunotherapy · Gene therapy · DBS Drug therapy

1 Introduction

Parkinsonism or Parkinson's disease (PD) is a progressive condition related to aging. After Alzheimer's disease, PD is the second most common neurodegenerative disease. It is considered a complex multifactorial disease in which unknown

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environmental factors, genetic alterations, and/or oxidative stress subsequently cause premature neuronal death mainly in catecholamine (dopamine, noradrenaline, and adrenaline) neurons, especially in dopaminergic neurons in substantia nigra [1] (Fig. 1). The pathological features in patients with PD show retardation of dopaminergic neurons and presence of increased levels of α-synuclein protein, which is accumulated in Lewy bodies [2]. Typical symptoms of PD are tremor, bradykinesia, rigidity, and postural instability, as well as non-motor symptoms such as constipation, insomnia, and depression [3]. The therapeutic strategy of patients with PD is focused on the strengthening of dopaminergic transmission with exogenous L-dihydroxy-phenylalanine (L-dopa) in combination with carbidopa and dopamine agonists [4]. Drugs such as monoamine oxidase B (MAO B) and catechol O-methyltransferase (COMT) inhibitors prevent the catabolism of brain dopamine [5]. Several anticholinergic medications such as benztropine and trihexyphenidyl are administered in addition to carbidopa-levodopa therapy and dopamine agonists so as to alleviate the tremor associated with PD [6, 7]. Apart from these, amantadine [8], an NMDA (*N*-methyl-D-aspartate) receptor antagonist; droxidopa, a prodrug of norepinephrine; pimavanserin, a 5-HT inverse agonist; and rivastigmine, an acetylcholinesterase inhibitor, are administered to provide relief from symptoms of PD [1]. The stated drug regimen facilitates symptomatic relief to maintain the dopamine levels. Nevertheless, these agents have failed to show an impact on the recovery/reestablishment of the dopaminergic neurons. Moreover, the benefits of these agents are offset by unwanted side effects [5]. Besides the loss of dopaminergic neurons, several other elements that contribute to PD progression include

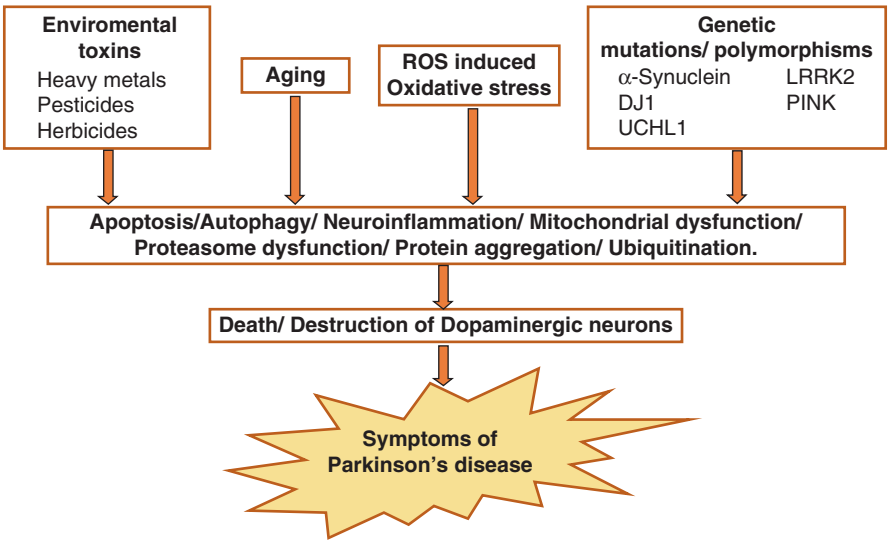

Fig. 1 Etiology of Parkinson's disease. *LRRK2* leucine-rich repeat kinase 2, *DJ-1* protein deglycase or Parkinson's disease protein 7, *PINK1* phosphatase and tensin homolog (PTEN)-induced kinase 1, *UCHL1* ubiquitin C-terminal hydrolase L 1

mitochondrial dysfunction, oxidative stress, proteasome dysfunction, ubiquitination, and neuroinflammation [9]. Based on these facts, there is a need that calls for alternative approaches that can impart better therapy with minimal side effects.

In recent times, major discovery and development have been achieved in the field so as to counteract and slow down the progression of PD. Some of the achievements are in the field of gene therapy, surgical interventions, cell-based treatments, and immune-based therapy. The introduction and/or application of these strategies have paved the floor for possible alternatives to the existing/developing therapeutic systems.

2 Drug Therapy

Several drug candidates, under clinical and/or preclinical trials for PD, have centered the attention on neuroprotection as well as symptomatic treatment. Nondopaminergic targets/systems are also potentially beneficial in the therapeutic approach for PD. These agents may help in dose reduction of levodopa or may be useful in treatments where levodopa is not responsive. These targets include adenosine, adrenergic, serotonergic, opioid, glutamatergic, and cholinergic pathways [10].

Among these, istradefylline (brand name—Nourianz) has been effective in treating the "off" episodes in patients with PD. "Off" episodes are identified when symptoms of PD are rapidly increasing. The drug is the first adenosine A_{2A} receptor antagonist, administered as an add-on medication to levodopa/carbidopa [11]. Two other A_{2A} receptor antagonists, preladenant and tozadenant, did not contribute significant results in Phase III clinical trials and hence were ceased from further investigations [12, 13].

Neurogenic orthostatic hypotension is commonly found in patients with PD. The response to postural changes to regulate blood pressure is usually maintained through the autonomic nervous system (ANS). Due to the insufficient release of noradrenaline, the ANS fails to regulate blood pressure and thus leads to orthostatic hypotension [14]. Pharmacological treatments used for orthostatic hypotension include pyridostigmine, fludrocortisone, midodrine, L-DOPS, octreotide, yohimbine, and erythropoietin. Pyridostigmine acts through cholinesterase inhibition to improve cholinergic transmissions in ganglia [15]. Studies have shown the effects of fludrocortisone on volume expansion by increasing reabsorption of sodium in the kidneys and also by sensitization of α-adrenoreceptors [15]. Midodrine is a short-acting α_1-adrenergic agonist used for symptomatic relief of neurogenic orthostatic hypotension. However, the clinical trial study results of the use of midodrine in PD are not yet published [16]. Droxidopa or (L-DOPS) is a prodrug which gets converted to noradrenaline via decarboxylation. Reports have demonstrated the effects of L-DOPS on improvement of dizziness due to orthostatic hypotension in PD [14]. Yohimbine is an α_2-adrenergic antagonist which has shown better control in regulating blood pressure than pyridostigmine [15]. Other drugs such as octreotide and erythropoietin have also been beneficial in the management of neurogenic orthostatic hypotension in patients with PD when given in combination than monotherapy [15].

Glutamate antagonists are vital nondopaminergic targets of interest because of the integral role of glutamatergic system in PD. Apart from amantadine [8], a clinically NMDA (*N*-methyl-D-aspartate) receptor antagonist, the other glutamate targets investigated for PD therapy include inotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists and metabotropic glutamate receptor (mGluR5) antagonists. Drugs such as perampanel (AMPA receptor antagonist), mavoglurant, and dipraglurant (selective mGluR5 inhibitors) have revealed no significant difference in symptoms with poor tolerability and efficacy [10].

Loss of serotonergic neurons and subsequent dysfunction in the serotonin system are also described in PD. Alterations in the $5HT_2$ receptors also add to the serotonin dysfunction in mood variations and psychosis in PD [17]. Drugs with serotonin receptor binding property such as clozapine ($5\text{-}HT_{2A/2C}$ receptor antagonist), buspirone ($5\text{-}HT_{1A}$ and α_1-adrenergic receptor agonist), eltoprazine (a $5\text{-}HT_{1A}$ and $5\text{-}HT_{1B}$ dual agonist), and SYN120 (a dual $5\text{-}HT_6/5\text{-}HT_2$ antagonist) are under evaluation for their possible benefits in patients with PD [10].

Famotidine (histamine receptor antagonist) has displayed antidyskinetic property in animal models. Nevertheless, there are no clinical trials under evaluation with histamine-based targets for PD [10]. Opioids have been studied for the management of nonmotor symptoms such as pain associated with PD. A Phase II/III is currently under investigation with prolonged-release formulation of oxycodone–naloxone [18].

Safinamide is a selective, reversible MAO-B inhibitor with both dopaminergic and nondopaminergic (glutamatergic) properties. The drug safinamide is approved as an add-on medication to levodopa alone or in combination with other drugs approved. It is mainly used for treatment in mid to late stages of PD [19].

Another add-on therapy accepted for new drug application by the US FDA is opicapone, which is a sustained COMT inhibitor. Nearly 30 clinical studies have been conducted which include two Phase III trials. Reports have revealed that the new treatment approach would be effective in prolonging the beneficial effects of levodopa with better control over motor symptoms [20].

A thiol-based antioxidant, *N*-acetyl cysteine (NAC), helps to restore the natural antioxidant, glutathione. Since oxidative stress also adds to the pathophysiology of PD, studies have shown that injectable administration of NAC has increased glutathione levels. The boost in glutathione may protect dopaminergic neurons from death by reducing oxidative damage through prevention of the accumulation of reactive oxygen species (ROS) and by increasing the activities in mitochondrial complexes [21, 22]. Furthermore, NAC administration has also shown to improve dopamine modulation which may enhance dopaminergic viability and functionality [21]. However, the potential improvement in symptomatic treatment of PD is yet to be realized.

3 Surgical Interventions for PD

Surgical procedures and ablative processes within the basal ganglia are currently being performed for relief in tremor and rigidity. Pallidotomy and thalamotomy were the standard techniques for treatment of motor symptoms of PD until the effectiveness of levodopa was initiated [23]. The emergence of deep brain stimulation (DBS) brought the recurrence of surgical interventions. DBS involves the implantation of electric stimulators which have the ability to discharge high-frequency electric waves to areas in the brain. DBS into the subthalamic nucleus has been applied to treat PD patients with motor dysfunctions such as tremor, rigidity, and dyskinesia [24]. Areas such as pedunculopontine nucleus and caudal zona incerta are currently under clinical trials as possible targets for DBS for management of PD. No results are posted as yet [25–27].

4 Immune-Based Therapy

The pathological accumulation of α-synuclein (α-syn) within the astrocytes, neurons, and oligodendrocytes causes the degeneration of these cells and subsequently leads to neuronal loss or degeneration. Recent studies have demonstrated the focus on therapeutic interventions to decrease the α-syn levels and its clearance and further to prevent its propagation [28]. As an alternative to the known therapeutic strategies, immunotherapy, either as active or passive immunization, is the focused rationale for tackling the protein. In active immunization, the immunity gets developed through production of antibodies against the toxic α-syn protein. However, the administration of antibodies against α-syn protein renders protection in case of passive immunization. In both the types, the microglial cells get stimulated by the antibodies to engulf or scavenge the protein. Thus, the protein transfer and propagation get prevented [29].

Prothena Biosciences Inc., in collaboration with Roche, has developed a humanized IgG_1-based monoclonal antibody, named as PRX002 [1] (prasinezumab). Single dose and multiple doses of PRX002 were tested in healthy volunteers and were found to be safe and tolerable. A randomized clinical trial of patients with PD treated with multiple ascending doses of PRX002 was also safe and well tolerated. The study also displayed the noticeable reduction in α-syn protein. The Phase II clinical trials are currently under investigation [30].

An advanced monoclonal antibody, BIIB054, was developed by Biogen to target α-syn [1]. This antibody also demonstrated encouraging results with safety and tolerability. The pharmacokinetic study was also safe in volunteers as well as participants with PD [31]. A single ascending dose study is also under evaluation [32].

Affiris AG had developed α-syn-conjugated vaccines named AFFITOPE® PD01A and PD03A [33]. These synthetic peptides would mimic the effect of natural α-syn

and thus would stimulate the production of α-syn antibody. The Phase I clinical trials conducted on the vaccines demonstrated clear immune response with safety and tolerability [34]. However, no peer-reviewed reports are available.

5 Gene Therapy

Gene therapy for PD involves the viral vectors that are capable of transferring gene for the expression of specific proteins. The targets for gene therapy are put into two: disease modifying or non-disease modifying. The disease-modifying approaches use the strategy of ceasing neuronal death with or without regeneration of lost neurons. The research has been focused on glial cell-based family of ligands (GFL) which transmits information for activation of the MAP-kinase and PI3-kinase pathways. These pathways are crucial in the survival of neurons and neuritogenesis. Moreover, the genes that encode for the proteins tyrosine hydroxylase (TH), dopamine transporter (DT), vesicular monoamine transporter 2 (VMAT2), and aromatic L-amino acid decarboxylase (AADC) are also activated [35]. The non-disease-modifying strategies aim to alleviate the symptoms by regulating the abnormal firing in the basal ganglia. This is also by expressing enzymes of the dopaminergic or GABAgenic systems. These approaches do affect or alter the disease pathological system and hence demonstrate therapy based on symptoms. Gene therapy using opto- and chemogenetics is sorted as a crucial alternate for treating symptoms of PD. In optogenetics, the expression of opsins (light-sensitive ion channels) could be activated using light of wavelength specific for opsins. This could be beneficial in the deconstruction of parkinsonian neuronal circuitry and also improvement of motor symptoms [36]. Chemogenetics, based on the technology called designer receptors exclusively activated by designer drugs (DREADDs), allows the signaling of G-protein-coupled receptor (GPCR) and regulates the downstream neuronal functions. Another form of personalized gene therapy is genome editing with CRISPR-CAS9 technology, which may be used for genes with known mutation(s) causing PD. Even though there are several investigations and studies on therapy for PD using gene therapy, the true treatment of gene therapy is yet to be realized [36].

A potential gene therapy for targeting the *α-syn* gene is antisense oligonucleotide (ASO). ASOs are synthetically derived fragments of DNA which are able to bind to mRNAs so as to interfere in the intermediary stage between the DNA and the protein. A study has reported the use of an amido-bridged nucleic acid (AmNA)-modified antisense oligonucleotide (ASO) to target the α-syn protein in PD mouse model that expressed human wild type of the protein. The modified ASO was found to improve the neurological defects in the PD mouse model with improved stability and cellular uptake [37]. Numerous reports have demonstrated different outcomes with the administration of different oligonucleotides in various animal models. AAV-ribozyme, AAV-shRNA, miRNA, exosomal siRNA, and PEI/siRNA complex are other oligonucleotides reported [38].

Leucine-rich repeat kinase 2 (LRRK2) is another protein which imparts to the etiology of PD. Mutations in *LRRK2* are proved to be associated with familial type of PD. Oligonucleotides like shRNA are studied for their action by targeting for mutations in *LRRK2* in human embryonic kidney (HEK)-derived 293FT cells [39]. Moreover, an intracerebroventricular injection of ASOs aimed to target *LRRK2* was found to decrease levels of mRNA, LRRK2, as well as α-syn proteins in the substantia nigra [39]. It is evident that the potential of ASOs is varying based on the different targeting approach. Thus, the safety and efficacy need to be established in the upcoming clinical studies.

6 Targeting α-Synuclein (α-Syn)

Other than immunotherapy and antisense oligonucleotides, the different approaches to block α-syn protein include degradation of the protein and aggregation inhibition. Autophagy or degradation involves multiple and complex pathways to break down the protein and unnecessary organelles that cause protein folding and aggregation. Mammalian target of rapamycin (mTOR) signaling pathway plays a key regulatory role in autophagy by controlling several processes of autophagy including initiation, process, and termination. A mitochondrial sensor (mTOR) is aberrantly overactivated in the brain during the pathogenesis of PD. Studies have shown that the autophagy and mTOR are crucial in the pathophysiology of PD [40]. MSDC-0160 is believed to reduce mTOR activity by regulation of mitochondrial pyruvate carrier (MPC), which is activated by mTOR. MSDC-0160 has shown to decrease the neuronal toxicity due to α-syn protein in *Caenorhabditis elegans* model and further investigations in humans are yet to be documented [41]. Another target of interest is c-Abl (ABL1, Abelson tyrosine kinase), which is effective in α-syn protein aggregation and neuronal degeneration. Inhibitors of c-Abl act via mitochondrial functions and also through posttranslational modifications of α-syn protein. As a result, the autophagic pathways get activated [41]. The clinical trials of c-Abl inhibitor, nilotinib, are still under examination [42].

The aggregation of α-syn protein is shown to be reduced or inhibited in the presence of intrabodies, which are small fragments of antibodies tailored to bind to the protein and prevent oligomerization. A small molecule, NPT200-11 (developed by Neuropore Therapies in connection with UCB Pharma), is reported to intervene with the interaction of membranes with α-syn and hence hinder its oligomerization [41]. A Phase I clinical investigation has been completed but no data from the investigation has been furnished [43]. Another protein, NPT-088 (developed by Proclara Biosciences), is reported to bind to amyloid protein. When tested in mouse models with overexpressed levels of α-syn, NPT-088 was found to decrease the levels of the protein α-syn [41]. A multiple-dose safety study was completed in patients with Alzheimer's disease and the results are yet to be furnished [44]. The study in patients with PS needs to be initiated.

7 Cell-Based Therapy

Replacement of dopaminergic neurons and reestablishment of the neural circuit using cell-based approaches are an attractive field for meeting the clinical challenges in PD. Many reports and investigations are currently in the pipeline on cell-based therapy. Some of the different stem cell types explored include embryonic stem cells (ESCs), fetal ventral mesencephalic (FVM) tissues, neural stem (NS cells), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs) [22].

ESCs are highly proliferative cells that are derived from inner mass of blastoclasts and these are able to retain the pluripotent property for long durations. Large-scale production and capability to differentiate into dopaminergic neurons have thus considered ESCs as a tool for PD-based therapy. Researchers have studied and demonstrated the ability of ESC-derived dopaminergic neurons to survive and reinnervate the striatum and consequent improvement in motor symptoms in animal models [22]. Despite the promising results, ethical issues and practical side of its availability have hindered its clinical application and thus limited the clinical use [45]. Furthermore, instability of grafts may risk out to form tumors.

Fetal ventral mesencephalic (FVM) tissues, derived from the midbrain of fetuses, have precursors for dopaminergic neurons [46], and have been transplanted into the striatum of patients with PD [46]. The results were good in many patients. Similar to the problems linked to ESCs, FVM dopaminergic cells also have major ethical issues and technical issues such as limited *in vivo* differentiation and inability to yield consistent dopaminergic neurons [22, 45]. A clinical investigation for grafting fetal tissue into the brain of patients with PD is ongoing with results expected to be published by 2021 [47].

Neural stem (NS cells) or precursor cells are isolated from an adult central nervous system and later cultured as neurospheres (freely floating) with the aid of supporting growth factor(s) like endothelium growth factor and fibroblast growth factor. These cells are able to differentiate in various cellular types (namely astrocytes, neurons, and oligodendrons) of the central nervous system. Thus, the replacement of the lost/degenerated neurons follows to reestablish the dopamine release and transmission [22]. Several reports have revealed poor survival and inability/mild ability of the cells to improve the progress of treatment on PD-induced animal models. This is due to poor differentiation into dopaminergic neurons. Other reports have stressed on the importance of NSCs that were isolated from the midbrain alone, as only these cells would be capable of differentiating into dopaminergic neurons. Later, another study proposed an alternative to use NSCs developed by genetic engineering and further cultured with the necessary developmental factors or signals. These cells would induce the differentiation of dopaminergic neurons and also enhance the yield of dopamine [48]. Nevertheless, the survival and stability of these grafts still remain to be proven, based on which transplantation effects could be investigated in humans.

Induced pluripotent stem cells (iPSCs) are reprogrammed skin or blood cells to pluripotent cells in its embryonic state that facilitates the development of any type of human cell as per the need for therapy. These cells have shown better genomic

stability, viability, and transcription ability as that of ESCs [22]. Research on iPSC grafting into the striatum of PD animal models has demonstrated the ability to survive, differentiate, and ameliorate the symptoms in PD animals. Despite the promising results, tumor formation can follow if differentiation is not complete. These type of cells are patient specific and thus will have no limitation. However, the differentiation protocols would be tedious till standardization and hence expensive [49]. The first human trial for iPSC transplantation for PD has marked off in 2018 [50]. Due to the nonhomogeneous differentiated tissues of iPSCs obtained, a new type of cell was sorted to be known as induced neural cells. These were developed through viral vectors from adult somatic cells that would circumvent the intermediate phase of stem cell. Human induced neurons have demonstrated survival and stability on rodents [39]. But, similar to that of iPSCs, the protocols still lack consistency and efficiency to differentiate as dopaminergic neurons.

Another possible treatment intervention under cell-based therapy is mesenchymal stem cells (MSCs). These cells are adult stem cells that are self-renewable and are capable to differentiate. These cells have surface markers and are devoid of hemopoietic surface markers. Initial studies have shown the ability of naïve and predifferentiated MSCs to stabilize and redevelop degenerated neuronal sites partially with no/minimal tumorigenicity and immunogenicity. The mechanism of differentiation and therapeutic effect was to be deduced [51, 52]. In the later years, secretomes were related with MSCs as the presence of immunomodulatory cytokines and neurotrophic factors in secretomes would reduce neuroinflammation and provide favorable environment for differentiation of MSCs into new dopaminergic neurons and also for survival of the remaining dopaminergic neurons. Based on the tissue from which they are extracted, MSCs are denoted as adipose tissue type (aMSCs), bone marrow type (bMSCs), umbilical cord type (uMSCs), and others. After isolation, the cells may be transplanted either in its raw (undifferentiated) or in the cultured (differentiated) form [53]. Due to the promising results obtained from the treatment of different types of MSCs in numerous experimental PD models, the approach was opened for testing in humans [54]. Currently clinical trials using MSCs for PD therapy [53] are under study from which relevant information for therapeutic reality, route of administration, immunological responses, and other related ones are to be known. Such clinical data will be contributory to the use of MSCs for treatment of PD.

8 Future Prospects

The therapeutic strategy for PD extends from the conventional pharmacological and non-pharmacological approaches (based on the symptoms) to the latest interventions, namely gene-based, cellular based, and immune-based therapy. Many of these lines are effective either as single or as combination therapy. The symptomatic therapy is managed by maintaining and reinstating the levels of dopamine through drugs such as levodopa, dopaminergic agonists, COMT, and MAO-B inhibitors. Apart from these, several new drugs are administered as add-on drugs to the existing

regimen. Recently, literature has revealed the newer methods and efforts that are focused on disease modifications instead of relying only on symptom-based therapy. Despite the effort, there has been very limited success in modifying the disease condition in PD. Hence intense research is still ongoing for a better therapeutic approach. Preclinical data are known in some biological pathways. A myeloperoxidase (MPO) inhibitor, AZD5904, reduces oxidative stress occurring during neuroinflammation, which is involved in the pathophysiology of PD [55]. LRRK2 inhibition is another target that is extensively under study. DNL151 and DNL201 are currently under clinical study for safety and tolerability [56, 57]. Similarly, G-protein-coupled receptor 6 (GPR6) is an indirect modulator of dopamine pathway for treating PD [58]. Glucocerebrosidase (GCase) is also found to be a target of interest in PD therapy as decreased activity of GCase is found to show increased levels of α-syn aggregates and other proteins associated with neurodegenerative disorders [59]. Furthermore, the concept of drug repurposing/repositioning has also been applied and analyzed by clinical trials for the disease-modifying potential in clinical trials. Drugs such as isradipine (calcium channel blocker), exenatide (glucagon-like peptide-1/GLP-1 agonist), nilotinib (c-Abl (Abelson) tyrosine kinase inhibitor), and simvastatin (3-hydroxy-3-methylglutaryl-coenzyme A/HMG-CoA inhibitor) are some of the drugs that have been extensively studied for their effect on PD. Mitochondrial based treatments have also been implicated as an emerging alternative for PD [60]. Table 1 summarizes the different potential targets/approaches that may be proven beneficial for the treatment of PD. These information, though not exhaustive, show an insight into different targets or approaches intended for clinical use in the future.

Table 1 Emerging potential targets or approaches for the treatment of Parkinson's disease

Target/approach	Possible mechanism
Myeloperoxidase (MPO)	Modulating oxidative stress in cellular environment by enzyme inhibition
G-protein-coupled receptor 6 (GPR6)	Pharmacological modulation through inverse agonism of dopaminergic neurons
Leucine-rich repeat kinase 2 (LRRK2)	Inhibition of genetic variants to offer neuroprotection
Glucocerebrosidase (GCase)	Inhibiting the heterozygous mutant forms
Mitochondrial oxidative stress pathway	Using antioxidants/drugs such as NAC, inosine, statins, glitazones to regulate redox balance and mitochondrial activity
Dynamin-1-like protein (DRP1)	Inhibition to block excess mitochondrial fission
Mitochondrial rho GTPase 1 (MIRO)	Reduction to reduce/avoid autophagy of mitochondria (mitophagy)
Restoration of dopamine	Gene therapy for proteins tyrosine hydroxylase (TH), dopamine transporter (DT), vesicular monoamine transporter 2 (VMAT2), and aromatic L-amino acid decarboxylase (AADC)
Replacement of dopaminergic neurons and reestablishment	Using embryonic stem cells (ESCs), fetal ventral mesencephalic (FVM) tissues, neural stem (NS cells), induced pluripotent stem cells (iPSCs), and mesenchymal stem cells (MSCs)

9 Conclusion

PD is a neurodegenerative disorder and is second in order after Alzheimer's disease. Numerous biological systems/targets/approaches are presently addressed to meet the therapeutic needs of PD. Apart from the newer drugs, clinically and preclinically under study, the advent of newer strategies like cell transplantation therapy and gene engineering has been extensively explored for meeting the disease challenges. Despite some crucial realizations, several areas still remain to be managed. This has to be predominantly tackled through appropriate knowledge and experience in upcoming technologies, especially when iPSCs, secretome-based MSCs, and gene engineering are concerned. Ongoing research with better understanding of various targets and approaches should no doubt assist in a multidimensional therapeutic regimen for PD.

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Post-traumatic Stress Disorders (PTSD)

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Abstract

Psychiatric disorders have proliferated very recently, in particular post-traumatic stress disorder that accompanies with traumatic events or stressful situations such as loss of loved person or family member, sexual assault, or war or battle. Children and young adults are more affected than grown up and female are more familiar to face post-traumatic stress disorder than male. To be diagnosed as PTSD patient, the symptoms should be severe enough and last for at least 1 month. Post-traumatic stress disorder's patients are represented by three kinds of symptoms including intrusion symptoms, avoidance symptoms, and negative alternation in cognition and mood.

Previous studies established three categories of PTSD including delayed PTSD, birth trauma, and complex PTSD that occur according to different circumstances of person's experience. Most of the people that are suffering from PTSD showed different hormonal imbalance as increased serum catecholamine

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level and decreased urinary cortisol level with high noradrenaline/cortisol ratio; it is also associated with anatomical changes such as diminished size of brain and hippocampus.

Regimen to suppress symptoms of post-traumatic stress disorder includes both psychotherapy, cognitive behavioral therapy (CBT) and eye movement desensitization and reprocessing (EMDR) in reducing psychological symptoms of PTSD, and pharmacotherapy, selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) that showed promising results to decrease symptoms of post-traumatic stress disorder.

Regular physical exercises combined with psychological and pharmacological treatment showed auspicious effects on the management of PTSD.

1 Introduction

Post-traumatic stress disorder is one of the most frequent behavioral and physiological disorders that might be apparent after witnessing or experiencing horrendous or terrifying circumstances [1]. The traumatic events might be hazardous life-threatening occasions such as military fight, disastrous occasions, and terrifying situations like terrorist attacks and physical or sensual rape in grown-up or adolescence [2].

People suffering from this traumatic disorder are at high liability of experiencing bad health status including respiratory, gastrointestinal, immunological, and cardiovascular abnormalities [3, 4]; it is also associated with increased tendency to attempt suicide [5] and considerable anxiety [6, 7].

The experience of traumatic events is more prevailing among youth; approximately 30% of young adults experienced at least one or more awful terrifying events by the age of 16; with 13% of those adolescent advocate manifestations of post-traumatic stress, about 9.7% of female and 3.6% of male experience traumatic events in their lifetime [8]. This percentage doubles in population affected by conflict [9] and reaches more than 50% in survivors of rape [10]. The feasibility of occurrence of PTSD is higher in well-developed countries than low-income countries. That distinctions show that the role of sex, social and situational factors in articulation, and development and persistence of post-traumatic stress disorder symptoms, especially in case of physical or sexual assault, might be differently perceived by male and female with different reported actions and expressions [11].

Not every person who faced traumatic events evolves chronic or acute post-traumatic stress disorder and not all people with post-traumatic stress disorder has been exposed to a risky occasion. Unexpected death of closed person such as one of parents or friends can likewise cause PTSD. Symptoms usually begin immediately after the trauma or even within 3 months after the traumatic event; otherwise some manifestations start to be clear few years later. Symptoms should resist for more than 1 month and be extreme enough to meddle the connections or then again work

to be considered as post-traumatic stress disorder. The prognosis of this psychiatric disorder differs; some people recoup within 6 months while other people's symptoms stay along for more years [12].

2 Clinical Picture

To confirm diagnosis of post-traumatic stress disorder, the patient must represent for at least 1 month the following three main categories of symptoms that have been updated essentially in the fifth edition of the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM-5) criteria. Post-traumatic stress disorder now belongs to a new category of psychopathological disorders named "trauma and stress-related disorders" as avoidance is recently added to the required diagnostic clusters of the stress disorder [2].

2.1 Intrusion Symptoms

Recurrent, involuntary, irritating memories, distressing dreams (flashbacks), intense or prolonged psychological distress, physical symptoms like tachycardia and sweating, and frightening thoughts [13].

2.2 Avoidance Symptoms

The patient intends to keep himself or herself away from any places or events that remind him or her with the previous bad experience and to avoid bad thoughts or to feel connected to traumatic occasion. Circumstances which remind the person with previous risky events may trigger avoidance symptoms leading to change in personal habits like people involved in car accident do not drive any more [13].

2.3 Negative Alternation in Cognition and Mood

Inability to recall any important clues related to the traumatic events due to dissociative amnesia, and excessive and persistent bad thoughts and beliefs about oneself, others, and the world (no one can be trusted). The person starts to blame himself or herself and other people due to distorted persistent cognition. They usually suffer from negative emotional state and decreased participation in main social activities [13].

On the contrary, the World Health Organization's anticipated International Classification of Disease, 11th Revision (ICD-11), reported six post-traumatic stress disorder-specific symptoms as diagnostic criteria. The new diagnostic approach highlighted PTSD-related negative self-concept, mood dysregulation, and persistent difficulty in sustaining relationship and feeling close to others and emboldens clinician to recognize these features in their assessments and interventions [14, 15].

There are other different screening methods used to estimate adults for post-traumatic stress disorder, for example Checklist for DSM-5 (PCL-5) [16] and the Primary Care Post-Traumatic Stress Disorders Screen for DSM-5 (PC-PTSD-5) [17]. There are numerous evaluation techniques used to assess both children and adolescence PTSD such as Child Post Traumatic Stress Disorders Symptoms Scale (CPSS) [18], Traumatic Screening Questionnaire for Children [19], and UCLA Post-traumatic Stress Disorder Reaction Index for DSM-IV [20].

3 Coexisting Disorders and Mortality

Almost 50% of post-traumatic stress disorder reported cases are associated with instable mental state and abuse of some drugs [21]. It is also accompanied with genuine incapacity, therapeutic collapse, and immature death [22]. Patients with PTSD develop emotionally announced well-being status and diagnosed diseases in all categories [23].

PTSD is additionally connected to self-destructive behavior [24]; however the relationship is neither explicit nor basic. The general danger to attempt a suicide among regular population with post-traumatic stress disorder (2.0) is relatively likewise the probability of generalized anxiety disorder (2.3) or addictive to alcohol (2.5) but the reported risk ratio is less than that recorded with depression cases (4.8) [25]. However, recent studies did not conduct any association between military officers' suicide and war-zone deployment [26] and thus the high suicide rate among civilians reflects cumulative life stressors, feeling of loneliness, or estrangement [27].

4 Do Children Show the Same Response as Adults?

Kids and teenagers can have outrageous responses to injury yet their symptoms may not be equivalent to grown-ups. In young kids (less than 6 years old), symptoms can be represented as wetting the bed in the wake of having figured out how to utilize the latrine, overlooking how to or being unfit to talk, and being uncommonly clingy with a parent or other grown-ups. Adolescents and teenagers are bound to demonstrate manifestations like those found in grown-ups. They may likewise create problematic, rude, or dangerous practices; they also might feel guilty in not preventing awful events or dangerous injuries or even they will think to take revenge from the causality [28].

5 Risk Factors Predispose PTSD

Not everyone who experience dangerous traumatic occasions develops PTSD; actually, huge percentage of these population do not suffer from this psychological disorder. There are categories of people more prone to develop PTSD like younger children, females, less educated ones, and those with stressful lifestyle (military persons) and current mental health issue [29, 30].

Numerous predisposing risk elements factors perform a critical role in case a person develops PTSD or not such as counties and recurrent dangerous circumstances, being close to someone loved likewise friend or family member becomes hurt, lack of social support, facing extreme stressful situations such as pain, injury, cancer, being jobless and homeless, having a previous history of mental or psychological illness or interpersonal violence, body disfigurement, and physical or sexual rape. Post-traumatic stress disorder prognosticators include endocrine and physiological imbalance like tachycardia, tachypnea, and decreased plasma cortisol level [31–33].

Potential parents and family affect the post-traumatic stress disorder's symptom co-occurrence. Parents and family act as a key feature in child anxiety as they are essential motivations for infant's adjustment meanwhile the traumatic event happens. Such as, high incidences of post-traumatic stress disorder's manifestations in parents of children are evolved with low infant rehabilitation [34]. Also emotional sensitivity associated with maternal factors is approved to precipitate PTSD symptoms of the children that face terrifying events [34].

Other factors which are approved to suppress the incidence of PTSD are called *resilience factors* such as seeking out other people's help and support, encouraging oneself to feel good and to do action to face the danger, joining group therapy after traumatic events, having a positive coping strategy, and convincing oneself that he or she is able to act and response in such an effective way in spite of feeling fear [35].

6 Different Categories of Post-traumatic Stress Disorder

- **Delayed PTSD:** This is a kind of psychic instability occurs if the psychological symptoms crop 6 months later to the terrifying situation.
- **Birth trauma:** The manifestations appear after traumatic experience of child birth.
- **Complex PTSD (CPTSD):** In this type, the person shows symptoms of post-traumatic stress disorder along with mental or psychiatric symptoms such as uncontrollable emotions, lack of trust towards the world, hopelessness feelings, staying away from any friendship, depersonalization, and suicidal feelings. This kind of post-traumatic stress disorder might be caused by childhood abuse, domestic violence, recurrent sexual abuse, kidnapping, or slavery [36]. In some cases the symptoms of complex post-traumatic stress disorder may be misdiagnosed to those of borderline personality disorder (BPD); even some reported cases experience both symptoms of PTSD and BPD so it is important to discuss these symptoms with the psychiatric professional to be sure of getting the proper treatment [37].

7 Pathophysiology and Biological Features of Post-traumatic Stress Disorder

Neuroendocrinology changes: Post-traumatic stress disorder symptoms become clear when there is an overstimulation of adrenergic receptors caused by witnessing horrible events that might lead to profound neurological changes in the cerebrum.

Those changes might persist for more time after the occasion which initiates the horror, leading to hyper-receptivity to future dreadful circumstances [38]. During awful encounters at terrible stituations the abnormal high level of chemical transmitter during concerning fear emitted decrease higher centers action that might be a main consideration through the progression of post-traumatic stress disorders [39].

PTSD leads to chemical disorders in the cerebrum and body that contrast from other mental psychological diseases as extensive depression. Persons that are recognized as PTSD cases represent more strong response to a suppression test of dexamethasone than persons that are known to have clinical depression [40]. Numerous studies showed that people with post-traumatic stress disorder showed high level of catecholamines and low level of cortisol in urine [41], with noradrenaline/cortisol ratio therefore higher than that in people that are prone to be negative to PTSD [42].

This is as opposed to the regularizing stressful reaction, in which epinephrine, norepinephrine, and cortisol measurements are raised following panic stimuli [43]. It is also observed that there is an imbalance in the hypothalamic-pituitary-adrenal (HPA) axis suggested by high level of brain catecholamines [44] and corticotropin-releasing factor (CRF) [45, 46].

The preservation of fear includes HPA axis, locus coeruleus-noradrenergic system (LC-noradrenergic system), and relation between the limbic system and the frontal cortex. Hormonal coordination between different parts of the body during fear is controlled by the HPA axis [47], which actuates the LC-noradrenergic framework and is involved in the over-union of recollections that happens in the fallout of trauma [48]. This over-combination improves the probability of one's creating PTSD. The amygdala (corpus amygdaloideum, almond-shape nuclei in the temporal lobe of the brain) [49] is in charge of danger recognition, and also the adapted and unconfined terrifying reactions [50].

HPA axis abnormalities in case of PTSD will lead to solid negative criticism hindrance of cortisol due to hypersensitivity of cortisol receptors [51]. PTSD has been conjectured to be a maladjusted training method to anxiety reaction due to hyperactive and hyper-responsive HPA axis [52]. Suppressed cortisol levels may incline people to PTSD after war injury; Swedish officers serving in Bosnia and Herzegovina with low pre-administration cortisol level in saliva had a higher susceptibility to PTSD side effects, after combat injury, than soldiers with ordinary pre-administration levels [53]. Due to the important role of cortisol in reestablishing equilibrium following the injury reaction, it is believed that the person who survives from major trauma with low cortisol experiences an ineffectively contained more stressing reaction. It is believed that the locus coeruleus-noradrenergic framework intercedes the over-combination of fear memory. Abnormally high level of cortisol diminishes noradrenergic action, and in light of the fact that individuals with PTSD will in general have decreased level of cortisol, it has been recommended that people with PTSD cannot manage the exaggerated noradrenergic reaction to awful stress [39].

Neuropeptide Y (NPY) had shown a strong evidence to reduce norepinephrine secretion and to suppress anxiety in experimental animals. Previous investigations approved that patients that suffer from PTSD showed decreased level of NPY leading to increase in their anxiety level [50].

Other literatures showed that people suffering from PTSD showed a chronic reduction of serotonin level which connected many behavioral symptoms like apprehension, aggressiveness, and suicidal tendency [54]. Serotonin is also important in controlling synthesis and release of glucocorticoid. Dopamine also performs a critical role in the progression of PTSD manifestations leading to apathy, anhedonia, impaired attention, and motor function [54].

Numerous studies showed that there is a connection between elevated concentration thyroid hormones (T3) and post-traumatic stress disorder which leads to hypersensitivity to catecholamine and other stress mediators [55].

Neuroanatomy: A meta-investigation of basic MRI studies found a relationship between PTSD with diminished all-out cerebrum mass and size of the hippocampus, insula cortex, and frontal cingulate [56]. Individuals with PTSD have diminished cerebral action in the dorsal and rostral front cingulate cortices and the ventromedial prefrontal cortex, regions connected to the control and guideline of feelings [57]. Amygdala is highly associated in passionate recollection formation, principally thoughts connected to horror and trauma. In case of highly injurious events, the hippocampus, place of memory, is suppressed and this may lead to flashbacks that harm people with PTSD [58].

8 How to Manage PTSD?

For getting better results, combination therapy (psychological and pharmacotherapy) showed more effective strategy for treatment of post-traumatic stress disorder than psychological therapy alone [59].

Counseling: Reviews of literatures approved with strong evidence the efficacy of social and psychological conduct treatments like delayed presentation treatment [60], cognitive behavioral therapy (CBT), and eye movement desensitization and reprocessing (EMDR) in suppressing psychological symptoms of PTSD. Further brief electric psychotherapy (BEP) and narrative exposure therapy (NET) also approved to be effective [61, 62]. A meta-analysis found that EMDR is as effective as CBT in the treatment of post-traumatic stress disorder [63]. Also school-based treatment is significant for kids with PTSD which is proven to be more effective than free clinic therapy [64].

Cognitive behavioral therapy (CBT) is a modern psychotherapy approach advance to make a person with PTSD think and behave in a different pattern away from negative feelings. United State Department of Defense has approved CBT as a viable technique for the treatment of PTSD [65, 66]. In CBT, a person who experiences traumatic events will be able to replace the terrifying and upsetting thoughts with more cheerful ideas to figure out how certain events lead to PTSD-related stress [67, 68].

Recent studies showed that contextually based third-generation behavior therapies give promising results in the treatment of PTSD compared to validated therapies [69]. Another competent method for PTSD management is disclosure therapy which is a kind of cognitive behavioral therapy [70] that plays an important role in

helping people who survive from awful situations to re-experience the memories related to those horrendous events to expedite habituation and rapid recovery. Most of the exposure therapy rehabilitation program depends on conceivable confrontations with the previous awful thoughts and actual trauma reminders' exposure which is supported by clinical evidences [71]. The U.S. Department of Veterans Affairs offered psychological wellness treatment program in delayed introduction treatment and intellectual social treatment [72] for better recovery rate of US veterans with PTSD.

Francine Shapiro developed a modern psychotherapy method for the treatment of PTSD, eye movement desensitization and reprocessing (EMDR) [73], as she noticed that she had a rapid eye movement during thinking in irritating memories, and when she had a full control on her eye movement, her thoughts became less irritating [73]. Shapiro and Maxfield announced a new adaptive information processing theory in 2002 that hypothesized that eye movement control can animate passionate preparing of recalling memories and getting more adaptive information by changing person's memory [74]. EMDR procedures depend on the fact that the psychotherapist starts rapid eye movement while the patient has a spotlight on bad thoughts or particular trauma [75], and then the therapist uses hand movement to guide the patient to move his or her eyes backwards and forwards. EMDR approach resembles cognitive behavior therapy in recalling the traumatic events either by thinking or by talking about it [76].

There were multiple controlled trials of EMDR in grown-ups and children that reported suppression of PTSD symptoms in the short period therapy but the sample size was small so further investigations are required regarding the efficiency of EMDR in decreasing symptoms of PTSD [77]. In kids and young people, an ongoing meta-examination of randomized controlled preliminaries utilizing meta-NUSE to compensate deficit data found that EMDR was comparable to CBT with better effects than placebo [63]. The prosperity of EMDR was greater in female who suffered from sexual abuse compared with other traumatic events such as car accidents and war. Also, it improves re-experience symptoms in children and grown-ups with less effect towards anxiety and depression [75].

Interpersonal psychotherapy involving social support is so important to suppress symptoms of PTSD through seeking backup and help by family and group therapy without the need for exposure therapy [78, 79].

Pharmacotherapy: Many literatures reported that medical treatment is not an enough therapy to suppress symptoms of PTSD while some medications such as fluoxetine, paroxetine, and venlafaxine (a class of antidepressant—inhibits serotonin reuptake selectively) are approved to have a little advantage over placebo in the treatment of PTSD [80].

Numerous studies showed that antidepressant drugs either selective serotonin reuptake inhibitors (SSRIs) or serotonin-norepinephrine reuptake inhibitors (SNRIs) showed promising results to reduce PTSD manifestations [80]. Tricyclic antidepressants showed similar effectiveness with less tolerance [76], so that sertraline, fluoxetine, paroxetine, and venlafaxine are considered as the choice of treatment for PTSD as they provide little to moderate improvement [80]. Other

studies do not recommend benzodiazepines for the treatment of PTSD because there is no clue of benefit and there is high risk of increasing mental and behavioral adverse effects [81] even though some psychiatric experts thought that benzodiazepines are contraindicated in case of acute stress as it can cause dissociation [82] but it could be used with cautions for momentary nervousness and insomnia [83–85]. Benzodiazepines had been proven to suppress acute anxiety with no proof of reversing or even stopping the progression of PTSD; moreover they might accelerate the development of PTSD two to five times [86]. Furthermore, benzodiazepines decrease the potency of psychotherapeutic intervention and may increase progression and chronification of PTSD leading to worsening of the psychotherapy outcome and causing exaggerated depression and substance abuse [86]. Benzodiazepines will lead to dependence, tolerance, and withdrawal symptoms; moreover, persons with PTSD are at great risk of benzodiazepine abuse [87].

Due to better efficacy of other treatment and lesser adverse effects (long-lasting behavioral exposure and cognitive therapy, eye movement processing and desensitization, restricting cognitive therapy, cognitive behavioral trauma-focused therapy, short eclectic psychotherapy, narrative therapy, inoculation stress training, serotonergic antidepressants, adrenergic receptor blockers, antipsychotics, and even antiepileptic), benzodiazepine is considered a contraindicated medication for PTSD [88].

Short-term therapy of glucocorticoids is approved to have a prophylactic effect against neurodegenerative diseases caused by traumatic events leading to PTS. However long-term therapy may promote neurodegeneration [89]. Some studies showed that therapeutic cannabis or its derived product is useful in suppressing psychological symptoms and nightmares of post-traumatic stress disorder [90]. A new face of α-1 adrenoceptor blocker, prazosin, is approved to decrease nightmares in veterans with PTSD [91, 92] and it even reduces overall symptom severity [93].

Regular physical exercise can positively affect patient physical and psychological state. The U.S. National Center for PTSD guides the people who suffer from psychological instability to perform moderate exercise to distract their attention from negative thoughts and irritating feelings [94].

Regarding PTSD in children, the psychotherapists advise the children to play to connect between their inner thoughts and the external world and to gain real experiences that help the child to relive his or her inner terrifying memories [95].

The United States Marine Corps has designed rehabilitation programs to help many war soldiers in Iraq and Afghanistan who experience many emotional and physical awful occasions to help them to readjust to live a regular civilian life. Walter Reed Army Institute of Research (WRAIR) develops imaginary battle program to help traumatized affiliates to avoid PTSD, and Wound Warrior Project provides a partnership with the US Department of Veterans Affairs to develop Warrior Care Network, a national health system for the treatment of PTSD [93].

So, we can conclude that PTSD is a common mental and psychological instability among different kinds of population that needs much interest and professional care of both psychotherapy and pharmacotherapy.

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Neuropharmacology: Looking Forward to the Future

E. N. Siju and G. R. Rajalakshmi

Abstract

Neuropharmacology is a field that utilizes the knowledge about drugs, especially their mechanism of action to develop safe and effective medicines for the cure of a variety of neurological disorders. Increasing number of patients suffering from the diseases all over the world have accounted for billions of dollars in the health-care industry. Thus the demand for effective medicines is increasing globally. Innovative methods are being explored for drug development as there is still no cure or any effective disease-modifying therapy because the existing drugs just aid in managing the symptoms of these diseases. With the help of advancing technology, efforts have been made to understand the molecular structure of receptors and neurotransmitters to synthesize target-specific drugs that would not produce any unwanted side effects. This review tries to discuss different approaches like omics technology, neural engineering, stem cells, gene therapy, and antiviral therapies for the successful understanding of pathology of disease that would lead to drugs that would be specific and free from any unwanted effects.

Keywords

Neuropharmacology · Gene therapy · Neurovirology · Stem cells · Neural engineering · Omics

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1 Introduction

Neuropharmacology is defined as a scientific study of the action of drugs on the central nervous system (CNS) and thereby to have a better understanding of how CNS works. The aim of this discipline is to utilize the knowledge about drugs especially their mechanism of action to develop safe and effective medicines for the cure of a variety of neurological disorders [1] as large number of population suffers from any one of the disorders of the nervous system [2]. These mainly include psychiatric disorders, epilepsy, Alzheimer's disease, Parkinson's disease, substance abuse, alcohol addiction, neurodegenerative diseases, viral infections, and pain [3].

Escalating number of patients who suffer from these neurological and neuropsychiatric diseases all over the world have accounted for billions of dollars in the healthcare industry. They create significant emotional, physical, and economic burden on the affected individuals, their peers, and society [4]. Thus the demand for effective medicines is increasing globally. Innovative methods for the development of medicines for neurological medicines have become the need of an hour as there is still no cure or any effective disease-modifying therapy because the existing drugs just aid in managing the symptoms of these diseases [5].

With the help of advancing technology, efforts have been made to understand the molecular structure of receptors and neurotransmitters to synthesize target-specific drugs that would not produce any unwanted side effects [6].

Some of the major areas that are being explored for the futuristic development of the field of neuropharmacology are gene therapy, neuronal stem cell therapy, neurovirology, multiomics technology, and neural engineering.

2 Gene Therapy

One of the propitious alternative approaches to overcome the unsated medical needs in the field of CNS is the gene therapy [7]. It involves the transmission of a transgene for the treatment of a disease. The transmission is done either by a replacement or by a correction of a defective gene [8]. This is mainly achieved through two methods which involve in vivo and ex vivo gene therapy [9]. In vivo gene therapy is the use of viral or nonviral vectors for the direct insertion of a new gene which also uses recent technology like clustered regularly interspaced palindromic repeats (CRISPR) [10]. Viral vectors use the inherent ability of viruses to infect a cell. The two most common viral vectors used for the neurodegenerative diseases are adeno-associated viruses (AAV) and lentiviruses which can infect both dividing and non-dividing cells [11, 12]. Naked plasmid DNA or their complexes with cationic lipids and polymers which have a localized effect come under the category of nonviral vectors [8]. However ex vivo gene therapy involves the in vitro genetic modification of cells which is proceeded by transplantation of a stable graft to either replace the damaged cell or administer therapeutic proteins in the desired patients [13–15].

Proper designing of clinical trials, usage of surrogate biomarkers, and sophisticated technologies like magnetic resonance imaging (MRI), diffusion tensor imaging (DTI), or positron-emission tomography (PET) have made it possible for gene

Table 1 Reported gene therapy approaches for treatment of neurological diseases [7]

Sl. no.	Disorder	Strategy	Genes	Therapeutic effect	References
1.	Alzheimer's disease (AD)	Vaccine	Aβ cDNA	Decreased Aβ deposition, improved memory and cognition ability, decreased plaque-associated astrocytosis in AD mouse models	Zhang et al. [17]; Mouri et al. [18]
2.	Parkinson's disease (PD)	Dopamine biosynthesis enzyme	AADC	Three phase I clinical trials for AAV2-AADC delivery into bilateral putamen reported alleviation of motor symptoms in moderate and advanced PD patients. Stable and persistent transgene expression for more than 4 years	Eberling et al. [19]; Christine et al. [20]; Muramatsu et al. [21]; Mittermeyer et al. [22]
3.	Huntington's disease (HD)	Mutant HTT knockdown	siRNA	Reduced brain atrophy, neural inclusion, rescue of motor deficits, and increase in survival in HD mouse models	Wang et al. [23]
4.	Amyotrophic lateral sclerosis (ALS)	Mutant SOD1 knockdown	shRNA	Delayed disease onset, expanded life span, enhanced survival of spinal motor neurons, and maintenance of neuromuscular junctions in ALS SOD1 rat model	Thomsen et al. [24]
5.	Stroke	Anti-ischemia induced apoptosis	NAIP	Reduced ischemic damage in rat model	Xu et al. [25]

cDNA complementary DNA, *AADC* aromatic L-amino acid decarboxylase, *AAV* adeno-associated virus, *siRNA* small interfering RNA, *shRNA* short hairpin RNA, *SOD* superoxide dismutase, *NAIP* neuronal apoptosis inhibitory protein

therapy to cross hurdles like complexity and limited accessibility for the cure of diseases [16]. Many strategies have been adapted to treat various neurological diseases by using the gene therapy approach (Table 1).

3 Neurovirology

Neurovirology is defined as an integrative field that connects different areas of virology, clinical/basic neurosciences, molecular biology, and immunology. Apart from the study of viral infections of the nervous system, it also includes methodologies like use of viruses as tracers for investigation of neuroanatomical pathways, as

vectors in gene therapy, and as certain tool that can eliminate definite neural cell populations in developmental anatomy and neuropharmacology [26]. Exploration of the routes by which a viral infection invades the nervous system was first done by Ernest Goodpasture [27]. The role of immunology (cellular and humoral immune responses) to eliminate viral infections or the role of immune responses in enhancing neurological diseases due to complicated viral infections has been investigated by Mike Oldstone and his colleagues [28]. The field of neurovirology has extended rapidly with increasing core of investigators and unique body of knowledge. But in spite of this great potential the translation of the fundamental knowledge for effective treatment of neurological diseases still remains an uphill battle [29]. Challenges that emerge during the designing of clinical trial for neurovirological diseases have been depicted in Fig. 1.

Various approaches can be adapted to overcome these challenges. Classic trial designs when not feasible can be substituted with innovative trial designs like pragmatic clinical trials [30], Bayesian designs [31], and platform trial [32]. *N-of-1* designs can be used as a tool to assess the comparative effectiveness [33]. With advancing clinical trials, a steadfast progression will be made for the treatment of virus-related neurological diseases [29]. Clinical trials for the neurovirological diseases have been tabulated in Table 2.

4 Neuronal Stem Cell Therapy

Animal models have an important role in the various stages of lead identification, lead optimization, and preclinical development as a part of the drug development process. They act as beneficiary tools to investigate the pathogenesis behind the human diseases, identify targets for drug development, and confirm the safety and efficacy of drugs before carrying out clinical trials. But often due to species

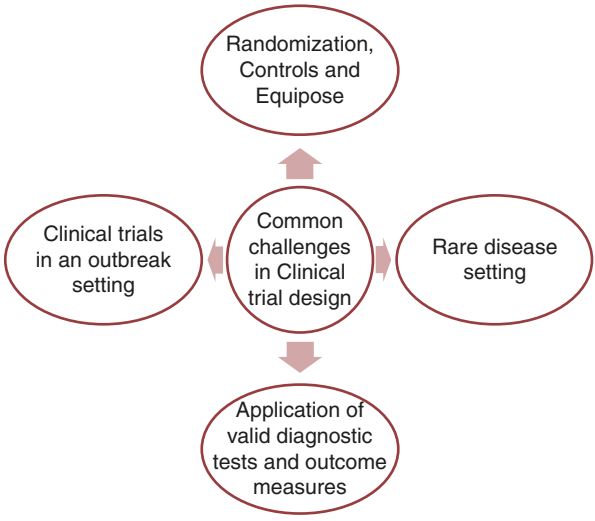

Fig. 1 Challenges in the designing of clinical trials for neurovirological diseases [29]

Table 2 Antiviral trials for fatal neurological diseases

Sl. no	Disease	Treatment	Study type	Phase	References
1.	Herpes simplex virus encephalitis	Dexamethasone	Interventional	3	U.S. National Library of Medicine [34]
		Valacyclovir	Interventional	3	U.S. National Library of Medicine [35]
2.	HIV-associated neurocognitive disorder (HAND)	IN insulin	Interventional	2	U.S. National Library of Medicine [36]
3.	Progressive multifocal leukoencephalopathy	Enfuvirtide	Interventional	2	U.S. National Library of Medicine [37]

variation, results are misinterpreted [38]. Many times there is also lack of consistency in the results when successful and positive preclinical animal studies are carried out at clinical levels [39]. Hence there is an urgent need to find out alternate methods for modeling human diseases. One such approach is the stem cell-based therapy for treatment of several neurological diseases.

Stem cells are defined as immature cells that have sustained self-renewal capacity and the ability to differentiate into a wide variety of cells [40]. In diseases that affect brain and spinal cord, stem cells provide an everlasting source of neuronal cells and glial cells for cell replacement therapies or neuroprotection. Over other strategies, they have an additional benefit of remyelination and neuronal replacement. In neuronal stem cell therapy, isolated stem cells after undergoing predifferentiation/genetic modification in culture that will be transplanted to the diseased are of brain or spinal cord [41].

In addition to the stem cell-based approach, a latest technology called induced pluripotent stem cell (iPSC) technology has become a notable feat and has paved a new way for disease modeling as they are very much suitable for phenotypic based drug screening due to the similarity in the genetic background with the patient [42]. They are prepared by introducing four reprogramming genes *Oct, Sox2, Klf4,* and *c-Myc* into differentiated somatic cells [43, 44]. They have the ability to differentiate into many cell types and thus enable disease modeling. iPSC can be used to study sporadic diseases like AD in which 95% is due to sporadic onset [45, 46]. iPSC technology can also be used in drug discovery for chemical library screening, as well as to check drug toxicity and efficacy [47]. At the same time certain challenges like incomplete cellular reprogramming and genetic and epigenetic changes that occur during lengthy culturing of iPSC and lack of environmental factors important in psychiatric diseases can be a hurdle for successful use of iPSC [48–50]. But with constant advancement in technologies, the pitfalls in iPSC will sure obscure and improve the representation of neuronal diseases in iPSC disease models [51].

Some of the iPSC applications in the treatment of neuronal diseases have been presented in Table 3 [51].

Table 3 Reported iPSC applications in the treatment of neuronal diseases

Sl. no.	Disease	iPSC model	Phenotype discovered
1.	AD	Neurons	Aβ pathology, cell death
2.	PD	DA neurons	Increased apoptosis, reduced neurites, impaired autophagy/impaired mitophagy, irregular DA metabolism, mitochondrial deficits, and oxidative stress
3.	ALS	Sporadic neurons	TDP-43 pathology
4.	HD	Neurons	Increased cell death, sensitivity to stressor glutamate toxicity, reduced electrical firing
5.	Epilepsy	GABAergic neurons	Influence channel currents and activation
6.	SZ	DA neurons	Reduced neurite count, dopamine release, delayed maturation, mitochondria perturbations
7.	ASD	iPSC	Smaller soma size, reduced dendritic spine, decreased glutamatergic synapse, lower Ca^{2+} transient, abnormal excitatory synaptic transmission, fewer excitatory synapses
8.	Depression	iPSC	Deficiencies of BDNF play a significant part

DA dopamine, *TDP* TAR DNA-binding protein, *GABA* gamma-aminobutyric acid, *SZ* schizophrenia, *ASD* autism spectrum disorder, *BDNF* brain-derived neurotrophic factor

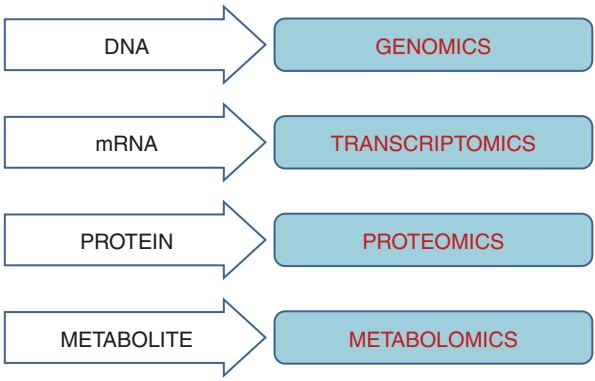

Fig. 2 The omics technologies

5 Multiomics Technology

The new universal method of measuring the cellular molecules such as DNA, RNA, proteins, and intermediary metabolites has been termed as the "omics" technology. The technology has been depicted in Fig. 2 [52]. This method has the ability to characterize all the molecules in a single analysis and thus provide complete information on the biochemical pathways and structural genetic variations among individuals and species. Omics technology covers the fields of genomics, transcriptomics, proteomics, and metabolomics. Pharmaceutical companies are using this approach to

overcome the hurdles that they face in the drug development pipeline that involves biomarker discovery and identification of mediators that are associated with cellular growth, metabolism, and cell death [52].

Developments in the field of genomics and metabolomics have created a strong basis for the identification of genetic and metabolic causes behind neurological disorders of unknown etiology. They help in identifying novel biomarkers and genes involved in the metabolic pathways and hence play a role in establishing the pathogenesis of diseases [53]. Apart from that, investigation of substantial disease-causing mutations and simultaneous metabolomic analysis of patient samples, patient fibroblasts, or mouse models reveal metabolic changes relevant to identified mutations in individual genes and hence provide evidence of disease causality [54–57].

Therefore, progress in the field of omics will revolutionize the disease diagnosis, prognostication, and evolution of novel therapeutics [52].

6 Neural Engineering

Neural engineering or neuroengineering is a collaborative field consisting of engineers, neuroscientists, and clinicians who address the problems related with the complexity of the nervous system. It not only creates an interface between brain and computers but also has the potential to treat diseases like stroke and epilepsy. Therefore it is an interdisciplinary field that connects neuroscience and engineering to investigate and analyze design problems associated with neurological diseases [58].

With advances in neural engineering, bandwidth of areas like brain computer interfaces (BCI) is increasing. BCI helps in understanding how the information transfers and gets processed in the nervous system. It involves better understanding of neurodegenerative diseases and can act as an interface for prosthetics and implants [59] like the use of chronic neural recording devices that control prosthetic limbs and help in the treatment of paralysis [60]. Thus neural engineering is a field with untapped potential that needs to be looked up more that would help in a great way to understand the basics of neurological diseases.

7 Conclusion

With increasing incidence of neurological and neuropsychiatric diseases, it has become essential to create permanent solutions that would not just cure the symptoms but also the disease at its core. For this, it is essential that the pathogenesis of the disease must be understood well that would simplify the tedious drug development process. This can be done by using technologies like “omics” and neural engineering that would give information regarding the basic aspects of the disease. Instead of the existing animal models that do not provide accurate preclinical information about the safety and efficacy of drugs, methods like stem cells and induced pluripotent stem cells can be used for successful screening of drugs. Approaches

like gene therapy and antiviral therapy can be utilized in cases where the conventional treatment strategy fails. Therefore, exploring these new avenues of neuropharmacology would open the doors for advanced treatment options that would help the population suffering from neuronal diseases.

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