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REVIEWS

The Role of Dietary Peptides Gluten and Casein in the Development of Autism Spectrum Disorder: Biochemical Perspectives

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Abstract

This paper examines the role of dietary peptides gluten and casein in modulating brain function in individuals with autism spectrum disorder (ASD) from a biochemical perspective. Neurotransmitter systems and neural networks are crucial for brain function, and alterations at the biochemical level can contribute to the characteristic symptoms and behaviors of ASD. The paper explores how dietary peptides influence neurotransmitter systems and neural networks, highlighting their potential as interventions to improve brain function in ASD. The evidence suggests that dietary peptides can impact neurotransmitter synthesis, release, and receptor interactions, disrupting the balance of neurotransmitter systems and affecting neural network function. The findings underscore the potential of dietary interventions in modulating brain function in ASD and call for further research to elucidate the underlying mechanisms and optimize clinical practice. Considering individual dietary sensitivities and preferences, personalized dietary approaches may be necessary for optimal outcomes. Dietary interventions' timing, duration, and integration with other evidence-based treatments are crucial considerations. Safety considerations and regular monitoring are important to ensure the implementation of dietary interventions safely and effectively.

Keywords Autism spectrum disorder · Dietary peptides · Gluten · Casein · Neurotransmitter systems · Neural networks · Biochemical alterations · Personalized nutrition

Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by challenges in social interaction, communication difficulties, and restricted and repetitive behavior patterns (American Psychiatric Association 2013). It affects individuals across a wide range of cognitive abilities and is typically diagnosed in early childhood. The prevalence of ASD has increased in recent years, with approximately 1 in 36 children aged 8 years diagnosed with ASD, according to estimates from the CDC's Autism and Developmental Disabilities Monitoring (ADDM) Network [1]. The worldwide prevalence of ASD is about 1 in 100 children, 1% approximately [2].

The variety of environmental factors that may affect the early development of the nervous system causes heterogeneity of ASD. Several hypotheses point to dietary factors, GI microbiota composition, and autoimmunity as risk factors for ASD development [3–6]. The potential role of dietary factors in developing and managing ASD has gained increasing interest. Emerging research suggests that dietary

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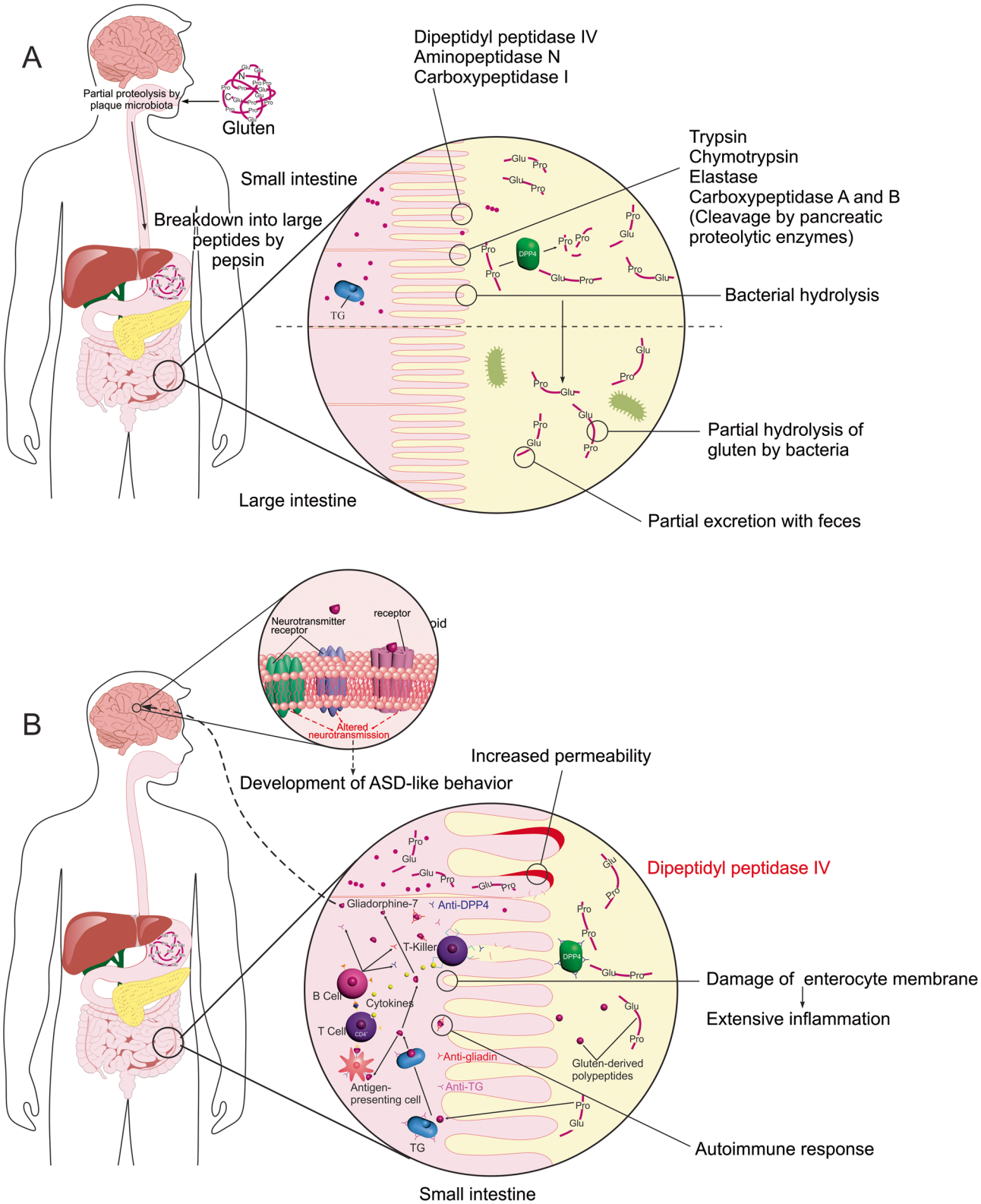

Figure 1A. Physiological digestion and absorption of gluten; B. Hypothetic digestion and absorption of gluten in ASD patients

◂**Fig. 1** Gluten digestion and absorption in physiological conditions and autism spectrum disorder (ASD) with brain alteration. **A** Dietary gluten is partially hydrolyzed in the oral cavity by plaque microbiota; however, the main proteolysis of the gluten happens in the stomach, where it is degraded into large peptides by pepsin. Pancreatic proteolytic enzymes continue the cleavage in the small intestine. Also, certain digestive enzymes, which include dipeptidyl peptidase-4 (DPP4), carboxypeptidase I, and aminopeptidase N, participate in the hydrolysis of peptides rich in proline and glutamine in the small intestine. Another enzyme, transglutaminase (TG), participates in the deamidation activities in the enterocyte. Bacteria partially hydrolyze residual gluten in the large intestine. A part of hydrolyzed gluten is eliminated in the feces. **B**. Pathological alterations in ASD patients begin in the small intestine. The potential hydrolysis of proline and glutamine-containing peptides (such as gliadins and gliadorphins) is reduced by DPP4 deficiency. In ASD patients, the permeability of the small intestine increases, and large peptides pass through the brush border, appear in the enterocyte, and commence inflammatory processes. Accordingly, B cells produce antibodies against big peptides (anti-gliadin), DPP-4 (anti-DPP4), and TG (anti-TG). Gliadorphins and other proteins can cross the intestinal and blood–brain barriers. As a result, they directly alter physiological neurotransmission and bind to opioid receptors

peptides, such as gluten and casein, may influence the symptoms and behaviors associated with ASD by modulating neurotransmitter systems and neural networks in the brain [7]. These peptides are commonly found in wheat and dairy products and can impact brain function and behavior in susceptible individuals [8]. The link between dietary peptides and ASD is based on the hypothesis that some individuals with ASD have difficulties breaking down and processing these peptides, resulting in their accumulation in the body. It is proposed that these accumulated peptides may interact with the brain's neurotransmitter systems, disrupting neural functioning and contributing to the core symptoms of ASD [7]. Understanding the potential mechanisms of this connection is essential for developing effective interventions and treatment strategies.

In this paper, we specifically pay attention to dietary peptides like gluten and casein and their role in modulating brain function in ASD for developing evidence-based nutritional interventions in ASD treatment.

Dietary Peptides in ASD

The role of nutritional and dietary interventions in ASD treatment has been proposed since the last century. Several studies indicate an effect of dietary restrictions and/or supplementations of some vitamins, minerals, amino acids, fatty acids, peptides, probiotics, and prebiotics on ASD symptoms [9–12].

Gluten proteins from wheat, barley, and rye and casein proteins from milk mainly include gliadin, glutenin, and casomorphine, which human proteases cannot completely digest due to the high content of glutamine and proline (Fig. 1A) [13]. The incomplete digestion results in the generation of large peptides with 10–30 amino acid residues, some of which can cross the small intestinal barrier and trigger an inflammatory process. In addition to digestive insufficiency, increased intestinal permeability was observed in children with ASD (Figs. 1B and 2B) [14, 15]. One of the studies showed that approximately 40% of ASD children had increased intestinal permeability, whereas excess permeability was found only in <5% of healthy children [16]. Among the intestinal peptidases, the important one involved in gliadin digestion is dipeptidyl peptidase 4 (DPP4), a cell surface peptidase in the brush border of the intestine, kidney, and liver. Several studies indicate abnormal peptide content (gliadin, casomorphin, diamorphine, deltorphin) in the urine of children with ASD. Many of them were potential substrates of DPP4 [17]. Reichelt et al. suggested the defect of the DPP4 as the cause of the mentioned urine metabolic alterations [18]. Other studies showed high levels of antibodies against the DPP4 and gliadin serum in children with ASD compared to healthy children [19, 20]. It was hypothesized that antibodies against DPP4 bind with it and significantly reduce its activity with the following increase of undigested peptides in the gut. Also, there are antibodies against transglutaminase-2, a damaged deamidation process [21]. Moreover, several dietary peptides can cross the blood–brain barrier and share structural homology with human brain tissue proteins; consequently, due to the cross-reactivity of antibodies, neural tissue may be targeted and damaged [14, 22]. This data suggests the hypothesis of the autoimmune etiology of ASD. The other hypothesis of ASD development is based on the fact that dietary peptides are potent agonists of opioid receptors and can be classified as exorphins (including casomorphins, gliadorphins, and gluteomorphins) (Figs. 1A and 2B). Zioudrou et al. first described the morphine-like activity of peptides isolated from wheat gluten and milk casein [22]. Later, Fukudome and Yoshikawa identified the amino acid sequence of exorphins and their subtypes [23]. At the same time, Panksepp and colleagues formulated a well-known concept, the "Brain Opioid theory of social attachment," postulating the dependence of social behavior on the level of endogenous and exogenous opioid peptides [24]. Some exorphins occur, especially during the digestion of gluten and casein, including casomorphins and gliadorphins. These exorphins can pass the blood–brain barrier (BBB) due to the amino acid special sequence linked to the opioid receptors (Figs. 1A and 2B) [21, 25]. In support of opioid theory, several studies reported increased levels of dietary peptides in the blood, urine, and cerebrospinal fluid of ASD children. Clinical studies with recommended gluten and casein-free diets (GFCF) did find significant differences between treated and control groups. Improvement in some behavioral aspects was detected, but not the core symptoms of ASD [26]. However, because of the small sample size and statistically non-significant results in most clinical research,

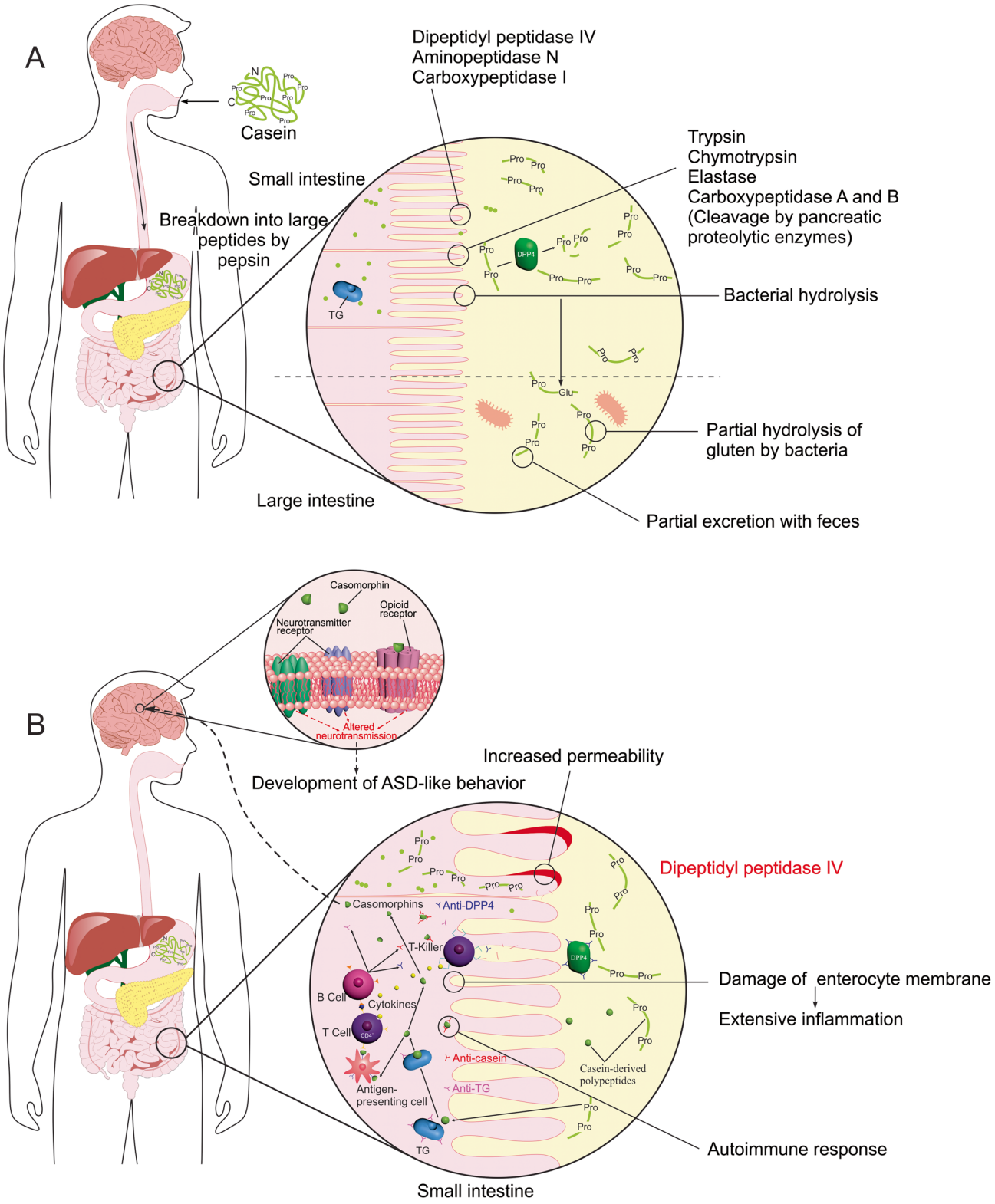

Figure 2A. Physiological digestion and absorption of casein; B. Hypothetic digestion and absorption of casein in ASD patients

◂**Fig. 2** Casein digestion and absorption in physiological conditions and autism spectrum disorder (ASD) with brain alteration. **A** Dietary casein proteolysis happens in the stomach, where pepsin degrades it into large peptides. Pancreatic proteolytic enzymes continue the cleavage in the small intestine, and certain digestive enzymes, which include DPP4, carboxypeptidase I, and aminopeptidase N, participate in the hydrolysis of peptides rich in proline in the small intestine. Another enzyme, TG, participates in the deamidation activities in the enterocyte. Bacteria partially hydrolyze residual casein in the large intestine. A part of hydrolyzed casein is eliminated in the feces. **B** Possible digestion, absorption, and brain alterations mechanism of casein in ASD patients. Pathological alterations in ASD patients begin in the small intestine. The potential hydrolysis of proline-containing peptides (such as casomorphins) is reduced by DPP4 deficiency. In ASD patients, the permeability of the small intestine increases, and large peptides pass through the brush border, appear in the enterocyte, and commence inflammatory processes. Accordingly, B cells produce antibodies against big peptides (anti-casein), DPP4 (anti-DPP4), and TG (anti-TG). Casomorphins and other proteins can cross the intestinal and blood-brain barriers. As a result, they directly alter physiological neurotransmission and bind to opioid receptors

more studies are required to provide evidence to support the general use of the GFCF diets. Some animal studies indicated increased brain-derived neurotrophic factor (BDNF) mRNA in ASD target regions of rats' brains after administration of a δ-opioid receptor agonist [26]. At the same time, it is a well-known fact that the level of BDNF in the serum of ASD children is significantly higher than in the control group [27]. The most critical function of BDNF includes regulation of neurogenesis, synaptogenesis, and brain plasticity, and the involvement of BDNF in the pathogenesis of ASD is proved by many preclinical and clinical studies [26].

On the other side, impaired protein digestion may alter amino acid levels in blood and tissues. Some amino acids represent neurotransmitters (glutamate) or precursors for them (glutamine, tyrosine, tryptophan). Recent studies showed an imbalance in plasma amino acid levels in children with ASD. For instance, increased level of glutamate, aspartate, and taurine was detected in the blood serum of ASD children; meanwhile, the level of glutamine was decreased [28, 29]. The effect of gluten and casein-restricted diet on blood amino acid profile was studied in many studies. Results showed a deficiency of mostly essential amino acids in children with ASD compared to age-matched control groups [28].

Gut-Brain Communication

The gut-brain axis is a complex bidirectional communication system that regulates various physiological functions, including digestion, metabolism, immune responses, and behavior. Recent evidence suggests that disturbances in the gut-brain axis may contribute to the pathogenesis of ASD. The gut microbiota, a diverse community of microorganisms inhabiting the gut, regulate gut-brain communication, and alterations in the gut microbiota composition have been reported in individuals with ASD [30].

Dietary peptides have been shown to modulate the composition and function of the gut microbiota [30]. For example, gluten-derived peptides have been shown to alter the gut microbiota in animal models, increasing pro-inflammatory bacteria and decreasing beneficial bacteria [31]. Similarly, a study on rats found that gluten-free diets reduced inflammation and increased the abundance of beneficial bacteria in the gut (Van den Abbeele et al., 2011). These findings suggest that gluten can significantly impact the gut microbiota and may contribute to the development of gut dysbiosis, which has been linked to various health issues, including inflammatory bowel disease and metabolic disorders [32]. Moreover, several clinical studies examining the gut microbiome of ASD children found higher levels of bacterial taxa with proteolytic activity, such as Clostridium, Lactobacillus, and Propionibacterium [33, 34]. The mentioned dysbiosis may be explained by a high level of undigested proteins entering the colon.

On the other hand, casein-derived peptides have been shown to positively impact gut health by increasing the abundance of beneficial bacteria. The breakdown of casein results in the formation of various bioactive peptides. A study on rats found that administering casein-derived peptides increased the abundance of Bifidobacteria and Lactobacillus species in the gut, which are known to have beneficial effects on gut health [35]. For example, some strains of Bifidobacteria have been shown to produce neurotransmitters such as gamma-aminobutyric acid (GABA) and serotonin, which can positively affect mood and behavior [36, 37]. In addition, the study found that casein-derived peptides reduced inflammation and improved gut barrier function. These findings suggest that casein-derived peptides have a prebiotic effect and may promote gut health. A clinical trial of microbiota transfer therapy showed improved GI and ASD-related symptoms and increased Bifidobacterium and Prevotella in 18 patients after 2 years of treatment [38]. Moreover, digestion and fermentation of dietary peptides result in the production of SCFAs like butyrate, propionate, and acetate, which can cross the blood-brain barrier and affect neural network function (Silva et al., 2020). These SCFAs have modulated gene expression, neuroinflammation, and synaptic plasticity in the brain (Bairamian et al., 2022). Certain dietary peptides can increase the availability of serotonin precursors, potentially enhancing serotonin synthesis and influencing mood and behavior in individuals with ASD (Garbarino et al., 2019).

The gut-brain axis involves multiple neural, endocrine, and immune pathways. The gut microbiota regulates these pathways, and alterations in the gut composition have been shown to affect behavior and brain function. For example, studies in animal models have demonstrated that gut

microbiota dysbiosis can lead to changes in neurotransmitter levels and altered behavior [39]. Additionally, the gut microbiota can modulate the production of cytokines and other immune molecules [40], leading to increased intestinal permeability (Meyer et al., 2023) and affecting brain function and behavior. Several studies indicate that gliadin activates intestinal macrophages and dendritic cells and induces the production of proinflammatory cytokines, such as IL-1b, IL-6, TNF-alfa, and INF-gamma. Gliadin, casein, and other compounds were shown to bind to the lymphocyte and tissue enzyme (CD26) and probably trigger inflammatory and immune reactions in children with ASD [41]. Released cytokines recruit other immune cells and trigger immune response. Moreover, macrophages directly induce the production of reactive oxygen species and cause tissue damage [42, 43].

In addition to the effects on gut microbiota, dietary peptides can directly affect gut-brain communication through their impact on the enteric nervous system (ENS), a complex network of neurons that regulates gastrointestinal function. The ENS communicates bidirectionally with the central nervous system (CNS), called the "second brain." It was shown that gluten-derived peptides have been shown to activate the ENS and increase intestinal motility in animal models, potentially leading to gastrointestinal symptoms commonly observed in individuals with ASD. Similarly, casein-derived peptides have been shown to modulate ENS function, affecting gastrointestinal motility and transit time [44]. Moreover, the ENS can also release neurotransmitters and neuropeptides, affecting brain function and behavior. For example, the neuropeptide vasoactive intestinal peptide (VIP) has been shown to modulate social behavior in animal models [45]. Interestingly, VIP-producing neurons have been found in both the ENS and the CNS [46], highlighting the potential for communication between these systems.

Dietary peptides can also affect gut-brain communication through their effects on the hypothalamic-pituitary-adrenal (HPA) axis, a major stress response system. Animal studies have shown that gluten-derived peptides can activate the HPA axis, increasing cortisol levels and potentially affecting behavior and brain function. On the other hand, casein-derived peptides have been shown to have a calming effect on the HPA axis, potentially leading to reduced stress and anxiety [47].

Challenges of Preclinical and Clinical Studies of ASD

Animal models have been instrumental in autism research, playing a crucial role in investigating the effects of dietary peptides on behavior and brain function. These models provide a valuable framework for exploring the underlying mechanisms behind dietary peptides' impact on ASD. Animal models have also served as platforms for testing potential treatments and interventions related to dietary peptides. Interventions such as gluten- and casein-free diets and/or enzymatic digestion of dietary peptides have shown promising results in animal models.

Several studies have demonstrated that a gluten- and casein-free diet can improve autism-related behaviors in rodents and humans [48]. Rodent models, including mice and rats, have proven particularly effective in studying the behavioral effects of dietary peptides. Studies have demonstrated that rats fed a diet containing gluten and casein exhibit increased repetitive behaviors, decreased social interactions, and altered levels of certain neurotransmitters compared to control rats [49]. Another study showed that mice fed a diet containing gluten and casein exhibited decreased social interaction and increased repetitive behaviors [50]. These findings suggest that dietary peptides may contribute to autism-related behaviors by influencing the brain.

In addition to behavioral studies, animal models have shed light on the neurobiological effects of dietary peptides. For instance, research using rats has shown that a gluten- and casein-free diet leads to changes in the expression of genes related to inflammation and immune function in the brain. These findings suggest that dietary peptides affect immune function in the brain, potentially contributing to the development of autism-related behaviors. Moreover, studies using rodent models have shown that gluten and casein can alter neurotransmitter signaling in the brain. Additionally, studies using models of opioid dysfunction have shown that the opioid system may mediate the effects of dietary peptides on behavior and brain function [51].

While animal models have provided valuable insights into the effects of dietary peptides on ASD, it is important to acknowledge their limitations. These models may need to fully capture the complexity of the disorder in humans, necessitating caution when interpreting findings. Another challenge is the difficulty in assessing and interpreting behavioral outcomes in animals. Behaviors relevant to ASD in humans, such as social interaction and communication, are difficult to measure in animals accurately [52]. This is especially challenging when studying dietary interventions, which may have subtle effects on behavior that are difficult to detect. Therefore, further research is necessary to confirm the relevance of these findings for human health.

Several key challenges are faced in conducting human studies on dietary interventions in individuals with ASD. Challenges in human studies related to dietary interventions in individuals with ASD encompass several methodological aspects. These challenges arise from the complexity of conducting research involving human participants and the unique considerations associated with studying dietary interventions in individuals with ASD. Small sample sizes, lack of control groups, and inconsistent outcome measures are some of the most common methodological limitations

in the field, affecting the reliability and validity of study results. As a result, findings from small studies may not be generalizable to the broader population of individuals with ASD, which can limit their impact on clinical practice. Small sample sizes are a particular concern in ASD research, as the condition affects a small percentage of the population. Recruiting participants can be challenging, and some studies may need more resources to enroll sufficient individuals to achieve statistical power. The lack of control groups is another significant methodological issue in ASD research. Control groups are essential to minimize bias and ensure that any observed effects are not due to chance. Studies that lack control groups make it difficult to determine whether observed changes are due to the intervention or other factors, such as natural development or placebo effects.

Understanding and addressing these challenges are crucial for obtaining reliable and meaningful results.

Recruiting participants willing to comply with the study protocols and adhere to dietary interventions can be difficult due to the requirement of strict dietary restrictions and sensory sensitivities, food selectivity, and routine preferences commonly observed in individuals with ASD [53].

Assessing and accurately measuring dietary intake in individuals with ASD can be challenging. Self-reporting of dietary intake may need to be more reliable, particularly in individuals with communication difficulties or limited self-awareness. Relying on caregiver reports or food diaries introduces subjectivity and potential recall biases. Objective measures, such as biomarker analysis or direct observation of food intake, complement subjective measures, and enhance the validity of dietary assessments. Inconsistent outcome measures are also a significant issue in ASD research. Different studies may use other measures to assess the same outcomes, making it challenging to compare findings across studies. This inconsistency can make it difficult to determine the efficacy of interventions and can limit the generalizability of study results.

ASD is a complex and lifelong condition; its manifestation and response to interventions can evolve. Longitudinal designs and careful planning are necessary to capture changes in ASD-related behaviors and monitor the stability and durability of dietary effects over extended periods. Evaluating the long-term impact of dietary interventions requires comprehensive monitoring and follow-up assessments. Long-term studies pose logistical challenges, including participant retention, data collection, and sustainability of research funding.

Despite several difficulties mentioned above, many clinical studies were conducted to investigate dietary intervention's effect on ASD. One of the first studies was done in a group of 15 patients, seven girls and eight boys, with a mean age of 11.1 and 10.1 years, respectively. All of them fit the criteria for pervasive developmental disorders in DSM-III. A year and 4 years after the intervention behavioral follow-up and urine test was conducted. Behavioral improvements and decreased epileptic seizures for children who suffered from epilepsy were found after the diet [54]. The other important outcome was a normalization of urinary peptides [55, 56]. At the same time, a further research group studied the effect of a gluten-free diet on the behavior and urinary profile of 22 children with ASD, which showed improvement in several behavioral measures without significant changes in urine tests [57]. The main limitations of the described studies non-randomized and open-labeled design. In another study, a randomly selected GFCF diet and control group with ten children in each group participated. Monitoring and testing were conducted before and after 1 year. The diet group's development was much better than the control group's [58]. Another crossover trial where 37 patients were recruited and consumed the GFCF diet for 6 months did not find significant behavioral changes after diet [59]. Studies with a larger sample size (72 patients) showed positive effects on behavior during the 12 months after the dietary intervention and plateau effect in the next 12 months [60]. A randomized controlled single-blind study of dietary intervention in ASD children (67 children with ASD and 50 non-sibling neurotypical controls) showed significant improvement in intellectual ability, improvement in autism symptoms, and developmental age [61]. In the previously described study, the dietary intervention includes a gluten- and casein-free diet and special vitamins/minerals, fatty acids, carnitine, and digestive enzymes supplementation. Despite the number of studies with positive effect of GCFD on autism traits, the main limitation is reappearance of symptoms after the diet break.

Several studies indicate that dietary interventions, such as elimination diets or targeted nutrient supplementation, can impact neural network connectivity and activity in individuals with ASD (Karhu et al., 2020). Functional magnetic resonance imaging (fMRI) studies demonstrate that these interventions can influence brain regions involved in social cognition, language processing, and sensory integration. These changes in neural network activity can potentially improve the behavioral and cognitive symptoms associated with ASD.

By recognizing and addressing these challenges, researchers can enhance the rigor and validity of human studies exploring the effects of dietary interventions in individuals with ASD. Addressing these methodological challenges requires meticulous study design, robust data collection procedures, and tailored participant engagement and support approaches. Strategies such as employing multidisciplinary teams, collaborating with ASD advocacy groups, and leveraging technology for remote data collection and monitoring can help overcome some of these challenges. Moreover, incorporating qualitative measures to gather insights into

participants' experiences and perspectives can provide valuable context and enrich the interpretation of study findings.

Dietary Interventions for Modulating Brain Function in ASD

The potential of dietary peptides to modulate neurotransmitter systems and neural networks offers promising prospects for their use as interventions to improve brain function in individuals with ASD. Understanding how specific dietary approaches can target and modulate brain function is crucial for developing effective treatment strategies. This section delves into the potential utilization of dietary interventions to modulate brain function in ASD.

Due to the heterogeneity of ASD and the diverse genetic, environmental, and physiological factors contributing to the disorder, personalized dietary approaches may be necessary to achieve optimal outcomes. Identifying individual dietary sensitivities and preferences can guide the selection of specific dietary interventions, considering the unique neurobiological profile of each person. This approach may involve eliminating specific peptides, such as gluten or casein, or targeting other dietary factors, such as nutrient deficiencies or imbalances, that may impact brain function.

Identifying and implementing dietary interventions as early as possible is important to optimize their potential benefits. The timing and duration of dietary interventions are critical considerations when aiming to modulate brain function in ASD. Early intervention during critical periods of brain development may have the most significant impact on neural network modulation and symptom improvement.

The duration of dietary interventions is another important factor to consider. Some dietary interventions may require long-term adherence to achieve sustained effects on brain function. Longitudinal studies assessing the long-term impact of dietary interventions in individuals with ASD can provide valuable insights into the optimal duration and maintenance of these interventions.

Furthermore, the effects of dietary interventions may vary depending on individual responses and the specific dietary factors targeted. Monitoring and evaluating the response to dietary interventions over time can help determine their effectiveness and guide adjustments if necessary. Regular assessments of behavioral, cognitive, and physiological outcomes can provide valuable feedback on the progress and impact of the interventions.

Dietary interventions should be considered part of a comprehensive treatment approach for individuals with ASD. They should not be considered standalone therapies, but adjunctive strategies complement other evidence-based interventions. Integrating dietary interventions with behavioral, speech, occupational, and other treatments can provide a multifaceted approach that addresses the diverse needs of individuals with ASD.

Collaboration among healthcare professionals is crucial to ensure the integration of dietary interventions into the overall treatment plan. Close communication between dieticians, physicians, therapists, and other relevant specialists can facilitate a comprehensive and coordinated approach to optimize outcomes for individuals with ASD.

While dietary interventions have shown promise in modulating brain function in ASD, safety considerations should not be overlooked. It is essential to ensure that dietary interventions are implemented safely and do not pose health risks or nutritional deficiencies. Consulting with qualified healthcare professionals, such as registered dieticians or nutritionists, can help develop individualized dietary plans that meet the nutritional needs of individuals with ASD while addressing specific dietary concerns.

Regular monitoring and follow-up assessments are also important to track the individual's progress and detect potential adverse effects. Monitoring may include nutritional assessments, biochemical markers, gastrointestinal function evaluations, and overall health and well-being assessments. This proactive approach helps identify and address issues promptly and ensures dietary interventions' ongoing safety and effectiveness.

Controversies in Dietary Interventions for ASD

Some studies have reported positive effects of dietary interventions on autism symptoms, while others have found no significant benefits (Karhu et al., 2020). This may be partly due to individual differences in response to dietary interventions and the types and severity of autism symptoms.

Conflicting findings regarding the effectiveness of dietary interventions in alleviating autism symptoms have been reported in various studies. While some studies have reported significant improvements, others have found no significant benefits. This can be partly attributed to individual differences in response to dietary interventions and the types and severity of autism symptoms.

One reason for conflicting findings could be the variability in the types of dietary interventions tested across studies. For instance, studies may vary in the kind of elimination diets, supplementation, or probiotics used, which could impact the effectiveness of the intervention. Additionally, some studies may not have accounted for other factors that could affect the results, such as the participants' medication use, sleep patterns, or co-occurring medical conditions.

Another potential factor contributing to conflicting findings is the need for standardized outcome measures. Studies may use different tools to measure autism symptoms, making it difficult to compare results across studies. Furthermore, some measurements may not capture changes in all aspects

of ASD, such as social communication, restricted interests, and repetitive behaviors, which could lead to mixed results.

The heterogeneity of the ASD population could also contribute to the mixed findings. Individuals with ASD may present with varying symptom profiles and levels of severity, which could influence the response to dietary interventions. Additionally, individuals with ASD may have comorbid conditions, such as gastrointestinal problems or nutrient deficiencies, that could affect the effectiveness of the intervention.

Furthermore, the duration and timing of the intervention also play a role in the effectiveness of dietary interventions. Some studies may have had shorter durations or started interventions at different developmental stages, which could impact the outcomes. Moreover, some studies may have tested the effects of dietary interventions on only a single symptom domain, such as gastrointestinal symptoms, without accounting for potential impact on other fields, such as social communication or repetitive behaviors.

It is also important to consider the potential biases that may influence study results. For example, studies that report positive effects of dietary interventions may be more likely to be published. In contrast, studies that report negative findings may not be published or may be less likely to receive funding for follow-up studies. This publication bias could create an overrepresentation of positive results in the literature, making it difficult to estimate the overall effectiveness of dietary interventions for ASD accurately.

There is currently no consensus on the optimal dietary intervention for ASD or the specific types of peptides that may be involved in the disorder's pathogenesis. This lack of consensus makes it difficult for clinicians and caregivers to make informed decisions about dietary interventions.

Despite numerous studies examining the effects of dietary interventions on ASD, there is still a lack of consensus on the optimal approach to treatment. This can be attributed to several factors, including differences in study design, participant characteristics, and dietary intervention types. Additionally, there is an ongoing debate over the specific kinds of peptides involved in the pathogenesis of ASD and whether targeting these peptides through dietary interventions can improve symptoms.

One challenge in reaching a consensus on dietary interventions for ASD is the variability in study design and outcome measures. Some studies have focused on specific dietary interventions, such as gluten- and casein-free, while others have examined a broader range of dietary factors. Additionally, the duration and intensity of the interventions may vary between studies, making it difficult to compare results.

Participant characteristics also contribute to the need for more consensus on dietary interventions. ASD is a highly heterogeneous condition, with significant variability in symptom severity and cognitive functioning. This variability may impact how individuals respond to different dietary interventions. For example, a gluten-free diet may effectively reduce symptoms for some individuals with ASD, while others may not see any significant improvement.

Another factor contributing to the lack of consensus is the ongoing debate over the specific types of peptides involved in ASD. Some researchers have suggested that certain peptides, such as opioid peptides, may contribute to developing ASD symptoms. As a result, dietary interventions aimed at reducing the intake of these peptides, such as gluten-free and casein-free diets, have been proposed as a potential treatment approach. However, few studies have found a significant link between these peptides and ASD symptoms. There is an ongoing debate over the precise mechanisms by which they may impact behavior and cognition in individuals with ASD.

Ethical Considerations in Dietary Interventions for ASD

Ethical concerns exist around using dietary interventions in vulnerable populations, particularly when they involve eliminating diets or restricting food choices. There is also a risk of children being put on restrictive diets without proper monitoring, leading to malnutrition and other health problems.

Dietary interventions have become an increasingly popular treatment option for individuals with ASD but are not without ethical concerns. One of the main ethical issues is the potential harm of eliminating certain foods or food groups from an individual's diet. For instance, restrictive diets may lead to malnutrition, exacerbating health problems and affecting cognitive development. This is especially concerning in the case of children with ASD, who are already vulnerable to a range of developmental and behavioral issues.

Another ethical concern is the potential for restrictive diets to interfere with a child's social and emotional well-being. For example, children with ASD may struggle with eating in social settings, and eliminating certain foods may make them feel even more isolated and excluded from their peers. Similarly, parents may feel pressure to conform to certain dietary restrictions to fit in with other families in the ASD community, even if those restrictions are not based on scientific evidence or are inappropriate for their child's needs.

There is also a risk of exploitation regarding dietary interventions in vulnerable populations like children with ASD. Some unscrupulous practitioners may take advantage of parents' desperation to find effective treatments for their children and recommend expensive or unnecessary dietary interventions. This can put families in a difficult financial position and do more harm than good.

Practitioners and caregivers must approach dietary interventions thoughtfully and informally to address these ethical concerns. This means seeking reliable sources of information on the potential risks and benefits of different diets and consulting with qualified healthcare professionals who can guide proper monitoring and follow-up care. It is also important to consider the child's needs and preferences and any cultural or social factors that may influence their diet.

In addition, research ethics committees should be involved in designing and overseeing studies on dietary interventions in ASD. This can help ensure that research is conducted ethically and responsibly and that the rights and welfare of study participants are protected. Researchers should also be transparent about their funding sources and potential conflicts of interest and should disclose any potential risks or adverse effects associated with the interventions being studied.

Conclusion

This paper explores the role of dietary peptides in modulating brain function in individuals with ASD from a biochemical perspective. Neurotransmitter systems and neural networks play crucial roles in brain function, and alterations at the biochemical level can contribute to the characteristic symptoms and behaviors of ASD. Understanding the impact of dietary peptides on neurotransmitter systems and neural networks is crucial for developing effective interventions to improve brain function in individuals with ASD.

The current evidence suggests that dietary peptides can influence neurotransmitter systems by affecting their synthesis, release, and receptor interactions. Peptides derived from gluten and casein, for example, have been shown to interact with opioid receptors, disrupting the balance of neurotransmitter systems and impacting neural network function. Moreover, dietary peptides can also modulate neural network connectivity and activity patterns, potentially improving behavioral and cognitive symptoms associated with ASD.

Personalized dietary approaches that consider individual dietary sensitivities and preferences may be necessary to achieve optimal outcomes in individuals with ASD. Identifying specific dietary factors, such as gluten or casein, or addressing nutrient deficiencies or imbalances can help tailor dietary interventions to target the unique neurobiological profiles of individuals with ASD.

Timing and duration are important considerations in implementing dietary interventions. Early intervention during critical periods of brain development may have the greatest impact on neural network modulation and symptom improvement. Long-term adherence to dietary interventions may be necessary to achieve sustained effects on brain function.

Although dietary interventions show promise, further research is needed to enhance our understanding of the mechanisms underlying their effects and to determine the optimal approaches for implementing them in clinical practice. Longitudinal studies assessing the long-term impact of dietary interventions and controlled trials comparing different dietary approaches can provide valuable insights into their efficacy, duration, and maintenance requirements.

Integrating dietary interventions with other evidence-based interventions, such as behavioral, speech, and occupational therapies, is crucial for a comprehensive and multifaceted treatment approach for individuals with ASD. Collaboration among healthcare professionals, including dieticians, physicians, therapists, and specialists, is essential to integrate dietary interventions into the treatment plan successfully.

Safety considerations should be considered when implementing dietary interventions. Regular monitoring and follow-up assessments are important to track progress, evaluate effectiveness, and detect potential adverse effects. Consulting with qualified healthcare professionals can help develop individualized dietary plans that meet nutritional needs while addressing specific dietary concerns.

The potential of dietary peptides to modulate neurotransmitter systems and neural networks offers hope for improving brain function in individuals with ASD. By furthering our understanding of the biochemical mechanisms underlying these effects and conducting rigorous research, we can develop evidence-based dietary interventions that contribute to the comprehensive treatment of individuals with ASD, ultimately improving their quality of life.

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Declarations

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Consent to Participate Not applicable.

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