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The role of glutamine in supporting gut health and neuropsychiatric factors

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ABSTRACT

Recent research has shown that the amino acid glutamine can positively affect gut health by supporting the gut microbiome, gut mucosal wall integrity, and by modulating inflammatory responses. As modulated by the vagus nerve, via the enteric nervous system, the gut-brain connection can impact the brain's neurochemical environment. Poor gut health can disrupt the balance of neurotransmitters, which can result in neuropsychiatric based conditions such as depression. Glutamine supplementation may provide significant adjunctive nutritional support in cases of depression by promoting proper gut health and function.

1. Introduction

Despite the generally high standard of living in the U.S., diet and lifestyle choices have exerted an overwhelmingly negative effect on both gut and overall health. This issue can, at least in part, be attributed to the prevalence of processed foods high in sugars and to the lack of healthy fiber and whole foods in most diets. This combination negatively impacts the balance of the gut microbiome or intestinal flora. Processed foods tend to increase both gut and systemic inflammation and may damage the gastrointestinal tract via several pathways, increasing gut permeability [1].

A growing body of research has shown a physiological connection between gut health, and the neurochemical balance in the brain as modulated by the enteric nervous system [2]. This connection makes understanding the increased use of prescribed medications for depression and other neuropsychiatric disorders, potentially less enigmatic.

An unhealthy gut may potentially lead to suboptimal brain function and even neuropsychiatric conditions. Research on the amino acid glutamine, the most abundant amino acid in the human body, has shown it to be a promising nutritional adjunct for mitigating gut damage, increasing gut health, which may indirectly, but positively, support the neurochemical environment in the brain. This review summarizes the current state of understanding of this topic. It should be noted that this proposition is novel and will require further research and substantiation.

2. Claim

Glutamine is a non-essential amino acid as it can be synthesized in the body. However, when in high demand during intense periods of stress either from illness, disease or lifestyle stress, it can be considered conditionally essential and must be further obtained from the diet. It is the most abundant free amino acid in the bloodstream and is an important substrate for intestinal cells. Glutamine can effectively enhance the function, proliferation, and life cycle of enterocytes in the small intestine.

The consistent consumption of low-quality, high carbohydrate processed foods low in fiber, can stress and potentially harm the gut. Considering that the intestines depend on glutamine more than other organs, stress on the gut will require much of the glutamine circulating in the body. Glutamine is recruited to maintain gut integrity, however once glutamine stores are depleted, the intestinal lining is left even

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more vulnerable to cumulative damage [3].

Glutamine directly supports gut health and function in three key aspects: 1) it has a positive impact on sustaining the balance of the gut microbiome, 2) it increases the expression of tight junction proteins and the integrity of the intestinal lining, and 3) it helps to minimize the inflammatory response in situations of gut mucosal irritation.

As modulated via the tenth cranial or vagus nerve, gut function directly impacts neurotransmitter balance. Unhealthy gut permeability, inflammation, and a suboptimal microbiome have been linked to depression. As the gut becomes inflamed, there is a direct effect on brain health and neurotransmitter balance. Glutamine may have an indirect role in supporting an optimal neuropsychiatric environment by protecting the intestinal lining from damage and chronic inflammation on the below way:

Glutamine → Gut health → Enteric nervous system → Neuropsychiatric environment

3. Incidence and Mechanisms of Gut Dysfunction

A growing body of literatures suggest that gut health has a significant correlation with immune system function and overall health. Current studies are expanding and deepening the understanding of this relationship.

One of the most important aspects of this connection is the gut microbiome. The human gut microbiome consists of strictly anaerobic bacteria that outnumber the host's cells by up to ten times. The microbiome is influential in major functions of the body, one of which is in metabolic processes that humans cannot perform independently. Microbiota are capable of synthesizing vitamins and amino acids and are essential for the digestion of different forms of carbohydrates. This makes the microbiome key for the efficient utilization of energy [4]. Metabolic disease has recently been shown to stem, at least partially, from dysbiosis of the gut microbiome [4,5]. The altered balance of the microbiome may also have implications in the pathology of type 2 diabetes. Considering that 65% of the nation's population is overweight and that 33% of the population is obese, gut dysbiosis may have very serious implications [6]. Additionally, intestinal bacteria improve immunity by preventing pathogens from attaching to the intestinal lining and infecting the body. People with chronic allergies and immune system problems have been shown to have a lacking or unbalanced gut microbiome [7].

The intestinal epithelium is a single layer of cells that line the inside of the gastrointestinal tract. This epithelial barrier provides protection from invading pathogens, though it is the second line of defense. The intestinal epithelium's ability to protect the body from foreign particles is predicated on the formation of intercellular tight junctions. Tight junctions are what make the intestinal epithelium selectively permeable to different substrates [8-10]. Unfortunately, the integrity of this protective layer is susceptible to damage caused by foods, inflammatory peptides such as cytokines, and stress. A. Fasono [11] has done extensive research on this problem, which is commonly referred to as "leaky gut." Many of his studies have focused on a protein called zonulin [12]. Zonulin is known to be one of the few if not only physiological regulators of intestinal tight junction permeability. It has the potential to disassemble intestinal epithelium, which compromises the selective and protective nature of the gut. Zonulin becomes especially relevant in foods that contain gluten. Glutens increase the amount of zonulin within the system, which causes the breakdown of tight junctions, leading to a leaky gut. Leaky gut permeability has a wide range of implications in the pathology of metabolic disease, systemic inflammation, autoimmune diseases, and tumor-related diseases [12].

Lifestyle choices and circumstances can directly influence gut health. Diets consisting of highly processed foods, refined sugars, saturated fat, and minimal healthy fatty acids and antioxidants can encourage chronic inflammation that will affect the microbiome. Foods with a high glycemic index cause a rapid change in blood glucose levels and insulin levels that have been shown to produce free radicals and cytokines in the body. This concept has become especially important for diagnosing and treating symptoms of depression [13-15]. Insufficient intake of the prebiotics found in foods can possibly leave the gut susceptible to inflammatory processes. Prebiotics are nondigestible food derivatives that support the proliferation of bacterial colonies in the microbiome of the gut [16]. Probiotic supplementation has been shown to potentially support immune system function by increasing the diversity of the healthy gut bacteria [16,17]. While probiotics and prebiotics can go beyond gut protection and the reduction of inflammation, they are both lacking in most diets.

Other factors like stress and medications can also jeopardize gut function. High stress associated with higher cortisol levels have been shown to increase oxidative stress and the production of cytokines, which in turn stresses the gut, brain, and immune system. Abnormal

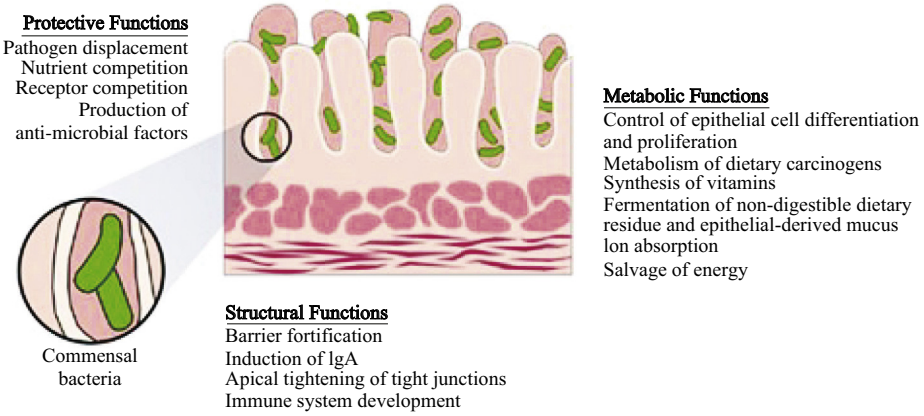

Fig. 1 Brain–gut–microbe communication in health and disease. Retrieved from S. Grenham, G. Clarke, J. Cryan, et al. (2011, November 18). https://www.frontiersin.org/articles/10.3389/fphys.2011.00094/full

cortisol levels can cause immunosuppression and can affect the bacterial balance of the gut by influencing the expression and prevalence of bacterial strains [13]. Prescription antibiotics can be important for treating illnesses and infections, however, the healthy bacterial colonies that live in the gut are also compromised, which can counterintuitively suppress the immune system and leave the gut epithelia exposed in the process. Non-steroidal anti-inflammatory (NSAIDS) and prescription painkillers can injure the gastrointestinal tract. These medications primarily inhibit the cyclooxygenase enzyme. Cyclooxygenase is found in the epithelial cells of the gastrointestinal tract and is what produces mucosal prostaglandins. Mucous secretions from the gut epithelium are what protect the lining from acids and pathogens. Inhibition of cyclooxygenase has been shown to correlate with the development of ulcers and inflammatory bowel issues, as the protective prostaglandins that form and maintain the mucous layer cannot be synthesized [18].

Alcohol consumption can also put optimal gut health at risk. Alcohol promotes the proliferation of unhealthy gut bacteria and can cause an accumulation of endotoxins and acetaldehyde within the gut. Acetaldehyde can increase gut permeability, which then allows the endotoxins to enter and circulate to other parts of the body. Additionally, the nitrous oxide that is created as a byproduct of alcohol consumption can break down the proteins that are important for the cell structure of healthy gut bacteria [19].

4. Mechanism of the Gut and Neuropsychiatric Relationship

The gut-brain axis can be understood in part by the functional relationship between the central nervous system (CNS) and the enteric nervous system. The key links in this connection are the paired tenth cranial, or vagus nerves. These nerves, often referred to in singular form, interface with the parasympathetic control of the digestive tract, as well as the heart and lungs. Neurons that travel from the CNS have been shown to synapse directly on the bacterial colonies in the gut, meaning that the microbiome is directly influenced by brain activity and neurochemistry [2,5]. Circumstances that cause a stress response in the body can change or upset the neurochemical equilibrium in the brain via the hypothalamus and pituitary, which may cause microbial dysbiosis in the gut.

While the efferent connections of the vagus nerve that lead from the CNS to the gut allow the brain to modulate gut function, the afferent connections of the vagus nerve are what allow the gut to directly influence brain activity. An inflamed gut that is lacking healthy strains of bacteria has been shown to alter the brain's neurotransmitter balance. Neurotransmitters like serotonin, acetylcholine, histamine, GABA, and glutamate may all be influenced by gut health and activity. The gut can also influence neuroendocrine activity through the hypothalamus. Secretions produced by the gut stimulate hypothalamic activity that can lead to the production of the adrenocorticotropic hormone (ACTH). When the gut is unhealthy, overproduction of ACTH can then cause hyperactivity of the adrenal cortex and the adrenal medulla. The result is the hypersecretion of catecholamines and glucocorticoids which may favor an environment conducive to the propagation of pathogens and may cause a continuous low-grade stress response in the body [4,5].

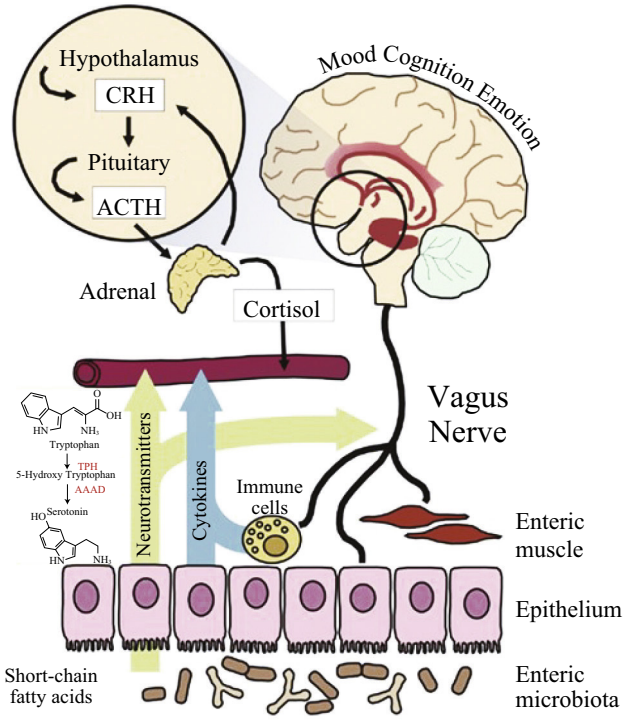

Fig. 2 Brain–gut–microbe communication in health and disease. Retrieved from S. Grenham, G. Clarke, J. Cryan, et al. (2011, November 18) https://www.frontiersin.org/articles/10.3389/fphys.2011.00094/full

5. Amino Acid Supplementation and the Neuropsychiatric Environment

Anxiety and depression disorders commonly affect the hypothalamic-pituitary-adrenal axis. As discussed above, factors like systemic inflammation and external circumstances can increase hypothalamic activity, even cause plastic changes, which may cause a continuous low-grade stress response throughout the systems of the body [20]. The hypothalamus is located within the diencephalon and functions, in part, to provide instructions for the pituitary gland, a major control center of the endocrine system. The pituitary gland functions to synthesize or store important hormones according to the feedback it receives from the hypothalamus. As such, a continued stress response in the body can lead to the exhaustion or disequilibrium of neurotransmitter balance. The monoamine hypothesis states that depressive disorders are often caused by a deficiency in monoamines, like dopamine and serotonin, or in the components that make them [21].

In *The neuroscience of clinical psychiatry: the pathophysiology of behavior and mental illness*, Higgins and George [21] discussed that all monoamines are synthesized from aromatic amino acids, including tyrosine, threonine, and tryptophan. Tyrosine has been the subject of considerable research, as it is the precursor to all neurotransmitters, including monoamines, and therefore catecholamines. While catecholamines are associated with the stress response, tyrosine does not increase catecholamine release as tyrosine supplementation only replenishes exhausted levels of neurotransmitters. Tyrosine also functions as a precursor to form the neurotransmitters that are so commonly associated with psychiatric disorders, dopamine and serotonin [22].

Gamma-aminobutyric acid, or GABA, is the primary inhibitory neurotransmitter in the brain. That is, it induces hyperpolarization in neurons, diminishing the likelihood of the propagation of action potentials. Neuronal inhibition may be important for reducing the hyperactivity of areas in the brain that are associated with fear, anxiety, and stress, for example, the hypothalamus and limbic lobe [23]. The GABA hypothesis explains that symptoms of depression and anxiety stem from the lack of the appropriate amount of GABA receptors. A 2007 study highlighted the overlapping neurological and neuropsychiatric issues between anxiety and depression. It was shown that GABA supplementation may be a useful treatment modality, particularly when combined with other antidepressants or benzodiazepines. Patient prognosis was measurably more optimistic when GABA use was combined with other prescribed medications. Anecdotally, a significant amount of endogenous GABA is synthesized in the gut, which connects the importance of optimal gut health and function with neuropsychiatric health [24].

Additionally, it should be noted that glutamine is a fundamental precursor to the most prevalent neurotransmitters, GABA and glutamate. Studies have shown that glutamine supplementation can affect cognitive functioning by influencing the amount of GABA and glutamate that is available to be utilized [25].

6. Glutamine, Gut Health, and Neuropsychiatric Factors

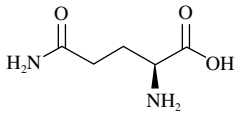

Fig. 3 Chemical structure of glutamine.

Glutamine may be most commonly known in the field of sports nutrition for supporting skeletal muscle development and muscle protein synthesis. However, as the most prevalent amino acid in the body, glutamine supplementation has been shown to be important in supporting recovery and immune system function in ICU patients [26]. Additionally, new research suggests that glutamine affects the gut in three significant ways: 1) it has a positive impact in sustaining the balance of the microbiome, 2) it increases the expression of tight junction proteins and the integrity of the intestinal lining, and 3) it helps to minimize the inflammatory response in situations of gut mucosal irritation.

Oral glutamine supplementation has shown a positive effect on the composition of the microbiome. A 2015 study randomly assigned either glutamine supplementation or alanine supplementation to a group of 33 obese individuals. A common biomarker for obesity is the ratio of Firmicutes to Bacteroidetes found within the gut. A high ratio of Firmicutes to Bacteroidetes strongly correlates to obesity and metabolic issues. After 14 days of supplementation, the glutamine group showed a significantly reduced Firmicutes to Bacteroidetes ratio, a result that has also been reflected in weight loss regimens. Glutamine was shown to positively influence the genetic expression of these different strains, which accounts for the change in the strain ratios [27]. An optimized gut microbiome is more likely to perform neurotransmitter synthesis and other functions more efficiently.

A 2017 review discussed the different ways in which glutamine can support intestinal function. The life cycle of intestinal mucosa cells is relatively brief, as they are replaced roughly every five days. Glutamine has been shown to activate protein kinases that facilitate intestinal stem cell differentiation and proliferation into enterocytes, goblet cells, and more. Glutamine increases gut enterocyte proliferation by maximizing the effects of growth factors like epidermal growth factor and insulin-like growth factor-I. These growth factors are responsible for influencing the DNA, RNA, protein synthesis, and replication of gut mucosal cells [9].

Tight junctions are protein structures that form intercellular connections in the gastrointestinal wall. Tight junctions largely determine what substrates are to be absorbed, as well as block the entry of pathogens. Disruption of tight junction functionality results in increased gut permeability, allowing larger proteins to leak into the bloodstream, which may initiate a systemic inflammatory response. As discussed above, lifestyle choices and dietary habits can affect the permeability of intestinal tight junctions. Glutamine may control the expression of tight junction proteins. This was confirmed by using multiple cell line cultures. Cells deprived of glutamine were shown to have reduced expression of proteins used for tight junction formation as well as increased permeability. However, this was reversed by introducing higher glutamine levels via supplementation. Considering that glutamine activates and maintains tight junction proteins through phosphorylation, glutamine supplementation may be a viable form of nutritional support when treating for celiac disease and inflammatory bowel disease [9,28].

Glutamine may also limit the inflammatory pathways involved in Crohn's disease or ulcerative colitis. Inflammatory responses cause a cascade effect, resulting in the production of proinflammatory cytokines, which stimulates the inflammatory response. Glutamine may inhibit the initiation of this process by increasing the activity of heat shock proteins. These proteins reduce the expression of the NF-κB transcription factor, which stimulates genes that are associated with inflammatory and immune responses. Short term glutamine supplementation showed a significant reduction in the transcription factors that support NF-κB. Additionally, glutamine also inhibits the activation of other inflammatory transcription factors, known as STAT proteins. Nitric oxide is also a necessary component of inflammation; however, it can be harmful if it is synthesized in excess. Glutamine has been shown to normalize nitric oxide production, which can reduce high levels of inflammation [9].

Considering the versatile impacts that glutamine has on the gut via the three main mechanisms discussed above, it may be reasonable to hypothesize that glutamine supplementation may optimize neurochemical balances by way of the gut-brain axis.

7. Discussion

In 2017, the Center for Disease Control reported that one in eight people in the U.S. population, over age 12, use antidepressant medication. This usage is up 65% in the last 15 years [29]. All antidepressant prescription medications potentially have significant undesirable side effects. With no apparent external factors driving this trend such as war, famine, economic or governmental collapse, as well as a high standard of living, other factors are likely to play a significant causative role. Coincidentally, the increase in antidepressant usage has

occurred simultaneously with an escalation in the incidences of obesity, diabetes, and processed food consumption. In this scenario, the health of the gut microbiome is at risk.

To further substantiate the hypothesis that the gut microbiome impacts the neuropsychiatric environment, and may be a causal factor in depression, numerous studies have documented the connection between antibiotic use and depression. Most notable in this relationship may be levofloxacin and ciprofloxacin, both belonging to the fluoroquinolone antibiotic family. A medical records survey in the United Kingdom found that a single course of quinolones was linked to a 25% higher risk of depression. A single course of penicillin showed a 23% higher risk and multiple courses more than doubled the risk of depression [30]. Serotonin, a neurotransmitter implicated in depression, has been shown to be an important component for gut-brain communication. A recent 2017 study confirmed that antibiotics negatively affect serotonin production in the body, which can lead to symptoms of depression [31].

Given the intense marketing of processed foods and the personal choices commonly made in terms of dietary and lifestyle habits, there has typically been low compliance and minimal success in changing a subject's diet from processed foods to more whole foods. In this situation, a simple, inexpensive and accessible nutritional supplement such as glutamine may offset some of the damage, both structurally and functionally, and should be explored in more detail. While glutamine can be found in relatively high concentrations in plant and animal proteins, using a glutamine supplement may be more efficient. For example, one would have to consume 15 oz. of beef, one of the best natural sources of the amino acid, to get just 5 g of glutamine [32]. The aforementioned studies that observed the effects of glutamine supplementation used doses of between 15 and 30 g. Human and animal models have proven that oral glutamine supplementation can be considered safe, though biochemical assessment prior to regimented use may be ideal [32].

Further research is warranted to explore the efficacy of glutamine adjunct to, or in lieu of, prescription medication in the treatment of depression. This would include studies with larger study groups, with longer use and with those suffering from recurrent episodes of depression as well as studies which could explore using glutamine in concert with other supportive amino acids, such as GABA and tyrosine, in an effort to restore neurotransmitter equilibrium.

8. Conclusion

Gut health, in terms of structure and function, is increasingly becoming recognized for its critical, foundational role in overall health, immune system function, levels of systemic inflammation and now, in the context of this paper, as a critical factor in maintaining neuropsychiatric balance. Disruption of this balance is highly correlated with depression and other psychiatric conditions.

Despite common societal insults to gut health via dietary habits which include low fiber, high carbohydrate processed foods, and lifestyle stresses, glutamine supplementation may provide an efficacious, economical and widely available way of restoring and maintaining gut health. Glutamine supplementation research suggesting benefits on the gut microbiome, gut integrity and inflammation, and the possible indirect effect on supporting a more optimal neuropsychiatric environment may merit scrutiny by practitioners in the fields of both gastroenterology and neuropsychiatry. Glutamine may offer a powerful adjunct as direct support for fundamental health maintenance, immune system function, microbiome balance, gut function and lower levels of gut inflammation as well as indirect nutritional support when addressing neuropsychiatric conditions.

Conflict of Interest

The authors confirm that there are no known conflicts of interest associated with this publication and there has been no financial support for this work that could have influenced its outcome.

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