Review Article

Neuropsychobiology

Neuropsychobiology 2020;79:13–19
DOI: 10.1159/000496294

Received: June 30, 2018
Accepted after revision: December 18, 2018
Published online: January 30, 2019

Could Dietary Glutamate Play a Role in Psychiatric Distress?

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Keywords
Diet · Fibromyalgia · Glutamate · Monosodium glutamate · Pain · Psychiatric symptoms

Abstract
Glutamate is an amino acid that functions as an excitatory neurotransmitter. It has also been associated with somatic and psychiatric distress and is implicated in the pathophysiology of psychiatric disorders such as schizophrenia. Ingestion of dietary glutamate, such as monosodium glutamate (MSG), has been mechanistically linked with greater distress among patients with chronic pain conditions, though findings have been equivocal. Preliminary research suggests that an MSG-restricted diet confers beneficial effects on somatic symptoms and well-being for some individuals with chronic pain conditions. In addition to associations with somatic distress, glutamate has been associated with the onset and progression of psychiatric symptoms. Thus, the role of dietary glutamate in psychiatric distress represents an underdeveloped and potentially important area for future research aimed at clarifying pathophysiological mechanisms and identifying targets for dietary intervention in psychiatric illnesses.

Overview

Glutamate functions primarily as an excitatory neurotransmitter in the central nervous system. However, more recent data has associated glutamate with somatic forms of distress such as pain intensity, pain sensitivity, and pain tolerance (for a review, see Cairns [1]). More recently, glutamate has also been associated with psychiatric distress, as accumulating research implicates glutamate in the pathophysiology of severe, chronic psychiatric disorders, including psychotic, anxiety, and depression disorders [2–5].

While glutamate is an endogenous amino acid, the bound form can also be obtained from dietary sources, such as those found in meat, and the free form can be found in food additives like monosodium glutamate (MSG) as well as soy sauce and parmesan cheese [6, 7]. Although the US Food and Drug Administration (FDA) has designated MSG as "generally recognized as safe" [8], dietary intake of MSG has been associated with somatic distress among both healthy controls and individuals with chronic pain conditions. However, less is known about the relationship between dietary MSG and psychiatric distress.

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The purpose of this article is to provide a brief review of associations between glutamate and distress (both somatic and psychiatric), dietary intake of MSG and somatic distress, and suggest future directions for research on dietary MSG and psychiatric distress.

Glutamate and Distress

In the context of diet, glutamate is an amino acid that also functions as an excitatory neurotransmitter. Dietary sources of glutamate include bound forms such as those found in meat and free forms which can be supplied through consumption of flavor-enhancing food additives like MSG as well as soy sauce and parmesan cheese [6, 7]. Dietary glutamate is absorbed from the gut and metabolized by mucosal cells [9] into metabolites such as glutamic acid, which then transforms into alanine in the intestinal mucosal cells and into glucose and lactate in the liver [10]. Estimates of daily MSG intake vary by region and have been suggested to be approximately 0.5 g per day in the United States [11], though this is likely an underestimate of the actual amounts consumed as MSG content in processed foods is proprietary information [12]. Notably, it has been suggested that the average daily consumption of glutamate from all dietary sources is approximately 12 g per day [13, 14], while MSG intake may be closer to 10 g per day [15, 16]. Previous calculations have shown that a man who weighs 70 kg has a daily intake of 28 g of glutamic acid derived from diet and the breakdown of gut proteins [9]. To illustrate this, a single fast-food meal of a hamburger and milkshake contains approximately 120 mg/kg of glutamate while 100 g (approximately 1.1 cups) of grated parmesan cheese contains 1,680 mg of MSG [10, 11].

Somatic Distress

Despite variability in estimated daily MSG consumption, a well-documented body of evidence shows a relationship between dietary glutamate, particularly MSG, and experiences of somatic distress, as symptoms associated with acute ingestion of MSG include muscle tightness, headache, arrhythmias, general weakness, and tachycardia (for a review, see Cairns [1]). However, recent research on the somatic effects of dietary MSG has increasingly focused on pain-related outcomes and has aimed at mechanistically linking dietary MSG with various factors contributing to pain. Specifically, MSG has been associated with increased pain sensitivity and pain experience, although findings in the literature are inconsistent [1]. Among healthy controls, it has been shown that single oral doses of 150 mg/kg of MSG acutely increase circulating concentrations of plasma glutamate by 700–800% [17]. An individual who weighs 70 kg would therefore consume 10.5 g (0.1 cups) of grated parmesan cheese to obtain 150 mg/kg of dietary MSG. These elevations in levels of glutamate following MSG ingestion have been suggested to account for dietary MSG-associated increases in somatic distress, including greater pain [18]. Research linking pain to glutamate concentrations peripherally has recently been extended to central processes. Specifically, using proton magnetic resonance spectroscopy (MRS), acute pain has been associated with increased glutamate concentrations (up to 18%) in various brain regions among healthy controls [19, 20], although associations with dietary MSG are underdeveloped.

Importantly, however, findings on the association between MSG ingestion and pain are equivocal and suggest important areas for consideration to clarify associations between MSG and pain. For instance, findings from a large multi-center double-blind, placebo-controlled study implicate a dose-response relationship between MSG and an individual's perceptions regarding their sensitivity to MSG [13]. Specifically, the study's findings demonstrated that, among participants who perceive themselves to be sensitive to MSG, large doses of MSG administered without food was associated with greater pain symptoms compared with placebo. Interestingly, the authors did not demonstrate this association when MSG was given with food, which may be because foods that supply metabolizable carbohydrates decrease levels of peak plasma glutamate [9]. In addition to concomitant food consumption, preliminary research has suggested that the absence of specific nutrients may alter glutamate metabolism. Specifically, vitamin B_6 deficiency has been associated with elevated serum glutamate and delayed glutamate clearance in animal models [9]. Follow-up research is needed to test whether these findings can be extended to humans. Indeed, research regarding patterns of association between specific dietary components of concomitant food consumption and metabolism of glutamate and its subsequent effects remains underdeveloped. This gap in research may be attributable to the fact that dietary sources of glutamate such as MSG are almost exclusively consumed with other food in everyday life. Altogether, in addition to MSG dose, perceptions regarding MSG sensitivity, concomitant food intake with MSG ingestion, and deficiencies in vitamin B_6, variability in symptom reports following orally ingested MSG may be

attributable to individual differences in first-pass metabolism and circulating levels of glutamate [21].

While the acute effects of MSG following a single dose of orally ingested MSG have been widely studied, accumulating research involving repeated administration of MSG points to potentially chronic effects of glutamate on somatic distress. For instance, in a study of healthy young adults, daily MSG intake over 5 days induced masseter muscle sensitization and increased reports of headache [18]. The authors additionally demonstrated that salivary glutamate concentrations increased over the 5-day period, suggesting that repeated increases in MSG intake contribute to a build-up of circulating glutamate, which in turn may explain observed reports of increased pain and pain sensitivity.

These results may therefore be very important for individuals with chronic pain conditions such as migraine, headache, and fibromyalgia, as research has demonstrated elevated levels of glutamate both peripherally, in the blood and saliva [21–23] as well as centrally, in cerebrospinal fluid [24] and specific regions of the brain [25, 26]. Together, these findings suggest mechanisms linking both central and peripheral glutamate dysregulation with chronic pain conditions and implicate a low MSG diet as a potential area for intervention among chronic pain populations. Indeed, dietary restriction of MSG may produce beneficial effects for symptoms associated with chronic pain conditions.

Among patients with fibromyalgia, a case series of 4 patients provided the first evidence demonstrating that eliminating dietary intake of MSG decreased symptoms of fibromyalgia, including pain reduction [27]. Furthermore, in a separate study among patients with fibromyalgia that utilized a double-blind, placebo-controlled design involving MSG restriction and subsequent challenge, reductions in dietary MSG were shown to have beneficial effects on pain for a subsample of participants [28]. Specifically, 84% of participants reported clinically significant symptom remission, including decreased pain and increased quality of life. When these participants subsequently underwent an MSG challenge in which dietary MSG was administered daily over a 3-day period, their symptoms returned. Additionally, when contacted 2 months following study completion, almost all participants who benefitted from the restricted MSG diet reported that they continued to restrict MSG intake and that their symptoms returned only when accidentally consuming MSG. However, in a separate study comprising 72 patients with fibromyalgia, decreased pain was associated with dietary MSG restriction after 1 month but not after 2 or 3 months [29]. These temporal differences are surprising given results from the preceding [28] study and may be attributable to issues such as participant noncompliance with the restricted diet (and corresponding lack of compliance assessments for verification), participant-specific concerns (e.g., potential changes in medical conditions and/or treatments) which the authors did not report or statistically control for, study design limitations (i.e., not blinded and no MSG challenge), and/or a lack of adequate statistical power. Therefore, results from these studies suggest that dietary MSG intake may be associated with increased somatic distress and decreased well-being. Additionally, the participants' post-study dietary compliance in the study by Holton et al. [28] provides evidence for the feasibility of dietary restrictions among a chronic pain population. Given the comorbidity between chronic pain conditions and psychiatric disorders, particularly depression [30], future studies examining the effects of these dietary interventions on psychiatric symptoms is warranted.

Psychiatric Distress

In addition to associations between glutamate and somatic distress such as pain, pain sensitivity, physical weakness, and fibromyalgia symptoms, glutamate has also been associated with psychiatric distress. Specifically, central system glutamate dysregulation has been associated with symptoms of anxiety, posttraumatic stress, obsessive-compulsive disorder (OCD), mania, depression, and psychosis [5, 31], with the strongest evidence for glutamate's role in schizophrenia [3, 4]. As outlined below, altered glutamate homeostasis across various psychiatric disorders suggests the potential utility for psychopharmacological interventions as well as dietary interventions targeted at the glutamate system. While an extensive discussion of glutamate's role in psychopharmacological intervention is beyond the scope of the current review, a brief overview is provided below. It is important to note that for each of these disease states, the role of dietary glutamate has not been thoroughly examined.

The symptomatology of anxiety disorders reflects heightened psychological and physiological arousal processes [32]. Accordingly, treatments primarily focus on increasing GABAergic or inhibitory neurotransmission [33]. Conceptually, however, decreasing glutamatergic or excitatory neurotransmission may produce similar neurochemical effects [33], particularly given that stress increases prefrontal glutamate [34]. Additionally, N-methyl-D-aspartate-receptor (NMDAR) treatment has been

associated with anxiogenic effects [35, 36] that can be reversed by anxiolytics such as lorazepam [37].

In the context of trauma-related disorders such as post-traumatic stress disorder (PTSD), behavioral treatment focuses on unlearning pathological associations previously learned in the context of extreme stress [32, 38]. While stress-induced decreases in neurogenesis and hippocampal plasticity may constrain memory unlearning, NMDAR has been uniquely linked to reversal learning. Specifically, NMDAR antagonists result in deficits in reversal learning but not in inhibiting learning of primary tasks [39, 40] while low doses of D-cycloserine (a glutamatergic receptor agonist) promotes reversal learning in hippocampally lesioned rats [41]. Findings from a pilot study among adults with PTSD showed that D-cycloserine treatment both reduced PTSD symptoms and improved performance on a cognitive task assessing the ability to unlearn previously learned concepts [42].

Furthermore, prevailing research has demonstrated glutamate dysregulation in OCD (for a review, see Pittenger et al. [43]), a psychiatric condition characterized by recurring, intrusive thoughts (obsessions) and repetitive behaviors that reduce distress (compulsions) [32]. Specifically, elevated central glutamate has been documented in studies measuring cerebrospinal fluid [44, 45] and in specific brain regions using MRS of unmedicated individuals with OCD [46]. Owing to this research on altered glutamatergic neurotransmission, pharmacotherapeutic studies have begun investigating glutamate modulators, particularly in NMDAR functioning (for a review, see Pittenger [47]). However, research on dietary glutamate and OCD symptomatology is underdeveloped.

In addition to anxiety, trauma, and obsessive-compulsive symptomatology and disorders, glutamatergic dysregulation has been demonstrated in mood disorders across both bipolar and depressive disorders (for a review, see Sanacora et al. [48]). Specifically, for bipolar disorder, which is characterized by periods of mania and depression [32], elevated glutamate neurotransmission has been demonstrated across multiple studies and converging methodologies, including post-mortem [49], neuroimaging in acute mania [50], and specific brain regions as measured with MRS [51, 52]. While research on glutamatergic homeostasis in mood disorders has associated bipolar disorder with excessive levels of glutamate, depressive disorders are thought to show reduced glutamate neurotransmission [53]. These findings have promoted much of the research on the use of ketamine in depression, as ketamine is a known NMDAR antagonist [54], which contributes to its antidepressant effect.

Notably, the role of glutamate in psychiatric distress has been most strongly documented in psychotic disorders, owing to research demonstrating that the unique behavioral effects of psychotomimetic agents or "dissociative anesthetics" (e.g., ketamine and phencyclidine) are induced via NMDAR blockade [55, 56]. While a thorough discussion of this work is beyond the scope of this review (for a review, see MacKay et al. [57]), glutamate dysregulation has been implicated in the pathophysiology of schizophrenia [3, 4, 56, 58, 59]. Consistent with the role of NMDAR in hippocampal long-term potentiation [60], deficits in learning and memory are among the greatest selectively affected cognitive processes in schizophrenia [61, 62]. Additionally, phencyclidine [63, 64] and ketamine [35, 65] produce thought and sensory dysfunction consistent with that seen in schizophrenia. Furthermore, acute treatment with NMDAR antagonists increases prefrontal glutamate release [55, 66, 67], which may lead to the cognitive deficits characteristic of schizophrenia [55, 57, 58]. Indeed, multiple glutamate models of schizophrenia have suggested a role for dysregulated glutamate neurotransmission in the onset and severity of its positive, negative, and cognitive symptoms [33, 57, 59, 67].

Inconsistencies in associations between glutamate and psychiatric distress have facilitated increased research aimed at clarifying the deleterious effects of glutamate on psychiatric functioning. Indeed, stress, a known contributor to the onset and exacerbation of both physical and mental illnesses, has been suggested to play a role in glutamate dysregulation. Among individuals with chronic schizophrenia, central glutamatergic dysfunction, particularly in the anterior cingulate cortex, has been associated with psychological stress [31]. This finding is particularly important given consistently demonstrated positive associations between stress and psychotic symptom onset and progression [68, 69].

Despite accumulating evidence regarding central glutamate dysregulation and psychiatric symptoms, particularly psychotic symptoms, associations between dietary glutamate and psychotic symptoms and disorders remain underdeveloped. Research demonstrating somatic symptom reduction following dietary interventions involving MSG restriction or elimination suggests a potential future direction for psychiatric research. Mechanistically focused research aimed at characterizing glutamate-symptom associations is needed in order to develop targeted dietary interventions among individuals with psychiatric disorders.

Summary and Conclusion

Accumulating evidence suggests that the functions of glutamate extend beyond excitatory neurotransmission in central processes and additionally involve peripheral processes, as glutamate has been mechanistically implicated in the onset and progression of both somatic and psychiatric distress. Preliminary intervention research suggests dietary restriction of glutamate, particularly MSG, confers beneficial effects on decreasing somatic symptoms and increasing well-being in some individuals with chronic pain conditions [28]. While more evidence is needed to clarify equivocal patterns of findings, additional research is also warranted to examine whether dietary interventions may be similarly beneficial among psychiatric populations. However, despite the current infantile stage of this research, there are some take-away points that could be applied to our current knowledge base. Particularly, as we continue to examine the mechanisms behind psychiatric illness, diet is often a factor not traditionally examined as part of this work. Compelling findings from methodologically rigorous studies have linked diet to mental health across various psychiatric disorders (for reviews, see Logan and Jacka [70] and Sarris et al. [71]), implicating diet as a crucial component in clarifying pathophysiological mechanisms and intervention targets. Given the strong evidence identifying glutamate as a major neurotransmitter associated with psychiatric symptoms, it may be *especially* important for future mechanistic work to examine how dietary intake of glutamate may be related to psychiatric symptomatology. Additionally, examination of a patient's dietary practices may be prudent practice for clinicians. Implementation of dietary interventions routed in health practices may be a potentially effective way to mitigate not only psychiatric symptoms but also to improve overall health and well-being in all psychiatric patients, as pain is often comorbid with many mental illnesses.

Disclosure Statement

The authors declare no conflicts of interest.

Funding Sources

Support for V.L.E. and A.Z.K. in the preparation of the manuscript was provided though the National Institute of Mental Health of the National Institutes of Health under Award Number R01MH082784. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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