Hypothesis

Dietary Glutamate Will Not Affect Pain in Fibromyalgia

RINIE GEENEN, ERICA L. JANSSENS, JOHANNES W.G. JACOBS, and WIJA A. van STAVEREN

ABSTRACT. Injection of glutamate into the masseter muscle has been suggested to evoke an increase in intensity of and sensitivity to pain. A case study showed that a diet low in monosodium glutamate (MSG) might accomplish pain relief in fibromyalgia (FM). To clarify the possible pain-modulating effect of dietary glutamate, theoretical considerations about modes of action and empirical findings of reduced intake, common daily intake, and ingestion of relatively large amounts of glutamate are discussed. Of the total amount of dietary glutamate, hardly any enters the circulation. When relatively high concentrations of glutamate are ingested without food, a short-lived increase in serum and intramuscular glutamate concentrations is observed. However, glutamate concentration in the central nervous system (CNS) is maintained fairly independently of fluctuations in serum concentrations. Even extreme serum glutamate concentrations are not expected to enhance pain via glutaminergic activation of N-methyl-D-aspartate receptors. The "MSG symptom complex" does not include widespread pain among the symptoms and is based on other processes than increase of glutamate in the CNS. Thus, based on present knowledge about glutamate consumption and its metabolism in humans, dietary reduction of glutamate will not accomplish pain relief in patients with FM. There is a possibility that pharmacological doses of glutamate may enhance pain in FM, but this needs further investigation. (J Rheumatol 2004;31:785–7)

Key Indexing Terms:
FIBROMYALGIA PAIN DIET GLUTAMATE
MONOSODIUM GLUTAMATE DIETARY AMINO ACIDS

Fibromyalgia (FM) is characterized by generalized musculoskeletal pain elicited by normally nonpainful stimuli (allodynia) and increased pain intensity and duration evoked by painful stimuli (hyperalgesia)[1]. Activation of N-methyl-D-aspartate (NMDA) receptors by glutamate is considered an important mechanism in pain amplification. The amino acid glutamate is present in virtually all protein-containing foods, and moreover, monosodium glutamate (MSG) is a well known additive enhancing food flavors. It has been suggested that dietary glutamate might affect pain in FM[2]. A PubMed search using the search terms fibromyalgia AND diet AND glutamate gave, however, only a single result. In contrast is the number of results in nonscientific sources. A search at the worldwide web with identical search terms as the PubMed search gave 1440 results. Many of these sites promote diets low in glutamate or MSG to alleviate FM symptoms. These recommendations are not based on thorough theoretical considerations about modes of action or findings of randomized placebo controlled trials. Our aim is to clarify the possible pain-modulating effects of dietary glutamate. Findings on reduced intake, common daily intake, and ingestion of relatively large amounts of glutamate are discussed.

A recent study in 35 healthy young women and men suggests that an increase of glutamate in muscles enhances pain[3]. After 2 injections of 0.2 ml (1.0 M) glutamate into the masseter muscle, visual analog scale scores of pain and pain pressure thresholds indicated an increase of pain intensity and sensitivity, respectively. This was not a controlled study, but the authors refer to animal studies showing that injection of gamma-amino butyric acid (GABA), dextrose, and isotonic saline evoked significantly less activity in nociceptive afferents than glutamate injections. The authors suggest that peripheral excitatory amino acid receptors, which appear to play a role in mechanisms of craniofacial pain transduction in rats[4], contribute to this increased pain perception. These findings will not be of relevance for common daily dietary glutamate intake, but they indicate the possibility of increase of pain in response to large intake of glutamate. A short-term 2-hour increase of intramuscular glutamate has been shown after bolus MSG ingestion[5].

From the Department of Health Psychology, Utrecht University; the Division of Human Nutrition and Epidemiology, Wageningen University; the Department of Rheumatology and Clinical Immunology and the Division Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands.

R. Geenen, PhD, Assistant Professor; E.L. Janssens, MSc; J.W.G. Jacobs, MD, PhD, Associate Professor; W.A. van Staveren, PhD, Professor.

Address reprint requests to Dr. R. Geenen, Department of Health Psychology, Utrecht University, PO Box 80140, 3508 TC Utrecht, The Netherlands. E-mail: R.Geenen@home.nl

Submitted May 21, 2003; revision accepted October 6, 2003.

Ingestion of Glutamate

Of more relevance for daily glutamate intake are the results of a case study. Four patients with FM who had undergone multiple treatment modalities with limited success showed a complete or nearly complete resolution of their symptoms within months after eliminating MSG or MSG plus aspartate from their diet[2]. Whether this pilot finding is promising enough to set up a clinical trial to evaluate the possibility of alleviating pain with a diet low in glutamate depends on how glutamate is metabolized in the body, and how much of it enters the circulation and passes the blood-brain barrier.

Glutamate and MSG are major intestinal fuels[6]. Almost all dietary glutamate, about 95%, is metabolized in the first pass by small intestinal mucosa[7]. Only 12% of glutamate tracers infused by nasogastric tube routes has been shown to enter the systemic circulation[8]. It is therefore unlikely that fluctuations between normal boundaries of dietary glutamate are able to affect serum glutamate concentration, a hypothesis that has been confirmed[9,10]. Circadian levels of serum and erythrocyte glutamate concentrations were not different after test meals without and with a substantial amount of MSG added[9]. A comparison of serum glutamate concentrations of regular users and nonusers of MSG showed that longterm intake of MSG was not associated with persistent elevation of fasting serum glutamate concentrations[10]. Thus, of the total amount of daily dietary glutamate intake, on average 16.6 g (SD 5.6) in The Netherlands (L. Janssens, MSc thesis, Wageningen University), hardly any enters the circulation. Glutamate is present in almost all dietary proteins. Serum glutamate concentration may even decrease after increase of protein intake, which could be explained, among other causes, by increased clearance of amino acids by the kidney and the splanchic bed[11].

Glutamate Neurotransmission

Another situation exists when glutamate is ingested without food. Subjects receiving 12.7 g of oral MSG after an overnight fast showed a short-lived 11-fold increase of serum glutamate concentration within 1 hour after MSG ingestion[12]. To play a role in pain amplification, such extreme serum glutamate levels should affect central nervous system (CNS) levels. However, the neurotransmitter glutamate does not cross the blood-brain barrier, but is instead synthesized from glucose and a variety of other precursors in neurons and glial cells[13]. Glutamate concentration in brain regions with an intact blood-brain barrier is only a fraction of that of serum and is maintained fairly independently of fluctuations in serum concentration[14]. Thus, even relatively high doses of nondietary glutamate that cause an extreme increase in serum glutamate concentrations are not expected to enhance pain via NMDA receptors in the CNS.

Or does a route perhaps exist with which the blood-brain barrier is circumvented? The circumventricular organs such as the hypothalamus do not have a blood-brain barrier and allow glutamate uptake from the circulation, as documented for high dose amino acid administration in animals[14]. However, in humans even an extremely high dose of oral MSG has no effect on the secretion of prolactin and other pituitary hormones[12]. If pituitary responsiveness had been observed, it could have been a consequence of glutamic acid stimulation of hypothalamic regions outside the blood-brain barrier. Conversely, the absence of a pituitary effect following a bolus of oral MSG strongly argues against a central effect. Thus, except perhaps in extreme circumstances such as pathologically increased blood-brain barrier permeability, even extremely high doses of glutamate will scarcely affect glutamate neurotransmission.

Monosodium Glutamate Symptom Complex

A final consideration has to do with the so-called "MSG symptom complex," referring to idiosyncratic intolerance for MSG in food that is used in some restaurants[15]. This complex consists of a burning sensation at the back of the neck, forearms and chest, facial pressure or tightness, chest pain, headache, nausea, upper body tingling and weakness, palpation, numbness in the back of the neck, arms and back, bronchospasm (in asthmatics only), and drowsiness[15]. The symptoms begin 15 to 30 minutes after eating and last about 2 hours with no residual effects. Numerous studies of the MSG symptom complex with varying degrees of rigor in experimental design have been published. Challenges in which relatively few subjects were included who reported adverse reactions to MSG failed to show significant reactions to MSG. As well, results of challenges with MSG in the general population revealed no evidence of untoward effects[16]. The largest study to date involved 130 subjects who reported symptoms from ingesting MSG, and suggested that large doses of MSG given without food elicit more symptoms than placebo, but the frequency of MSG intolerance was low, the responses reported were inconsistent and not reproducible, and MSG intolerance was not observed when MSG was given with food[16]. Several mechanisms have been proposed to account for the "MSG symptom complex," for instance, acetylcholinosis, esophageal irritation, vitamin B6 deficiency, and histamine intoxication[16]. Increase of glutamate in the CNS is not among the suggested mechanisms and widespread pain is not among the symptoms. This circumstantial evidence in non-pain patients suggests that dietary MSG intake does not play a role in glutaminergic sensitization of NMDA receptors and pain amplification.

In conclusion, based on present knowledge about glutamate consumption and its metabolism in humans, dietary reduction of glutamate will not accomplish pain relief in FM. There is a possibility that pharmacological doses of glutamate may enhance pain in patients with FM, but this needs further investigation.

REFERENCES

1. Henriksson KG, Sörensen J. The promise of N-methyl-D-aspartate receptor antagonists in fibromyalgia. Rheum Dis Clin North Am 2002;28:343-51.
2. Smith JD, Terpening CM, Schmidt SOF, Gums JG. Relief of fibromyalgia symptoms following discontinuation of dietary excitotoxins. Ann Pharmacother 2001;35:702-6.
3. Svensson P, Cairns BE, Wang K, et al. Glutamate-evoked pain and mechanical allodynia in the human masseter muscle. Pain 2003;101:221-7.
4. Cairns BE, Sessle BJ, Hu JW. Evidence that excitatory amino acid receptors within the temporomandibular joint region are involved in the reflex activation of the jaw muscles. J Neurosci 1998;18:8056-64.
5. Graham TE, Sgro V, Friars D, Gibala MJ. Glutamate ingestion: the plasma and muscle free amino acid pools of resting humans. Am J Physiol Endocrinol Metab 2000;278:E83-9.
6. Wu G. Intestinal mucosal amino acid catabolism. J Nutr 1998;128:1249-52.
7. Reeds PJ, Burrin DG, Stoll B, Jahoor F. Intestinal glutamate metabolism. J Nutr 2000;130:978S-82S.
8. Matthews DE, Marana MA, Campbell RG. Splanchic bed utilization of glutamine and glutamic acid in humans. Am J Physiol 1993;264:E848-54.
9. Tsai PJ, Huang PC. Circadian variations in plasma and erythrocyte concentrations of glutamate, glutamine, and alanine in men on diet without and with added monosodium glutamate. Metabolism 1999;48:1455-60.
10. Tanphaichitr V, Leelahagul P, Suwan K. Plasma amino acid patterns and visceral protein status in users and nonusers of monosodium glutamate. J Nutr 2000;130:1005S-6S.
11. Forslund AH, Hambraeus L, van Beurden H, et al. Inverse relationship between protein intake and plasma free amino acids in healthy men at physical exercise. Am J Physiol Endocrinol Metab 2000;278:E857-67.
12. Fernstrom JD, Cameron JL, Fernstrom MH, McConaha C, Weltzin TE, Kaye WH. Short-term neuroendocrine effects of a large dose of monosodium glutamate in fasting male subjects. J Clin Endocinol Metab 1996;81:184-91.
13. Dingledine R, McBain CJ. Glutamate and aspartate. In: Siegel GJ, Agranoff BW, Albers RW, Fisher SK, Uhler MD, editors. Basic neurochemistry. Molecular, cellular, and medical aspects. 6th ed. Philadelphia: Lippincott-Raven; 1999:315-33.
14. Smith QR. Transport of glutamate and other amino acids at the blood-brain barrier. J Nutr 2000;130:1016S-22S.
15. Walker R, Lupien JR. The safety evaluation of monosodium glutamate. J Nutr 2000;130:1049S-52S.
16. Geha RS, Beiser A, Ren C, et al. Review of alleged reaction to monosodium glutamate and outcome of a multicenter double-blind placebo-controlled study. J Nutr 2000;130:1058S-62S.