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Soy, Headaches and MSG

Introduction

Migraines and headaches are prevalent among Americans. Approximately 1 out of every 6 American adults self-reported migraines and severe headaches during a 3-month period, and headache is consistently the fourth or fifth most common reason for emergency room visits.[1] Worldwide, approximately 14% of the global population report experiencing migraines.[2] Consequently, evidence suggesting that diet can affect the onset of or pain from headaches has important public health implications.[3-7] There are three possible ways certain soyfoods might theoretically impact headaches, but much more research is needed before any meaningful conclusions can be made.

Tyramine

Tyramine is a breakdown product of the amino acid tyrosine and is found in some foods, especially aged and fermented foods. In 2013, a small study found that serum levels of tyramine were elevated in patients with chronic migraines as compared to controls and persons with other headache disorders.[8] Tyramine was first contemplated as a headache trigger nearly 60 years ago as a result of case reports of hypertensive crises and severe headaches that developed in persons receiving monoamine oxidase inhibitors (MAOIs) that eat foods high in tyramine.[9] MAOIs inhibit the activity of monoamine oxidase, an enzyme which is responsible for degradation of brain neurotransmitters such as norepinephrine, serotonin, dopamine, and tyramine.[10] In 1988, Bieck and Antonin[11] demonstrated that an 8 mg oral dose of tyramine is sufficient to increase systolic pressure by 30 mm Hg in 50% of subjects receiving the MAOI tranylcypromine. But in older research, increases in blood pressure in response to 6 mg of tyramine were observed.[12,13] For this reason, most investigators use a conservative upper limit of 6 mg of tyramine as a guideline for safe ingestion.[14] However, clinical trials evaluating tyramine as a headache trigger have produced inconsistent results.[6]

More than 20 years ago, Shulman and Walker[15] advised patients taking MAOIs to avoid all soy products, especially soy sauce and tofu. However, the tofu to which these authors referred was fermented, whereas nearly all tofu consumed worldwide is unfermented. This distinction is important because while soy sauce and fermented soy products such as miso and natto can contain high amounts of tyramine, unfermented soy products such as soymilk and tofu, contain amounts of tyramine markedly below the levels thought to theoretically trigger a headache.[16]

One slight caveat about unfermented tofu is that with storage the tyramine content can increase. For example, one study found that the tyramine content of tofu went from 0.0628 mg/100 g when stored for 7 days to 0.5983 mg/100 g when stored for 9 days.[15] Importantly, even the

higher value is well below the amount that might raise concern. Interestingly, some patients on MAOIs may be able to ingest some brands of soy sauce without serious consequences because of the variation in tyramine content.[14,17] Finally, no data on the tyramine content of soy protein isolate or soy protein concentrate was found. However, given that these concentrated sources of soy protein are not fermented and that they have a long shelf-life indicating they are relatively stable, it is reasonable to speculate that their tyramine content is low. Research supporting this speculation shows that the concentration of tyramine of protein isolate from fava bean, a high tyramine food,[18] is only 1-2% of the concentration in the bean itself.[19]

Isoflavones

In 2002, Engel[20] described a case report of a 53-year-old male whose isoflavone intake was associated with a reduction in prostatic discomfort and improvement in urinary stream, but also with the onset of headaches with aura (sensory disturbances which can include flashes of light, blind spots, and other vision changes or tingling in the hand or face). As this individual reduced his isoflavone intake from foods and supplements by 62 mg from 135-177 mg/d, headaches were reduced and discontinued altogether when isoflavone intake was reduced by another 50%, such that isoflavone intake was about 60 mg/d. The prostatic symptoms did not return. For comparison, average isoflavone intake among older adults living in Japan is about 30-50 mg per day.[21,22] Although no other case reports describing headaches triggered by isoflavone intake were identified, a Taiwanese cross-sectional study by Chiu et al.,[23] found that among men, use of isoflavone supplements was associated with a nearly fourfold increased risk of headaches or migraine complaints (adjusted odds ratio, 3.86; 95% confidence interval: 1.68, 8.85). However, because this study utilized a cross-sectional design, it isn't clear whether isoflavone use preceded the onset of headaches. Among the 15,414 participants in this study, 17.2% of 7,912 men and 32.4% of the 7,502 women reported headache or migraine complaints whereas only about 2% of the cohort reported using isoflavone supplements. Importantly, among women, isoflavone supplement use was unrelated to risk. Somewhat parenthetically, it is notable that a meta-analysis of 174 controlled trials involving isoflavone supplement use evaluating possible side effects from treatment did not find headache was one such effect. [24]

Chiu et al.[23] suggested that the interaction of isoflavones with estrogen receptors (ERs) may be involved in the mechanism whereby isoflavones triggered headaches or migraines since ERs are extensively distributed in the central nervous system. Several case reports described migraine auras in women that were related to the use of estrogen replacement therapy.[25] Also, attacks of common migraines are both more frequent and severe around the time of menses within the general migraine population.[26] However, as previously noted in the study by Chiu et al.,[23] isoflavone supplement use was not associated with headache among women.

Furthermore, some evidence suggests isoflavones might alleviate headaches in women. For example, in a 24-wk placebo-controlled clinical trial involving 38 women with menstrual-triggered and intercurrent migraine attacks, use of a supplement comprised of 60 mg soy isoflavones, 100 mg dong quai, and 50 mg black cohosh reduced the frequency of headaches by 56%.[27] These results align with a previously published pilot study in which 10 women with a history of menstrual migraine (i.e., attacks occurring exclusively on day 1 ± 2 days of menstruation and at no other time of the cycle) taking a daily supplement containing 76 mg isoflavones experienced a significant decrease in the average

number of days with migraine compared with the baseline period ($P < 0.005$). However, this trial did not include a placebo group.[28]

The results of a seven menstrual cycle, double-blind, placebo-controlled, crossover intervention trial involving 23 women with prospectively confirmed premenstrual symptoms showed that isoflavones may ease headaches. Daily consumption of soy protein isolate containing 68 mg isoflavones was found to significantly reduce headaches in comparison to baseline whereas no such decrease was observed in the control group.[29]

Another study reported similar findings. In this small cross-sectional study of 84 Korean women living in the U.S., isoflavone intake (mean, 20.29 ±13.02 mg/d) was associated with fewer menstrual symptoms[30] as determined by the Moos Menstrual Distress Questionnaire (MDQ).[31] Headache is one symptom included in this questionnaire. However, in a Japanese cross-sectional study involving 189 women aged 19-34, isoflavone intake was unrelated to the MDQ score in the premenstrual phase.[32]

Finally, in a recently published Japanese cross-sectional study involving 405 women, isoflavone intake was associated with a lower risk of headache among peri-menopausal and postmenopausal women but not premenopausal women.[33] Importantly, the results were adjusted for background factors related to frequent headaches including vasomotor symptoms, depression, insomnia and anxiety.

Monosodium glutamate

Monosodium glutamate (MSG) is classified as a causative substance of headache in the International Classification of Headache Disorders 3rd edition (ICHD-III beta).[34] MSG is a sodium salt of glutamic acid – a non-essential amino acid present in all protein foods – used globally as a food flavor enhancer. Despite its classification, there is considerable uncertainty about the ability of MSG to invoke headaches. Only one study, which was published 3 decades ago, was identified that listed the MSG content of a soy protein (soy meal).[35]

The health effects of MSG are potentially relevant to soyfoods because some soy products are listed as being high in free glutamic acid.[36] Whether this is the case is a bit unclear because few data are available. Some soy products may be assumed to be high in free glutamate as a result of the processing they undergo, such as fermentation or hydrolysis in the case of soy sauce or perhaps as a result of exposure to high heat in the case of some concentrated sources of soy protein.[37]

A possible link between the intake of MSG and headache was first described more than 50 years ago.[38] Although some data continue to support this association in sensitive individuals,[39] according to a review by Henry-Unaeze,[40] researchers have not been able to consistently trigger reactions in double-blind studies with such individuals using MSG or placebo in food. This conclusion aligns with the position of the U.S. Food and Drug Administration (FDA) which says that adding MSG to foods is "generally recognized as safe"[41] and mostly algins with a systematic review by Obayashi and Nagamura.[42] In the latter, studies that administered MSG with food did not show an effect except for the female group in one study, whereas studies administering MSG without food did show an effect. However, the authors noted high concentrations of MSG were used in those studies and the participants were not likely sufficiently blinded. Consequently, Obayashi and Nagamura[42] concluded that further studies are required to evaluate whether or not a causal relationship exists between MSG ingestion and headaches.

Finally, according to the FDA, the glutamate in MSG is chemically indistinguishable from glutamate present in food proteins. Humans ultimately metabolize both sources of glutamate in the same way. The average adult consumes approximately 13 grams of glutamate each day from the protein in food, while intake of added MSG is estimates at around 0.55 g/d.[43]

Conclusion

There is no persuasive evidence that soy intake affects risk of having a headache as some studies show favorable effects, whereas others suggest some soy products may increase risk. Given that a large number of individuals suffer from headaches and that soyfoods are increasingly available, research aimed at understanding this relationship is warranted.

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