

EDITORIAL

MONOSODIUM GLUTAMATE AS FLAVOR ENHANCER QUESTIONS ON ITS SAFETY

The studies on physiological and toxicological aspects of glutamate have received much interest in the past several years, and many books entirely devoted to glutamate have been recently published (1-3). These studies can be basically divided into 3 major areas.

1. The study on glutamate as a neurotransmitter and/or as other physiological regulators. This is probably the most extensively studied area, and the evidence obtained can be considered as established. Glutamate biosynthetic pathways, release and reuptake mechanisms, and receptor characteristics are all compatible with a neurotransmitter role. The association of these properties to specific neuronal pathways in the brain has been well demonstrated. Possible functional roles of these glutamate pathways and their alterations in certain brain disorders have been suggested, although from mostly indirect evidence. For example, cortico-striatal glutamate fibers may be involved in basal ganglion psychomotor regulation and glutamate- or kainate-induced lesions of cell bodies in the striatum are used as animal models of human brain disorders such as Huntington's chorea, whereas glutamate pathways in the hippocampus may be related to several functions of this brain region ranging from mental processes to epilepsy. Comparing to enormous number of literatures on the properties of glutamate regulatory processes, less study has been focused on elucidating their functional roles. The available information, many of which are very recent, may encourage much more study in this aspect in the near future.

2. Animal study on neurotoxic effects of glutamate. The early reports of this line of studies are of Lucas and Newhouse(4) and Olney(5) who injected monosodium glutamate (MSG) subcutaneously to neonate mice and observed necrosis of the retina and the hypothalamic neurons respectively. Since then, there have been numerous attempts to assess MSG toxicity in variety of animal species. With the use of different strains as well as

species, and with varying experimental conditions, some interlaboratory discrepancies, especially in the interpretation of the data, are not uncommon. Factors influencing the observed toxic effects include animal species and strain, age, route of administration, dosage and duration of MSG given. Furthermore, the metabolism, blood brain barrier transport, placental transfer, excretion in milk, and the plasma versus brain levels of glutamate are not fully understood; these factors determine whether there will be adverse effect of MSG in the different experimental conditions. With these complexities, the data must be carefully presented and interpreted. Hundreds of studies in this aspect had been recently reviewed by several authors (see 6-9, for example) and some of the confirmed observations will be summarized here.

The retinal degeneration in mice, rats, rabbits, and the hypothalamic nerve cell destructions in mice, rats, guinea pigs, hamsters, chicks, and Rhesus monkeys are among the established observations when MSG was given systemically to neonatal animals. Glutamate-induced brain damage has also been demonstrated following oral administration of MSG to mice, rats, guinea pigs and monkeys (see 7) but discrepancies were reported by other investigators (see 8). Other toxic manifestations associated with systemic administration of MSG include convulsions and vomiting in animal species. Consequent to the hypothalamic lesion, several neuroendocrine disturbances after neonatal exposure to MSG have been reported; these include normophagic obesity, skeletal stunting, impaired reproductive capacity, reduced mass of the anterior pituitary and gonads, and reduced pituitary contents of growth hormone, prolactin and luteinizing hormone (LH). Lower dose of MSG which is not sufficient to cause hypothalamic lesion was found to stimulate LH release and to enhance serum LH levels in rats (9). Interestingly, long-term behavioral and somatic alterations in rats after neonatal exposure to MSG have been reported by several investigators (see 10, 11, for example); these alterations include irritability, decreases in incidence of tail-automutilation and spontaneous motor activity, and deficits in learning ability.

Animal ages and routes of MSG administration are among the important factors to be considered in extrapolating animal toxicological

data to human. It has been widely recognized that newborn animals of all species are more sensitive than weanlings or adults to the neurotoxicity of MSG; thus, hypothalamic lesion in adult animals can be induced by MSG administration with several folds higher doses than the toxic doses in neonatal animals. Higher doses of MSG are required when given by gavage comparing to subcutaneous administration to cause the same extent of neurotoxic effects. The important pitfalls in extrapolation of animal studies to human is that MSG administration in most of these studies, where neurotoxic effects are observed, are not compatible to human consumption and, moreover, in several chronic studies where MSG is mixed with food, none have reported evidence of CNS damage (6,8).

3. Toxicological studies in human. Several anecdotal observations of "Chinese Restaurant Syndrome" have been reported since 1968 (12-15) and it has been recognized that the symptoms are associated to consumption of food containing MSG. In addition to several subsequent anecdotal reports, number of other studies were directed to either a) metabolism and kinetics of glutamate in man, b) human reactions to oral MSG and c) a questionnaire study.

Metabolic and kinetic studies were reviewed by Garattini (8) and concluded that "in adults doses of MSG manyfold greater than those likely to be eaten with a meal even under extreme conditions do not cause marked elevations of plasma GA, particularly if the MSG is consumed with a meal." Since plasma levels of glutamate in human vary widely from individual to individual and from season to season in a year, probably up to a factor of 10, so it is difficult to correlate glutamate plasma levels to food consumptions and to adverse effects.

The double blind studies on human reactions to oral MSG reported agreeable results that the appearance and severity of adverse effects are dose related (14,16-18), although there are differences in minimal dose to produce the responses. These differences can be due to either subject variations or different food contents in which MSG was added or both. Certain volunteers demonstrated higher sensitivity and responded to less than 3 g of MSG, whereas the 25 g dose did not produce

the reaction in nonsusceptible persons.

The questionnaire studies on the prevalence of adverse effect of MSG consumption (Chinese restaurant syndrome) had reported different results varied from 25% (19) to 1-2% (20) of general adult public. These are mainly due to methodological variances.

With the available information, it may not be accurate to conclude as in the recent symposium (21) that "glutamate ingestion is free of toxic hazard to man." It would be more agreeable to state that, to date, there is no convincing evidence that human consumption of MSG will cause brain damage and several consequent responses as have been reported in animals. This statement is based on the observations that: a) oral intake of MSG, with food, is not found to induce hypothalamic lesion and marked elevation in plasma glutamate level as is observed after MSG given parenterally or by gavage, b) primates may be less sensitive (not insensitive) to MSG than experimental rodents (it is still equivocal whether MSG-induced hypothalamic lesion can be demonstrated in Rhesus monkey). The fact that brain lesion may not occur does not imply that there will be "no toxic hazard (21)" or "no effects on the brain (22)." Eventhough little amount of MSG can cross the blood brain barrier, circumventricular organ such as arcuate nucleus and area postrema (the main sites of lesions in animal studies) may be affected by small increase in plasma glutamate and complicate functional roles of these brain regions may be altered. Recent suggestion that there may be psychiatric reactions to MSG (23) supports this notion.

Conclusion from the controlled studies of human reactions to MSG is even more difficult; individual variations are among major problems. Thus, symptom experience may not relate to the plasma concentration of glutamate and several symptoms may not specific to MSG (21). The normal volunteers in these studies may not include susceptible persons and thus may underestimate adverse effects. We cannot simply reject anecdotal case reports and non-scientific complaint of layman and conclude that MSG is non-toxic to human and that Chinese restaurant

syndrome is not related to MSG, or is idiosyncratic experiences. We have to admit that many people have those discomfort experiences after consuming food with added MSG. Whether there is any defect of glutamate metabolism in these persons is not known to date. While keeping in mind that scientists should not frighten people by over-emphasizing toxic hazard of any agent, one should not over-stating for its safety when evidence is not conclusive and, especially, when the compound has very little usefulness to mankind.

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