Milestones in the Safety Evaluation of MSG

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The claim of adverse effects of MSG first emerged in the late 1960s, with a report by a U.S. physician that he experienced a series of unpleasant symptoms whenever he consumed food in Chinese restaurants. He described feelings of numbness at the back of the neck, general weakness and palpitation, and speculated that the effect might be due to any of several components of the food, including soy sauce, salt, alcohol and/or MSG (*Kwok RHM, New Engl J Med 278: 796, 1968*). The phenomenon was labeled Chinese Restaurant Syndrome (CRS) by the journal (not by Dr. Kwok). Within several months, a study by Schaumberg took up Kwok's observation and reported that a common set of symptoms could be associated with CRS, which were (a) facial pressure, (b) chest burning, and (c) chest pressure/pain (*Schaumburg HH et al., Science 163: 826, 1969*). In Shaumburg's study, 100% of the subjects responded! And, soon thereafter, another article appeared demonstrating that MSG injected into mice produced focal toxicity in the brain (hypothalamus), stunted growth, and obesity (*Olney JW, Science 164: 719, 1969*). A related article reported that a single oral dose of MSG, given to mice by stomach tube, also produced hypothalamic damage (*Olney JW, Ho O-L, Nature 227: 609, 1970*), and raised the issue of whether it was advisable to supplement the diet of the human infant with MSG.

Thus began a robust public debate over the safety of MSG in the food supply. A great deal of research was conducted over the succeeding 30 years, in animals and humans, supported by both government and industry, which has led regulatory bodies to the conclusion that MSG is essentially safe in the food supply (e.g., *Walker R, Lupien JR, J Nutr 130:1049S, 2000*).

The investigation of the key issues regarding MSG safety in the food supply, in addition to establishing safety, has revealed a great deal of information about glutamate physiology and biochemistry. Indeed, the physiological and biochemical findings show that the manner in which the body handles glutamate is not an issue of safety at all, but rather one of the normal use of glutamate by the body. This is best illustrated in relation to the original claim that the ingestion of MSG produces hypothalamic lesions. In order for dietary MSG to cause such lesions, it must cross the intestines into the blood, and elevate plasma glutamate levels sufficiently to cause the amino acid to enter brain. Moreover, the plasma glutamate elevation must be sufficiently great to cause brain levels to become high enough to over-stimulate neurons and cause their death (termed "excitotoxicity"). Indeed, in this latter regard, in mice, the plasma glutamate level must rise to about 1,000 nmol/ml before any hypothalamic damage can be detected after an oral load of MSG. (*Takahashi Y et al., Glutamic Acid: Advances in Biochemistry and Physiology, Filer LJ et al., eds., New York: Raven Press, pp. 255-275, 1979*). This is an *enormous* elevation in plasma glutamate, one that is never seen in humans (or animals) under even extremes of MSG intake (including ingesting 12.5 grams all at once on an empty stomach; this amount is more than that consumed in dietary protein in one day; see *Fernstrom JD et al., J Clin Endocr Metab 81: 184, 1996*). One way to view this set of data is to imagine that MSG is toxic, and that the intestines and liver are barriers to the entry of glutamate from the diet into the blood. They protect the body from the toxic substance. This is why so much MSG has to be ingested to cause plasma glutamate levels to rise. Moreover, it might also be argued that glutamate must be toxic to the brain, because it does not let the amino acid into the brain until plasma glutamate levels become abnormally high. Looking at it in this manner, we might draw the conclusion that MSG must be a toxic substance, because the gut and the brain exclude it very carefully.

But there is another way to view the findings, based on the results of research in metabolism and physiology over the past three decades. MSG and glutamate do not easily penetrate from the gut into the blood or from the gut into the brain

because of the ***importance*** of glutamate to normal intestinal function, ***not*** because of its imagined toxicity. In the intestines, dietary glutamate has been shown to be rapidly metabolized, and used mostly for energy production in this tissue (*Reeds PJ et al., Amer J Physiol 270: E413, 1996*). Indeed, Reeds suggested that glutamate is a dominant source of metabolic energy for the intestine during digestion, sparing glucose for use by the brain and other tissues. Hence, what was thought to be a barrier (intestines) to glutamate penetration into the circulation is not a barrier at all; dietary glutamate simply serves a key function in this organ, leaving very little left over to enter the circulation. Plasma glutamate levels therefore do not rise when glutamate is ingested in the normal diet as glutamate in dietary proteins or as free glutamate in the form of MSG (*Tsai PJ, Huang PC, Metabolism 48: 1455, 1999*).

In the same manner, the brain does not exclude glutamate from entering brain because it is a toxic molecule. The apparent barrier to glutamate penetration into brain should instead be viewed from the perspective of how the brain manages the glutamate it uses for neuronal function. Glutamate is the dominant excitatory neurotransmitter in the brain (so far as is known), functioning in well over half of all brain nerve terminals. As an excitatory transmitter, it causes neurons on which it acts to depolarize (become excited electrically), leading to the propagation of electrical signals within neuronal circuits. Under certain abnormal circumstances, in which neurons become exposed experimentally to excessive amounts of glutamate, they can become overexcited and die. This has led to glutamate being labeled as an “excitotoxin”. However, glutamate is not an excitotoxin; it is simply an excitatory neurotransmitter, and the brain has evolved to have powerful mechanisms for carefully compartmentalizing glutamate within brain neurons and surrounding support cells (glia). The amino acid is thus normally released in discrete amounts by neurons into very small intracellular spaces (the synapses between neurons), which allows for focused inter-neuronal excitations, after which the glutamate is instantly reabsorbed into surrounding cells. Essentially all cells in the brain have mechanisms for removing glutamate from the extracellular space, to help keep glutamate focused on its primary function, that of neurotransmission.

One of these cells is the capillary endothelial cell, which is the cellular basis for the "blood-brain barrier" (*Hawkins RA, Amer J Clin Nutr 90: 867S, 2009*). The capillary endothelial cells extract glutamate from the extracellular fluid of the brain, to help keep brain extracellular concentrations low, and dispose of it by sending it into the circulation. From the blood side, this looks like a barrier to the penetration of a toxic compound, glutamate. In reality, the function is rather to extract glutamate from the brain and excrete it into the circulation. The mechanism is so powerful that, as noted above, plasma glutamate in newborn mice (considered the most susceptible species) must rise almost 10-fold before glutamate overwhelms this cellular transport mechanism and there is net flow of glutmate from the blood into the brain. In sum, therefore, the apparent barrier to the penetration of a toxic molecule into brain is not really that at all – it is simply one expression of a physiologic mechanism for carefully compartmentalizing within brain cells and synapses a key excitatory neurotransmitter.

This perspective can also be applied elsewhere in the body. For example, glutamate does not cross the placenta from the maternal to the fetal blood, except when maternal glutamate concentrations are raised to astoundingly high levels (*Stegink LD et al., Am J Obstet Gynecol 122: 70, 1975*). One view of this might be that the placenta is excluding a toxic molecule from the fetus, whose brain would be very sensitive to damage from an excitotoxin. However, this is physiologically not the case. Indeed, Battaglia and associates (see *J Nutr 130: 974S, 2000*) demonstrated that the placenta uses glutamate as an important source of energy, stripping off the nitrogen and channeling the carbon backbone into the Krebs cycle. Glutamate is absorbed from the maternal circulation by the placenta and used for this purpose. It is also absorbed from the fetal circulation and used for energy production. In fact, the fetal liver produces glutamate and releases it into the fetal circulation to supply the placenta and fetal organs with the amino acid, which is used to generate energy. Battaglia argues that in the fetus, the liver synthesizes and supplies glutamate as an energy substrate to peripheral tissues in a manner identical to that in the adult, in which the liver synthesizes and supplies glucose as an energy

substrate. From this perspective, maternal glutamate, however supplied into the circulation, is not viewed as a molecule that is toxic to the fetus. Rather, it is a molecule essential for normal placental function. And, glutamate is so important to the development and function of fetal organs that the fetal liver makes it for their use!

In passing, it is worth noting that early concerns about nursing infants being exposed to elevated levels of glutamate in breast milk, because the mother has consumed MSG in her diet, were unwarranted: The glutamate concentration in milk is unaffected by the elevations in plasma glutamate produced by lactating women who ingest a high dose of the amino acid (100 mg/kg – about equivalent to the amount ingested in dietary protein over the course of an entire day) (*Baker GL et al., Glutamic Acid: Advances in Biochemistry and Physiology, Filer LJ et al., eds., New York: Raven Press, pp.111-123, 1979*). Moreover, metabolic studies in post-nursing infants showed that they metabolize glutamate at the same rate as do adults. They thus show no special metabolic sensitivity to dietary glutamate, an issue originally put forth based on studies in mice (*see: Stegink LD et al., Pediat Res 20: 53, 1986*). In sum, there was (and is) no basis for thinking that exposure of the human infant to dietary glutamate, whether as a newborn or post-nursing infant, would present a hazard.

Turning to the issue of CRS, currently known as the “MSG symptom complex” in the United States (see *Walker R, Lupien JR, J Nutr 130:1049S, 2000*), the human study of Schaumburg et al (cited above) stated that 100% of their subjects showed a CRS response to the ingestion of MSG. In essence, they stated that everybody shows CRS in response to MSG ingestion. Of course, their study was not appropriately blinded to the investigators. Hence, as experimental design was subsequently improved by other laboratories, the reported incidence of CRS declined markedly. The most recent study followed a design specified by a special scientific panel contracted by the US Food and Drug Administration to the Federation of American Societies for Experimental Biology (*Analysis of Adverse*

Reactions to Monosodium Glutamate: MSG; Raiten DJ et al., eds. Bethesda MD, American Institute of Nutrition, 1995. ISBN 0-0943029-1; FDA Contract 223-92-2185). In this study, conducted in subjects who identified themselves as sensitive to MSG, which involved double-blind, multiple-dose tests using MSG alone and in food, *no* subject showed a consistent, reproducible reaction to MSG. Indeed, it is of interest that this study was conducted as a multi-center trial, in Boston, Chicago and Los Angeles, a combined population base approaching 15 million. Repeated advertising for MSG sensitive subjects resulted in 178 subjects applying to be included in the study. Had Schaumburg been correct in his initial assessment that all humans are MSG sensitive, then one would have anticipated that a great deal more than 178 individuals would have applied to enter the study. And, as noted, when the study was completed, none of the subjects consistently displayed symptoms associated with CRS (or the MSG symptom complex) (*Geha RS et al., J Allergy Clin Immunol 106: 973, 2000*). Hence, the most recent findings, obtained from a highly-controlled study, indicate that CRS does not exist.

Very recently, an epidemiologic study has associated MSG use with weight gain in a rural Chinese population (*He K et al., Obesity 16: 1875, 2008*). However, this finding could not be confirmed in a Chinese study of similar design (*Shi Z et al., Brit J Nutr doi:10.1017/S0007114510000760, 2010*). Animal studies also do not support the notion that dietary MSG induces weight gain (*Kondoh T, et al., Physiol Behav 95: 135, 2009*).

Finally, a report has just been released by the Institute of Medicine (U.S.) concerning dietary salt and hypertension (*Henney JE et al., eds., Strategies to Reduce Sodium Intake in the United States. Institute of Medicine. Washington DC, National Academies Press, 2010. ISBN: 0-309-14806-5, 480 pp. Available at http://www.nap.edu/catalog/12818.html in PDF format*). The daily salt intake in the U.S. diet is more than 50% above the recommended intake level. Most of the sodium consumed in the U.S. diet derives from packaged foods and foods prepared in restaurants. Public health officials would like to reduce salt intake in the

American diet, because salt intake is associated with hypertension (e.g., *He J et al., J Hypertens 27: 48, 2009*), and is thus a serious health risk. Among the ways suggested in the report for helping Americans to reduce salt intake is the use of MSG to reduce the salt content of prepared foods. Indeed, MSG is known to be capable of maintaining the pleasantness of foods when the salt content is reduced (e.g., *Yamaguchi S, Takahashi C, J Food Sci 49: 82, 1984; Ball P et al., Eur J Clin Nutr 56: 519, 2002*). Moreover, gram for gram, MSG contains much less sodium than salt. Thus, an especially positive note on which to end is by pointing to the possibility that dietary MSG might finally be coming to be recognized as a food ingredient for promoting good health!