Glutamic acid: the Jekyll and Hyde molecule behind the obesity epidemic

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Already known about the subject

Free glutamate accumulated in quantity becomes excitotoxic, causing brain lesions in the arcuate nucleus of the hypothalamus as well as in other areas of the brain.

Immature brains of fetuses and neonates are among those vulnerable to glutamate-induced brain damage.

Today there is so much excitotoxic free glutamate added to foods and beverages, that a person can easily consume a sufficient quantity of free glutamate to cause it to become excitotoxic.

New findings

Obesity can be caused by excitotoxic amino acids ingested by pregnant and nursing women and delivered to fetuses and neonates who exhibit obesity as they reach maturity.

The onset of the obesity epidemic can be traced to the introduction of excessive amounts of manufactured free glutamate that became available to humans following the modernization of MSG manufacture in 1957.

Results should broaden the focus of clinical practice

The focus of clinicians should be on identifying overweight people who are challenged by damage to the arcuate nucleus. For those people, the guilt, shame and blame that have long been associated with obesity should be replaced with appropriate counseling, allowing the health care practitioner to work with those patients to understand their limitations and set realistic goals for weight control.

Abstract

There are countless factors that contribute to obesity, but none that by themselves explain the ongoing obesity ***epidemic***. In this review, we have traced the roots of this public health crisis to the decade following introduction of excessive amounts of manufactured free glutamate (MfG) made available and accessible to humans following the 1957 modernization of MSG manufacture, when vast amounts of excitotoxic – brain damaging -- MfG in monosodium glutamate (MSG) and other excitotoxic food ingredients began to appear in processed food.

Three conditions must be met in order to produce food-induced neurotoxicity:

A vulnerable brain (immature or damaged).

A sufficient quantity of excitotoxic free glutamate to cause that free glutamate to become excitotoxic.

A way for that excess of glutamate to be delivered to the vulnerable brain.

We have reviewed the literature demonstrating that pregnant and lactating women who ingest large amounts of readily available MfG will pass excitotoxic amino acids to their fetuses and neonates, causing brain damage in the arcuate nucleus of the hypothalamus followed by intractable gross obesity.

Introduction

It has long been recognized that there are high concentrations of glutamate in the brain, but only gradually over the course of more than a century has there been recognition of its various functions.

Glutamate was first identified in 1866 by Karl Ritthausen with its structure established in 1890 by Wolff (1).

Thirty years later, Kikunae Ikeda was championing its use as a flavor-enhancer (2).

In the 1930s, with recognition of the high concentrations of glutamate in the brain, the interest/curiosity of researchers was heightened, leading to a variety of glutamate-related studies. In 1952, Hayashi suggested that glutamate might function as a neurotransmitter (3), a chemical messenger that carries signals between neurons and their target cells throughout the body. Not until the 1980s, however, was glutamate's function as a neurotransmitter generally accepted (4).

It was another 10 years before glutamate was identified as an excitotoxic – brain damaging -- neurotransmitter. When consumed in controlled quantities, glutamate is essential to normal body function as a neurotransmitter and building block of protein. But when consumed in excess, in quantities greater than needed for normal body function, it becomes excitotoxic, firing repeatedly and killing its targeted glutamate receptors. Olney coined the term "excitotoxin" in 1969 to describe the actions of glutamic acid which had been delivered in monosodium glutamate (MSG) (5). At the time, researchers were administering glutamate to laboratory animals subcutaneously using Accent brand MSG because it had been observed that MSG was as effective for inflicting brain damage as more expensive pharmaceutical grade L-glutamate (5).

In the 1980s, researchers focused on identifying and understanding abnormalities associated with glutamate, often for the purpose of finding drugs that would mitigate glutamate's adverse effects (6-9). By the end of the 1980s, glutamate-associated disorders such as headaches, asthma, diabetes, muscle pain, atrial fibrillation, ischemia, trauma, seizures, stroke, Alzheimer's disease, amyotrophic lateral sclerosis (ALS), Huntington's disease, Parkinson's disease, depression, multiple sclerosis, schizophrenia, obsessive-compulsive disorder (OCD), epilepsy, addiction, attention-deficit hyperactivity disorder (ADHD), frontotemporal dementia and autism were on the rise, and evidence of the toxic effects of glutamate were generally accepted as such by the scientific community (10-11).

By and large, the glutamate in question was, and still is, glutamate from endogenous sources. The possible toxicity of glutamate from exogenous sources, such as glutamate-containing flavor enhancers, has generally not been considered. Only Olney and a few others have suggested that ingestion of free glutamate might play a role in producing the excess

amounts of glutamate needed for endogenous glutamate to become excitotoxic (12-32).

Little consideration has been given to possibility that exogenous glutamate might contribute to producing the excess amounts of glutamate needed for endogenous glutamate to become excitotoxic, or might cause brain damage through an entirely different pathway.

Excitotoxic free glutamate

Glutamate is an excitotoxic amino acid, meaning it will kill brain cells when accumulated in quantity in interstitial tissue or elsewhere, or when ingested in quantity.

When present in protein or released from protein in a regulated fashion (through routine digestion) glutamate is vital for normal body function. It is the principal neurotransmitter in humans, carrying nerve impulses from glutamate stimuli to glutamate receptors throughout the body.

Glutamate becomes toxic only when present in greater quantity than a healthy human needs for normal body function. Then as an excitotoxic neurotransmitter, it fires repeatedly, damaging targeted glutamate-receptors and/or causing neuronal and non-neuronal death by over exciting those glutamate receptors until their host cells die (33-38).

The first study to address the possibility that glutamate from exogenous sources (from eating, for example) might cause brain damage was published in 1969. At the time, it was demonstrated that glutamate-induced brain damage to the arcuate nucleus of the hypothalamus of neonatal animals was followed by obesity, reproductive dysfunction, behavioral disturbances and more (5).

In the decade that followed, research confirmed that glutamate given as monosodium glutamate administered or fed to neonatal animals causes hypothalamic damage, endocrine disruption, and behavior disorders after either subcutaneous (39-60) or oral (46,52,53,55,61-65) doses.

Since the 1980s, researchers have focused on identifying and understanding human abnormalities associated with free glutamate, often for the purpose of finding drugs that would mitigate glutamate's adverse effects.

The possibility that glutamate from exogenous sources might contribute to those abnormalities and/or might cause brain damage in humans leading to gross obesity, has not been considered.

Glutamate-induced brain damage (the evidence)

The toxic action of glutamic acid (glutamate or GLU) was first reported by Lucas and Newhouse in 1957 (66). Prior to that time, and throughout the 1960s, a considerable body of research had focused on potential positive or curative effects of various forms of GLU used as a drug. During this period "side effects" of GLU were noted, but there is no record of consideration that these "side effects" might be toxic reactions to GLU. And there was no mention that the flavor-enhancer called monosodium glutamate might in any way be related.

In 1968, someone in Olney's lab observed that mice treated with GLU for the purpose of studying retinal degeneration became grotesquely obese, and Olney became suspicious that the obesity in mice, which was observed after neonatal mice were treated with GLU for purposes of inducing and studying retinal pathology, might be associated with hypothalamic lesions caused by GLU treatment. In that research and the research that followed, MSG was used as the source of GLU because MSG had been found to be just as toxic as pharmaceutical grade glutamate, but considerably less expensive.

Thus in 1969, Olney reported that GLU treatment given as MSG caused brain lesions, particularly acute neuronal necrosis in several regions of the developing brain of neonatal mice, and acute lesions in the brains of adult mice given 5 to 7 mg/g of GLU subcutaneously (5).

Subsequent research confirmed that GLU induces hypothalamic damage when given to immature animals after either subcutaneous (39-60) or oral (46,52,53,55,61-65) doses.

Work by Lemkey-Johnston and Reynolds (65) published in 1974 included an extensive review of the data on brain lesions in mice. They confirmed the phenomenon of GLU induced neurotoxicity, described the sequence of the lesions, and emphasized the critical aspects of species variation, developmental age, route of administration, time of examination of brain material after insult, and thoroughness of tissue sampling methods. A review of GLU induced neurotoxicity, published by Olney in 1976 mentioned species (immature mice, rats, rabbits, guinea pigs, chicks, and rhesus monkeys) demonstrating GLU induced neurotoxicity and efficiency of both oral and subcutaneous administration of GLU in producing acute neuronal necrosis, discussed the nature and extent of the damage done by GLU administration and the impact of GLU administration to GLU levels in both brain and blood, and discussed the similar neurotoxic effects of a variety of acidic structural analogues (67).

Hypothalamic Lesions: Non-Human Primates

Studies of non-human primates (40,53) were felt to be particularly meaningful to the study of GLU toxicity, particularly because GLU toxicity found in laboratory animals might be relevant to humans. As early as 1969 Olney had suggested that GLU could be involved in the unexplained brain damage syndromes occurring in the course of human ontogenesis (40). Olney demonstrated that the infant rhesus monkey (Macaca mulatta) is susceptible to GLU-induced brain damage when administered a high dose (2.7g GLU/kg of body weight) subcutaneously.

Olney et al. (53) expanded Olney's earlier work (40) with a study of eight additional infant rhesus monkeys and, using light microscopy and the electron microscope, reconfirmed Olney's earlier findings (40) of hypothalamic lesions, and discussed the findings of both Abraham et al. (54) and Reynolds et al. (68) who had questioned his work. Olney found his data to be entirely consistent with studies done previously by his own and other laboratories on all species of animals tested.

Neuroendocrine Disorders

Olney found not only hypothalamic lesions in 1969, but described stunted skeletal development, obesity, and female sterility, as well as a spate of observed pathological changes found in several brain regions associated

with endocrine function in maturing mice which had been given GLU as neonates (5).

Longitudinal studies in which neonatal/infant animals were given doses of GLU and then observed over a period of time before being sacrificed for brain examination, repeatedly supported Olney's early findings of abnormal development, behavioral aberration, and neuroendocrine disorders (5). Developmental dysfunction or abnormalities in growth and behavior have been noted in a number of animal studies. Animals treated with GLU as neonates or in the first 12 days of life suffer neuroendocrine disturbances including obesity and stunting, abnormalities of the reproductive system, and underdevelopment of certain endocrine glands (5,47,49,65,69-86) and possible learning deficits either immediately or in later life (72,75,76,87-93).

In addition, Bhagavan and others have reported behavioral reactions including somnolence and seizures (94-101); tail automutilation (74,88); and learned taste aversion (90). Irritability to touch was interpreted as conspicuous emotional change by Nemeroff (74). Lynch (102) reported hyperglycemia along with growth suppression. He noted that hyperglycemia did not occur when subjects were given intact protein that contained a large amount of GLU.

Olney et al. (103-105) have written a number of review articles which summarize the data on neuroendocrine dysfunction following GLU treatment, as has Nemeroff (106).

Focus on Ad Libitum Feeding

Findings of neurotoxicity and neuroendocrine dysfunction in laboratory animals, following GLU administration, raised questions about the effects which GLU might have on humans. One such possible effect was GLU involvement with still unexplained brain damage syndromes. Since it would be unthinkable to administer doses of GLU to humans which might produce the same sorts of neurotoxicity and neuroendocrine dysfunction as found in laboratory animals, researchers had no alternative but to make decisions based on the best of the animal studies. "Best," in this case, would be studies which would most closely parallel the true human condition.

A seemingly logical first step would be to study the effects of GLU on non-human primates; and, as already noted, hypothalamic lesions were

demonstrated in monkeys as early as 1969 (40). A seemingly logical second step would be to study what might be considered “normal” ingestion of GLU as opposed to some kind of forced feeding. It was felt by many that ad libitum feeding of laboratory animals parallels the human situation more closely than either subcutaneous or gavage administration of GLU, and that ad libitum feeding studies were, therefore, the vehicle of choice. Others tended to disagree, feeling that the ad libitum feeding studies were, by and large, studies which had the greatest potential for minimizing the amount of GLU actually ingested while registering the irrelevant amount of GLU **available**. These studies were largely industry-sponsored studies initiated and designed to “prove” that ad libitum feeding of GLU to laboratory animals did not result in the brain lesions and or neuroendocrine disorders found using other routes of administration.

Only two studies which demonstrate neurotoxic reactions after ad libitum feeding of GLU are reported here. Actually, one would expect few positive studies, because those who are employed by the food industry rarely, if ever, publish them, and no one else appeared to be interested in “proving” that GLU is, or is not, safe.

In a 1979 study by Vorhees (89), done as part of a project designed to evaluate a developmental test battery for neurobehavioral toxicity in rats (in which rats were exposed to GLU and other food additives mixed with ground Purina rat chow, beginning five days after arrival at the laboratory), it was demonstrated that high doses of dietary GLU produce behavioral variations. GLU was mixed with food as opposed to being administered subcutaneously or by gavage. Positive effects were found.

A year later, dietary studies reported by Olney demonstrated that weanling mice will voluntarily ingest GLU (and/or aspartate) and that such voluntary ingestion results in readily detectable brain damage (107).

Focus on Older Animals

Most studies demonstrating retinal necrosis, brain lesions and/or neuroendocrine dysfunction, focused on neonatal or infant animals. The reason for this focus is simple. Researchers were primarily interested in producing lesions in order to expand their knowledge of brain function, and the lesions were most easily produced in the young. It was, however, also of scientific interest to understand the relationship of age to the type and

severity of lesion or dysfunction. Thus, older animals were studied, but not to the same extent as the young.

Hypothalamic lesions have been produced in adult animals using considerably greater doses of GLU than those required to produce lesions in younger animals. Nemeroff reported that the smallest effective dose for a ten day old mouse, given orally, is .5g/kg of body weight, and given subcutaneously is .35g/kg of body weight(69). According to Olney, the dose required to damage the adult rodent brain is given as 1.5-2 mg/g of body weight as compared to 0.3-0.5mg/g required to damage the brain of an infant rodent (108). Only minimal damage is induced unless very high doses (4-8 mg/g) are used (104).

Although advances in technology have facilitated the observation of brain lesions to some extent, it was still true in 1991, as it was in the 1960s, that simple light microscopes are adequate to identifying GLU induced lesions if one looks in the right (sensitive) locations within 4-5 hours of GLU administration. By 24 hours after insult, lesions will be filled in ("healed") with cells, but the cells will be cells other than neurons. Thus the "hole" is filled in, but the lost **neurons** are not replaced. The damage will have been done but will be virtually impossible to see. Although in 1991 it was possible, under optimal circumstances, to count neurons in well-defined areas, the arcuate nucleus is not a well-defined area, and lesions in that area will defy detection after as little as 24 hours after GLU administration. One could not, therefore, ascertain whether or not an adult animal given GLU as an infant, had suffered a lesion in the arcuate nucleus.

Focus on Pregnant Females

There has been considerable interest in possible transplacental neurotoxicity of GLU, particularly on the part of food technologists who have attempted to demonstrate that GLU fed to a pregnant rodent has no adverse effects on its offspring. We have made no attempt to do a comprehensive review of the literature, but cite here only one study which demonstrates that pregnant rats administered subcutaneous doses of GLU develop acute necrosis of the acetylcholinesterase- positive neurons in the area postrema (109). The same effect was obtained in the area postrema of fetal rats.

The case for the safety of MSG

In the 1960s and 1970s, research done by people not employed by the glutamate industry demonstrated that monosodium glutamate fed to laboratory animals causes brain lesions, endocrine disorders, and observable adverse reactions.

In response, glutamate-industry researchers **pretended** to replicate those animal studies; but changed the methodology enough to make certain that there would be nothing negative to report.

Overview

Challenges to reports of brain damage following administration of free glutamic acid (GLU) promptly followed the 1969 report of glutamate-induced brain damage (5). Adamo and Ratner (110) and Oser et al. (111) challenged the findings of brain lesions and neuroendocrine dysfunction resulting from administration or ingestion of GLU, as they failed to reproduce Olney's findings of neurotoxicity affecting the brains of non-primates. Adamo and Ratner (110) used rats, not mice as Olney (5) had, but maintained that otherwise the experimental approach used was "very similar." Oser et al. (111) studied mice, rats, and beagles (dogs). Although their methodology varied considerably from Olney's, they concluded that they could "...offer no explanation for the fact that [their]...observations...do not confirm those of Olney...."

Arees and Mayer (43) reproduced Olney's findings (5,40) only in part. Their discussion focuses more on the question of human consumption of GLU as food than on reasons for differences between the various studies.

Both of these negative studies were refuted by both Olney (39,112) and Burde (52) who independently reviewed the literature and found that these early discrepancies could be attributed to:

1) Failure on the part of investigators to **attempt** to replicate Olney's methods; and

2) Use by investigators of entirely different (and inappropriate) methods of preservation and staining of brain tissue in the analysis of results

Burde (52) speculated that the method of fixation and staining used by Adamo and Ratner (110) obscured the existence of the lesion, and noted that their dose schedule was not appropriate; that Oser et al. (111) used a minimal effective dose and did not examine the rats and mice until 24 hours after insult, even though it was known that by 24 hours after insult, in a minimal dose, such as the one used by Oser, which would produce edema, all signs of edema would have disappeared, and that necrotic cells would already have been phagocytized. Burde found the interpretation by Arees and Mayer (43), that the lesion produced by GLU is limited to "microglia," to be puzzling, particularly in light of the fact that most of the cells of the arcuate nucleus are known to be small neurons. Furthermore, using Olney's exact methods, Burde (52) replicated Olney's previous findings.

Olney's review of the discrepancies (39), pointed out that the failure of Oser et al. (111) to detect brain damage in any of the three species they studied following administration of GLU might well be accounted for by their having limited the GLU dose to a single, minimally effective dosage; failure to use a feeding tube to assure that the full dose was received by orally treated animals; failure to examine brains in appropriate post treatment intervals (which are particularly relevant in cases of minimal effective dosage); and use of relatively unrefined techniques for tissue preparation.

Olney (39) also noted that in a 1971 study done by Arees et al., the authors were able to demonstrate that neuronal degeneration **does** occur in the infant mouse brain following subcutaneous treatment with GLU. Thus, the discrepancies noted by Arees and Mayer previously (43) became resolved.

Finally, Olney (39,112) suggested that methodological variables might well explain the failure of Adamo and Ratner (110) to demonstrate lesions in the rat.

The subject of tissue preparation (relevant at the time) has been addressed by a number of people. Takasaki (48) stated it clearly: "...changes disappeared at least 24...[hours] after injection....The results should be borne in mind when histological examination is performed on changes of the hypothalamus caused by administration with MSG. It is [especially] so in animals administered with a small dose of MSG, because necrotic neurons are few and the glial reaction that occurs secondarily is very mild in the arcuate nucleus. Without punctual preparation after administration, the effect upon the hypothalamus is apt to be overlooked in these animals" (48).

In 1973, Filer and Stegink (115) published an editorial in the *New England Journal of Medicine* which suggested that the neurotoxic effects of GLU and its related amino acids, aspartate and cysteine, in species other than the mouse, are debatable. In turn, Olney et al. (60) pointed out that neurotoxic effects of GLU and its related amino acids had been well documented, and that the "null effect" reported by Filer and Stegink was a function of faulty methodology, not strain specificity--a fact which had been pointed out earlier by Burde (50,53). Olney noted that Filer and Stegink supported their argument by pointing to the "fact" that no neurotoxic effects of GLU had been reported in the guinea pig, which was, at the time, an unstudied species. Olney further reviewed the criticisms of his own research proffered by Filer and Stegink and suggested that a more careful reading of the research as presented would resolve their concerns.

There were other studies which failed to confirm toxic effects of GLU, and there were criticisms of Olney's work. Abraham (54), mentioned earlier, found toxic effects when GLU administration was subcutaneous, but very little when administration was oral. His work is discussed in some detail in the section devoted to non-human primates.

Lowe (116) criticized Olney (40) for failure to provide data on plasma GLU concentrations, and for lack of a control in his single infant monkey study. Zavon (117) criticized Olney for lack of a control animal and for lack of detail in reporting the same study. Olney (118) responded to both Lowe and Zavon with detail gathered from mouse studies and an apology that he had had only the one monkey available at the time of his study.

Blood, Oser, and White (119) criticized Olney (5) for questioning the safety of GLU after parenteral, as opposed to oral, administration; failure to clearly elucidate his methodology; and use of doses which far exceeded the Blood et al. estimate of "...the total daily intake [of GLU] from all reasonably possible uses... (.7 g per day) in an average adult" (119).

"Critical tests for the safety evaluation of food additives are based on the effects of oral, not parenteral, administration," state Blood et al., leading one, possibly to infer that Olney considered his studies of mice to be "critical tests for safety," when in fact that was not true. Olney has **never** suggested that his work be used in this way. It is one thing to report an observation, as Olney did. It is quite another to claim that it is a critical test for something. This was a seemingly purposeful creation of false information by innuendo.

Olney (120) in reply to Blood et al. (119), provided the figures requested, suggested that he (Olney) had been misquoted, and suggested that to truly establish the safety of GLU if, indeed, that could be done, solid research was needed.

Focus on Non-Human Primates

Two studies took exception to Olney's finding of hypothalamic lesion in non-human primates due to loading of GLU. Abraham et al. (54) treated four monkeys and failed to reproduce the findings of Olney and Sharpe (40). Reynolds et al. (68,121,122) treated 16 non-human primates which were compared to five controls. They, too, failed to reproduce the findings of Olney and Sharpe (40), and found, instead, a "spectrum of degenerative changes" which they attributed to inadequate fixation procedures rather than to the effects of GLU.

Among the criticisms Olney (53) made of the research design and methodology of Abraham et al. (54) and Reynolds et al. (68,117,118) which distinguished his study from theirs, was the fact that Reynolds et al. used only a spot sampling technique when two of the rhesus infants treated with low oral doses of GLU were examined by electron microscopy, so the possible occurrence of small lesions in these brains was not actually ruled out. Moreover, the method used for preparation of brains for examination by light microscopy has been found unsatisfactory for evaluating even large GLU-induced lesions in infant rodent brains; and subsequent information provided by Reynolds indicated that some of the infants vomited an unknown portion of the administered dose.

Abraham et al. (54) supported their findings with a single light micrograph from a rhesus infant sacrificed 24 hours following oral intake of an emetic dose (4 g/kg of body weight) of GLU, although four monkeys were studied. Moreover, little or no evidence of lesion would be expected 24 hours after GLU insult because damaged elements are removed from the scene of an GLU-induced lesion with such remarkable efficiency, that 24 hours after insult, without pre- and post-insult comparison, it is virtually impossible to determine if damage has been done. In general, Abraham's work appears to be vulnerable to the criticisms of most studies, in that he maintains that he is replicating work done by Olney, but does not do as he says. A careful comparison of the two studies will demonstrate that age of subject, dosage administered, time between insult and examination of tissue, and methods of tissue preparation all differ. Abraham's study can also be criticized for

use of methodology known to be inappropriate for identifying GLU lesions. Finally, it was also noted by Nemeroff (106) that Abraham et al. (54) found in both control and GLU treated monkeys a "very small proportion of necrotic or damaged neuronal cells and oligodendrocytes...in the arcuate nuclear region of the hypothalamus." One would suspect that this might happen if the placebo, as well as the test material, contained small amounts of an excitotoxin identical, or similar to, GLU.

Also failing to reproduce neurotoxicity in primates, were studies of Abraham et al. (123), Newman et al. (124), and Stegink et al. (125). Stegink et al. (125) used the same data as Reynolds et al. (68,117,118) with two additional monkeys, and used the same methodology for tissue staining. His work, then, is subject to the same criticisms as hers. Abraham et al. stated that their present investigation was undertaken in an attempt to resolve some aspects of the controversy. However, the details of this methodology were identical to those of their earlier study (54) and are subject to the same criticisms. There would seem to have been no point to doing this study.

Newman et al. (124) claimed to have found no evidence in any instance of any change that could be attributed to MSG as described by Olney and Sharpe, although there were artifacts in some inadequately fixed areas as recorded by Reynolds and her co-workers. The study, as suggested by the following, gives the appearance of having been designed to facilitate the conclusion that GLU is a safe food (emphasis added by this author to highlight criticism):

> "Rhesus monkeys were maintained and observed in the primate buildings of HRC, where **most of them** were bred."
>
> The initial study was carried out with animals of 108, 99, 60, and 3 days, with unspecified histories.
>
> "The test solution was **readily** consumed voluntarily by all animals on all occasions throughout the study;"
>
> "The 3-day-old monkey had a **few** hypochromatic nuclei, and a **minimal** degree of vacuolation in the ventral hypothalamus, but **these findings were not regarded as significant**." "By electron microscopy, changes of the type reported by Olney and Sharpe were

seen in both test and control animals, **and were attributed to fixation artefact**."

Information pertaining to the animals is incomplete. Their history is uncertain No information is given about what transpired in the first 108 days of an animal's life.

Description of both procedure and findings is highly subjective and/or incomplete. "Readily" consumed does not necessarily mean **fully** consumed. If a "few" hypochromatic nuclei were quantified, how many would that be? What is "minimal?" On what basis were the findings "not regarded as significant?" What changes were seen? How **many** were test animals; and how **many** were controls?

A 1976 study by Reynolds et al. (126) which produced negative results relative to abnormalities of the subinfundibular region of the monkey brain provided yet another vehicle for allegedly "proving" that GLU is safe. Both mice and monkeys were studied. Mice, but not monkeys, were reported to show brain lesions. The monkeys were infant macaques with age ranging between 30 minutes and 14 days. It is of interest (and concern) to note that the cross section presented in Figure 4 of "...a 7-day-old infant Macaca fascicularis monkey that ingested 4 g/kg GLU..." appears, in every aspect, to be identical to a section of an "...infant rhesus monkey which received 4 g/kg of GLU by stomach tube..." presented in Figure 3 of the report by Stegink et al. (125) The GLU in Reynolds et al. study was prepared as a 20% w/v solution in water and administered as a single dose of as much as 4 g/kg GLU. We are told how many monkeys received each dose, but we are not given dosage by age. The techniques for evaluation of mouse brains is the same used by Lemkey-Johnston and Reynolds(86) and Reynolds et al.(88) in previously reported studies. These had been found by Olney (53) to be inappropriate. No information is given about the timing involved or the techniques used for evaluation of monkey brains.

In general, this study Reynolds concludes, "Neither aspartame nor MSG is **capable** of eliciting a lesion in the neonatal monkey brain." (Emphasis added.) In addition to the study's other faults, Reynolds et al. take a single finding of "...did not elicit..." and generalize it to "...it is incapable of eliciting...."

Neuroendocrine Disorders / Ad Libitum Feeding

The bulk of the studies dealing with neuroendocrine dysfunction were done in an obvious effort to discover and piece together bits of information which would help resolve the mysteries of the endocrine system. For most researchers, GLU was important not because of any importance in and of itself, but because its use produced certain effects in the body, and monitoring the relationships between administration of GLU, cell damage (particularly lesions) in various locations, and resultant changes in anatomy, physiology, and behavior elsewhere, might provide important clues to the secrets of human body function. As an excitotoxin, GLU has been used not only for its ablative effects, but also as a provocative tool (103,104).

But here again, a number of studies were done to "prove" that as a food additive, GLU is safe. One of the favorite strategies appears to have been to examine those factors which cause the "unwanted" result--in this case, neuroendocrine disorders associated with intake of GLU--and design a study which focuses on, or makes use of, non-relevant levels of otherwise relevant variables, betting, or knowing, that the levels used will not produce the "unwanted" result. Thus, females exhibit reproductive disorders and males do not, use males. Or if a neuroendocrine change is not exhibited in less than 20 days, examine the animals after 15 days. Then, when no significant differences between control and experimental groups are found, conclude that GLU is safe to use in food. Only someone with intimate knowledge of the subject could discern manipulation of this kind.

While these sorts of studies might well be grouped with others, they have a slightly different twist which sets them apart. The first studies give the **appearance** of attempting to replicate studies done already, while this new class of study makes no such pretense, but provides for the introduction of new variables. The logical fallacy in these studies comes when it is concluded that finding nothing while studying irrelevant variables "proves" that GLU is safe.

Most of these negative studies focused on ad libitum feeding. It would appear sensible to attempt to approximate the model of human ingestion of food in studying the safety of human ingestion of GLU. And that's the stated purpose for the bulk of the studies presented. As Olney (107) pointed out, however, the ad libitum animal studies fall far short of approximating the human condition.

Almost all of the studies which focused on ad libitum feeding of GLU to laboratory animals were underwritten by the food industry, and have, predictably, negative results. Over and above the fact that given the statistical model used, one cannot "prove" through these studies that GLU is safe, they are subject to the same range of criticisms as other industry sponsored studies.

The 1979 study by Matsuzawa et al. (79) will serve as our first illustration. The authors did a series of studies using both neonatal and 10-day old rats, given oral and subcutaneous doses of GLU at a total of 4 different doses. Controls were given saline solution. One might legitimately question the precise nature of the "...ad libitum diet containing 5% (w/w) MSG...," but that is not of immediate importance. One must note, more importantly, that the ad libitum diet was given "...for 10 days after weaning (at 20 days)." By 1979, the date of the study, it was well understood that the timing used was outside of the range of the animal's most susceptible age.

The conclusion is classic glutamate-industry: "MSG therefore produces marked reproductive endocrine abnormalities after maturation **only** when injected parenterally early in postnatal life, in repeated, very large doses. The development of reproductive endocrine function is not affected by MSG unless neurological damage occurs in the hypothalamus by any route of administration." (Emphasis added.)

Matsuzawa et al. have done one study, on one species, of a particular age, given a particular diet for 10 days, and conclude that because that one set of conditions did not elicit either neurological damage to the hypothalamus or **marked** endocrine abnormalities after maturation, that GLU produces marked reproductive endocrine abnormalities "...after maturation **only** when injected parenterally early in postnatal life, in repeated, very large doses." (Emphasis added.) They exclude all other possibilities.

The identical strategy is found in a 1979 study by Takasaki et al. (78). They report that, "Adverse effects from MSG have **never** been reported from dietary administration." (Emphasis added.) In this case, "never" equals four studies. Using logic similar to that used by Matsuzawa (99) they concluded that "MSG does not exert an adverse effect on somatic growth in that the hypothalamic neurons are not injured by any routes of administration, and the MSG did not induce somatic deficiency under the conditions of our experiments, which mimic the intended conditions of use of this material as a food additive."

In their 1979 summary of GLU toxicity in laboratory animals, Heywood and Worden (127) cite nine chronic animal studies in which various species were given ad libitum feedings of GLU over extended periods of time. These include studies by Ebert (128), Owen et al. (129,130), Semprini et al. (131), and Wen et al. (132). Because we have no data on chronic animal studies from persons other than those with close ties to industry and, therefore, have no records of positive results, we have no basis for evaluating the levels of variables used in these studies. And because they are incomplete and imprecise in detailing their methodology, it is difficult to evaluate the research as a whole. Ebert (128,133) used mice that were clearly older than Olney's mice (67). Ebert apparently used data from a 1953 study done at Arthur D. Little, Inc., entitled, "Report on a study of L-monosodium glutamate, DL monosodium glutamate and L glutamic acid with respect to potential carcinogenicity." The 1970 report of these data (128) was in the form of an abstract. The 1979 reports (133,134) were expanded abstracts done, "...to comply with the suggestion of the Select Committee on GRAS Substances during hearings on glutamates, held at Bethesda, Maryland on July 25-27, 1977" (133). We know that these studies producing negative results and thereupon claiming to "prove" that GLU is a safe food additive, are subject to the limitations of the statistics that they use, and that from the point of view of the statistical model, any conclusion of safety based on failure to find a difference between two groups is an invalid one. We also know that the procedures of Wen et al. (132) are subject to the same criticisms (39,52,112) as studies by Adamo and Ratner (110).

In another 1979 summary of the results of dietary administration of GLU, Anantharaman (135) stated that studies indicated that "...dietary administration of MSG at even very high doses was not found to result in any of these symptoms [produced by other routes of administration], including the endocrine disturbances." They cited Huang (136), Wen (132), Takasaki (137), Bunyan (138), Owen (129), and Trentini (85). They also cited two-year rat studies by Ebert (128) and Owen et al. (129), where no abnormalities were found in successive generations. And in their own study (135), they also produced negative results.

Studies by Owen (129), Takasaki (137), and Wen (132), have already been discussed in some detail. The additional studies mentioned here are, at the very least, subject to previously discussed statistical limitations.

The study reported by Anantharaman(135) must be criticized on different grounds. Unlike most of the research reported, Anantharaman provides a great deal of detail, including detail of the exact nature of the basal diet provided. And in that basal diet we note that "yeast food" is listed as a component of the protein (page 236, Table 3). At this point in time (1990), yeast food invariably contains either protease (which creates GLU during manufacture) or L-cysteine which produces neurotoxic effects somewhat different from, but more extensive than, the effects of GLU. We are suspicious, then, that the failure to find differences in growth of control and experimental groups **may be** due to the fact that both groups were receiving neurotoxic substances in their basal diet." (Emphasis added.)

Using inappropriate placebo materials has been discussed by others before. In 1981, Rippere (139) criticized the use of common food allergens as placebo materials, noting that even a minute trace of an allergen might trigger severe symptoms in a sensitized individual. In a study by Abraham et at. (123) cited earlier, it was noted that the control group exhibited some small evidence of brain damage just as the experimental group did, raising a question of what placebo materials might have been used. In 1990, this author questioned research done by Goldschmiedt, Redfern, and Feldman (140) which used beef broth as a placebo for controls. In the United States, one cannot purchase commercially prepared beef broth that does not contain some form of GLU (hydrolyzed protein, yeast extract, textured vegetable protein, flavoring, etc.) This author questioned the possible unwitting bias in placebo material in a letter to the editor of the *American Journal of Clinical Nutrition*. The letter was not published and no informative reply was received. The author questioned Feldman about the contents of the placebo. He replied that he did not know the contents of the various materials used.

A 1977 study by Heywood et al. (141) which focused on neurotoxicity, came to the same conclusion as Anantharaman. Heywood et al. concluded from **one** study of ad libitum feeding of GLU over a period of four days, using 20-day old mice that, "There is indeed no evidence from any dietary study yet reported that would suggest a lack of safety of MSG as a food additive." It should be noted that details of the amounts of GLU consumed are not given. In the discussion where it states that "...dose levels as high as 45.5 g GLU/kg body weight were achieved...", we are not told if that is per day, per animal, or total. Nemeroff (106) noted that their study did not present representative histological micrographs for evaluation (127).

In a second 1979 report, Takasaki et al. (142) again reviewed a number of studies and this time reported that, among other things, "Weanling, pregnant, and lactating mice fed large amounts of MSG in the diet ... did not develop hypothalamic lesions." As evidence they cited studies by Semprini et al. (143), Huang et al. (136), Wen et al. (132), and Takasaki (137). In addition, they reported findings from their own research (142) which compared the effects of GLU fed ad libitum to other routes of administration. In their report, they build from a discussion of findings of brain lesions to relationships of lesions to plasma GLU levels, to relation of ad libitum dietary feeding to plasma GLU levels, to histological effects of ad libitum feeding of GLU, to the statement that "...plasma glutamate levels... remained much lower than those **required** to induce hypothalamic lesions." (Emphasis added.) It must be understood that it has never been determined that any particular level of plasma GLU is required for the production of brain lesions. The logic used here is faulty.

Unfortunately, Takasaki (164) did not provide sufficient detail for one to evaluate the reports, and the reports, themselves, are lacking. Again, it will be observed that Wen (154) appears to have used the same techniques as Adamo and Ratner (110) and Oser (111) which Olney (39,112) and Burde (52) criticized in 1971.

A study by Iwata (88) failed to find behavioral abnormalities as a function of ingestion of GLU. The study is limited by the same design deficiencies noted in other studies. Iwata did not examine the brains histologically, yet concluded that there had to be lesion damage prior to there being behavioral effects. The overgeneralization from this study is that "...dietary administration... caused no behavioral latent effect in later life."

Prabhu et al. (144) failed to demonstrate differences in a battery of behavioral tests and drug applications. They mentioned that the results are based on surviving mice, but fail to state the mortality rate. Lengvari (145) also reported no differences between control and experimental groups in a number of variables. One must question the meaning of their failure to find a significant difference when they report a mortality rate of 45.1% (to day 30) as opposed to a 20% mortality rate for controls.

Related, but with a slightly different focus, are a pair of studies reported by Takasaki in 1979 (63) and 1980 (64), in which he studied the effect on brain lesions of administering various materials simultaneously with GLU. Takasaki reported that certain mono- and disaccharides and arginine

hydrochloride, leucine and the prior injection of insulin significantly reduced the number of necrotic neurons in the arcuate nucleus. In general, the detail provided about the study is incomplete, and the procedure is difficult to follow. It is not clear whether reduction in effect of GLU might have been due to inclusion of additional materials, thus diluting the test material. Moreover, statistics pertaining to the values for number of necrosed neurons observed appear to be based on analysis of **one** representative section from each animal. And values for representative brain sections appearing in Tables 1 and 2 (61) have vastly different values (195 +/- 18 and 263 +/- 15) for what would appear should be the same thing. One is compelled to question the meaning of "representative" under these circumstances.

Although data found in the 1979 review of GLU toxicity in laboratory animals, done by Heywood and Worden (127) have already been discussed here, the review, in and of itself, is of interest for the way in which it develops the discussion of GLU toxicity. First, we are told that there is a classical toxicological approach to doing research on food additives. Second, findings of chronic animal studies are reported, arranged by species of animal tested. Nine studies by four authors are presented. Very little detail of procedure is given along with the results. And, finally, the conclusion is drawn that "dietary administration of GLU in these conventional studies was found to be without significant toxic effect over the varying periods of administration."

Acute toxicity studies follow, again arranged by species. In this case, reports of lesions (or failure to find lesions) were accompanied by extensive discussion of plasma GLU levels, and some discussion of levels of GLU found in the brain. It will not be denied that the subject of plasma GLU levels is of interest in the study of GLU toxicity. But the tenor of the discussion, and, in some instances, the discussion itself, would have one assume or believe that toxic reactions can occur **only after** plasma GLU levels have become raised. The following quote from Heywood and Worden illustrates the point.

> "A fourfold increase in the levels of glutamate in the arcuate nucleus of the hypothalamus followed the elevation of plasma glutamate after a single subcutaneous injection of MSG (reference Perez and Olney, 1972). Peak plasma levels occurred after 15 min, and peak levels in the arcuate nucleus were attained after 3 hr. The results indicate that

> plasma concentrations above a certain level were necessary to induce brain lesions" (127).

The logic which says that plasma concentrations above a certain level are necessary to induce brain lesions, is false. If the work of Perez and Olney (42) cited by Heywood and Worden (127) does, indeed, demonstrate that GLU levels in the arcuate nucleus are increased after plasma levels are raised following a single subcutaneous injection of GLU, it does nothing to demonstrate that this is the **only** condition under which GLU levels in the arcuate nucleus can be raised. Unlikely as it might seem, it might be discovered some day that **smelling** petrochemicals increases GLU levels in the arcuate nucleus, but has no effect on the blood. There are **no data** that established that "...plasma concentrations above a certain level are **necessary** to induce brain lesions." (Emphasis added.)

Focus on Pregnant Females

Stegink and others (146,147) have done a number of studies on the subject of transplacental neurotoxicity of GLU which purport to demonstrate that GLU is safe. Neither lesions nor potentially abnormal behavior is studied in either of the papers cited. Observing increases and/or decreases in plasma GLU and/or other body fluids without observing concomitant variations in brain damage or other dysfunction has little meaning.

Establishment of excess MfG

Today there is sufficient excitotoxic free glutamate in processed foods, dietary supplements, snacks, protein powders and protein drinks, protein substitutes, enteral care products, and pharmaceuticals for a person to consume the quantity necessary for that free glutamate to become excitotoxic. Only a portion of that comes in an ingredient called monosodium glutamate or E621.

In 1957, bacterial fermentation was introduced as a new and improved method for production of free glutamic acid for use in food. From that point forward, with genetically modified bacteria secreting free glutamic acid through their cell walls, unlimited production of free glutamic acid was virtually assured (148).

It wasn't long before competing manufacturers added dozens more excitotoxic food additives to the American diet. Following MSG's surge in production and its manufacturer's aggressive advertising, there was broad recognition that profits could be increased if a company produced its own flavor-enhancing additives. Since that time, the market has been flooded with flavor enhancers and protein substitutes that contain manufactured free glutamate (MfG) such as hydrolyzed pea protein, yeast extracts, maltodextrin and soy protein isolate, as well as MSG.

Although there have been studies in which mention was made of the fact that there are substantial amounts of free glutamic acid in processed food (2,149-156), a search of the medical literature failed to return a single study that provided detail.

However, you have only to compare the ingredients listed on the labels of processed and ultra-processed foods to a list of the hidden sources of MfG to realize just how much MfG there is in the food supply. Table 1 lists the food ingredients that include free glutamate as an ingredient or a constituent of an ingredient (Table 1). By virtue of the fact that ultra-processed foods are made, at least in part, with inferior foods and/or chemicals, every ultra-processed food contains flavor-enhancers, which will contain MfG regardless of the ingredient names on the labels describing those ingredients.

In addition, there are numerous market reports with promotional materials that speak of MfG history and forecast. A sample will be found in Table 2. Market reports for monosodium glutamate focus on that commodity. Market reports for glutamic acid generally take into account all flavor enhancers.

Since the 1957 change in method of MSG production, there are so many products that contain excitotoxic ingredients that it is easy for a consumer to ingest an excess of excitotoxic material during the course of a day.

Effective delivery of excitotoxic free glutamate

Effective delivery of excitotoxic free glutamate would depend in large part on the integrity/health of the brain to which it is being delivered.

In children and adults with mature brains, delivery can be accomplished by providing the subject with free glutamate to ingest in sufficient quantity to cause it to be excitotoxic.

Delivery of excitotoxic free glutamate to a fetus and/or neonate will be accomplished when a pregnant or lactating female passes excess free glutamate to a fetus or neonate through the placenta or in mothers' milk.

Nourishment (and not so nourishing material) is delivered to the fetus in the form of material ingested by a pregnant woman and passed to the fetus through the placenta.

MSG can cross the placenta during pregnancy (157-159), can cross the blood brain barrier (BBB) in an unregulated manner during development (160-163), and can pass through the five circumventricular organs which are leaky at best at any stage of life (161,164). Glutamate is an ingredient that passes to the fetus. The placenta does not filter out glutamate (157). Moreover, the BBB is easily damaged by fever, stroke, trauma to the head, seizures, ingestion of MSG, and the normal process of aging (98,165).

And the fetus will be more vulnerable to glutamate-insult than the newborn.

Similar to drugs and alcohol, free glutamate can also be passed to infants through mothers' milk. Newborn humans will receive glutamate through mothers' milk or through infant formula, both of which routinely contain free glutamate.[1]

The glutamate in mothers' milk, however, will not be excitotoxic unless lactating mothers ingest excessive quantities of free glutamate – quantities sufficient to cause free glutamate to become excitotoxic.

Onset of the obesity epidemic

According to the Surgeon General's Vision for a Healthy and Fit Nation, the prevalence of obesity changed relatively little during the 1960s and 1970s, but increased sharply over the ensuing decades (166). That

[1] Centers for Disease Control (CDC). Environmental Exposures/Toxicants: Do Chemicals in the Environment Pass to Infants through Breast Milk? https://www.cdc.gov/breastfeeding/breastfeeding-special-circumstances/environmental-exposures/index.html exposures/index.html (Accessed Feb 18 2020)

information is consistent with information that comes from the National Health and Nutrition Examination Surveys (NHANES) which periodically collect measured height and weights in representative samples of the population. The first records of weight came from the CDC's 1960-1962 report with subsequent reports confirming that the prevalence of obesity among adults more than doubled between 1976-1980 and 2007-2008.[2]

Summary and conclusions

We have spoken briefly about excitotoxicity, the phenomenon underlying the obesity epidemic, drawing attention to the fact that a possible role for excitotoxins from exogenous sources has not previously been considered.

We have reviewed the studies that present evidence of glutamate excitotoxicity and those that challenge them. Underscoring the role of glutamate-induced brain damage leading to obesity, is the fact that since 1980 it has been common practice to use monosodium glutamate or glutamic acid to produce brain-damaged obese animals for use in studies of various glutamate-related abnormalities.

We have described the way in which excitotoxic free glutamate can be delivered by pregnant women to fetuses and neonates, causing brain damage and subsequent obesity.

The single challenge to the assertion that the brains of the fetus and neonate are vulnerable to the toxic effects of glutamic acid from exogenous sources has been mounted by the International Glutamate Committee (IGTC) based on a paper Richard Hawkins presented in September 2008 at the IGTC's 100th Anniversary Symposium of Umami Discovery: "*The Roles of Glutamate in Taste, Gastrointestinal Function*."

In 1969, the IGTC was organized to represent the interests of Ajinomoto in the United States. Hawkins received both travel expenses and an honorarium from the IGTC, and acknowledged the sharing of ideas and advice from Andrew Ebert, Ajinomoto's agent in charge of providing test and placebo materials to their researchers doing double-blind studies on the safety of MSG. It was Ebert who provided his researchers with

[2] https://www.cdc.gov/nchs/data/hestat/obesity_adult_07_08/obesity_adult_07_08.pdf

placebos containing aspartic acid, an excitotoxic amino acid known to cause adverse reactions and brain damage identical to that caused by the excitotoxic glutamic acid in MSG test material.

Without taking into consideration the unique properties of an immature brain, Hawkins asserted that the human brain is impervious to glutamate damage. Moreover, while Hawkins studied the brain, he did not study the arcuate nucleus and, therefore, his findings are irrelevant to the role of glutamate-induced brain damage in the area that plays a role in regulation of obesity.

It has been demonstrated that following the 1957 modernization of glutamate production, there has been sufficient free glutamate available and accessible in processed and ultra-processed foods to cause accumulated glutamate to become excitotoxic.

From National Health and Nutrition Examination Surveys (NHANES) documenting the prevalence of overweight, obesity, and extreme obesity, We have observed increased incidence of obesity dating from 1960, as well as the demonstration of racial disparities. In the 2012 article "*The Nation's childhood obesity epidemic: Health disparities in the making,*" Suzanne Johnson makes a case for the obesity epidemic being, in part, a product of an environment that promotes overeating -- over time having changed types and quantities of food we eat. She cites less time for in home food preparation, the consumption of a plethora of fast food and convenience food, and the fact that fast-food restaurants are more common in ethnic-minority neighborhoods.[3]

The reader has only to connect the dots between 1) the vulnerable brain of the fetus and neonate receiving excitotoxic amino acids in processed and ultra-processed food, and 2) the fact that prior to the surge in production of glutamic acid triggered by the modernization of manufacture of the glutamic acid in MSG, there was no obesity epidemic. Then trace the unfolding of the obesity epidemic from reformulation of free glutamate in 1957 to the early 1970s when those made obese by the influx of free glutamate began to become noticeable.

[3] https://www.apa.org/pi/families/resources/newsletter/2012/07/childhood-obesit

Thus, it has been demonstrated that obesity can be caused by excitotoxic amino acids ingested by pregnant and/or nursing women and delivered to fetuses and neonates who exhibit obesity as they reach maturity.

No discussion would be complete without considering why this information has not been discussed previously by others. With the first suggestion that MSG might have toxic potential, those with financial interest in promoting MSG as a valuable flavor-enhancer launched well-funded, well-articulated campaigns to promote their product, and deny its toxicity. That included rigging studies to come to the foredrawn conclusion that MSG is a harmless food additive and securing the active cooperation of regulators as well as the help of medical professionals (167).

That might account for the fact that to date, the roles of MSG and MfG in the obesity epidemic have been overlooked.

Recognition of the fact that glutamate-induced brain damage in fetuses and neonates lies at the root of the obesity epidemic should serve as a valid starting point for new ground-breaking research. It should put an end to the shame and blame that have long been associated with obesity, and facilitate appropriate counseling and medical interventions for those who are afflicted.

Excitotoxic amino acids delivered to fetuses and neonates by pregnant and nursing women should be included as recognized risk factors for obesity.

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