Monosodium Glutamate: An Assessment of Health Implications in Human and Animal Studies

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Abstract: This review assesses many of the health implications associated with monosodium glutamate (MSG) in humans and animals. MSG is a salt derivation of the amino acid glutamate. The prevalence of this salt as a food additive in Asian cuisine and other diets makes MSG a relevant aspect of the human diet worldwide. Debate over the healthiness of MSG and its effects on human obesity and other health problems has led to a negative public opinion of the additive. This literature review assesses studies that pertain to weight gain and obesity in rats and humans after consumption of MSG, as well as studies concerning the effects of MSG consumption on asthma attacks in humans and behavior and memory in rats. Findings suggest that MSG is neurotoxic in rats when injected neonatally. When consumed orally, the effects of MSG are reduced. The food additive is correlated with obesity in weight gains and humans, but there is no evidence that suggests MSG causes weight gain or increased body mass in humans. Findings suggest that MSG is part of an interaction between metabolism and neuronal inhibition in the arcuate nucleus of the hypothalamus that can increase leptin resistance, inhibit growth hormone (GH), and increase central adiposity and body mass. Both humans and rats are likely to consume high fat foods that contain MSG and other substances such as trans fatty acid (TFA) that could increase adiposity, body mass, and lead to weight gain. High fat TFAs and MSG combined account for greater negative findings that MSG or TFAs and high fat alone. The amount of MSG consumed daily varies from .3 to 5 grams according to several studies. The dosage level in both rats and humans has mixed effects. While the effects of MSG on rats seem directly related to the neurotoxicity of neonatal injections, human studies fail to assess the neurotoxic levels reached in rats. Increased
obesity and body mass in rats is also associated with diabetes mellitus, hyperinsulinemia, steatosis of the liver, and other ailments. Although findings confirming that MSG induces asthma are suspect, other results show that MSG could agitate asthma in a small subset of the asthmatic population. While the manner in which MSG causes impaired spatial memory and learning in rats could range from impaired vision to reduced physical activity, MSG negatively affects spatial memory and learning in rats. This review asserts that both oral and neonatal consumption of MSG leads to scarring of the neurons in the hippocampus and inhibited glutamate synthesis, resulting in impaired spatial memory and learning.

In humans, MSG is correlated with a decline in overall health that includes increased risk for obesity, body mass increase, and weight gain. A small subset of asthmatics appears vulnerable to MSG-induced asthma. In rats, both neonatal and oral consumption of MSG shows more severe effects, including increased adiposity and body mass, scarring of the arcuate nucleus of the hypothalamus, increased vulnerability to diabetes mellitus, steatosis of the liver, hyperinsulinemia, and decreased proficiency in tasks of spatial memory and learning. MSG was shown to improve the health of malnourished children in rural Indonesia, yet beyond this finding, MSG is associated with or directly contributes to decreased health in both animals and humans.

**Introduction:**

Over the past several decades, debate over the health implications involving monosodium glutamate (MSG) has led to a predominantly negative public opinion about the food additive (He et al., 2008). Animal studies have consistently shown that animals respond
negatively to injections of MSG at levels considered to be neurotoxic. This study will assess not only the validity of the claims that MSG is neurotoxic when injected in animals, but also consider the implications of MSG for weight gain and obesity in human beings, the suggested relationship between MSG and asthma reactions, and the inhibition of cognitive functioning posited in several studies. Through analysis of human studies and relevant animal studies, this review seeks to provide a holistic perspective on the health implications of MSG in humans and animals.

Several studies assert that the average consumption of MSG in Chinese adults is upwards of 3.6 grams (Zhou et al., 2003; He et al., 2008); however, other studies suggest between 1 and 5 grams (Shi et al., 2010). This makes MSG an important part of the human diet. MSG is a salt derivation of the amino acid glutamic acid, or glutamate, that is commonly found in Asian cuisine associated with Chinese restaurants and now frequently found in the Western diet (Shi et al., 2010). Because MSG is both an additive and a chemical in natural foods, exposure to this substance is worldwide. Glutamate is an amino acid that is vital in metabolism specifically involved in the breakdown of protein (Matyskova et al., 2007). MSG, like salt in the United States and other Western nations, is one of the most common food additives and flavor enhancers in Asian food. MSG is commonly found in high fat foods associated with unhealthy eating (Collison et al., 2010). In the last several decades, the public’s negative opinion of MSG has led to identification of the presence or absence of MSG by food processors. Research views the increase in MSG and other food additives in human diets as having a correlation with the alarming increase in overweight and obesity across all age ranges, genders, and
populations. This review will, in part, look at several studies, including those involving the INTERMAP study regarding weight gain and health in China and other nations, to assess the relationship between MSG and weight gain and obesity. Looking at MSG and its method of consumption within animal studies, specifically using rats, to understand further the complexities of MSG’s relationship with weight gain and body mass will provide insight into the mechanism, if any, that allows MSG to increase weight and body mass. Considering that glutamate is an important aspect of metabolism, as well as a neurotransmitter that relays signals between the brain, nervous system, and digestive system, the amount of consumption of MSG could play a role in weight gain (Shi et al., 2010). This study will assess the methods of consumption, its effects on voracity, growth hormone, leptin levels, and areas of the brain such as the arcuate nucleus of the hypothalamus that can help determine the effects of MSG on weight and obesity.

Before investigating MSG further, it is important to identify the areas of the brain and other biological aspects that play a role in MSG consumption. Many studies will suggest that the scarring of the arcuate nucleus of the hypothalamus indirectly contributes to the increase in adiposity and body mass measured in rats and humans, as well as facilitating leptin resistance and the level of food consumption (Pepino et al., 2005, Sasaki et al., 2009). The arcuate nucleus contains neuron bundles that are associated with neuroendocrine functioning, specifically human growth hormones, as well as subject to the effects of leptin and insulin inhibition that is known to affect appetite and the amount of food consumption (Matyskova et al., 2007). Leptin is a protein hormone involved in the regulation of appetite and metabolism. Leptin is produced mainly by white adipose tissue
and its levels are related to the amount of adipose tissue and affects both food consumption and hunger. Adiposity refers to the amount of fat found in adipose tissue (Matyskova et al., 2007).

Asthma is a disease rooted in the inflammation of the lungs that results in obstrution of the air passages as well as bronchospasms of the lungs. Asthma attacks are characterized by wheezing, coughing, and chest tightness (Schwartzstein et al., 1987). Assessments of pulmonary functioning measure the lung capacity and the level of pulmonary output in percentage units referred to as forced expiratory value (FEV), as well as measurements of peak expiratory emission rate (PEER) (Woessner et al., 1999).

In a study by Allen and Baker (1981), researchers posited that MSG induced asthma attacks in two subjects. From this research, attempts to replicate the findings of this study and Allen et al. (1987) have sparked a debate over the implications of MSG-induced asthma. Although questions concerning MSG and “Chinese restaurant syndrome” began to surface in the 1980s, the debate regarding asthma was initiated with the findings of Allen and Baker (1981). This review seeks to summarize the overwhelming findings suggesting that MSG does not induce asthma. The long delay between consumption and asthma attack presents a controversial proposition that MSG affects only a small subset of the asthmatic population after MSG has been fully digested. This study will focus less on the mechanism of MSG and asthma, as there exists very little research on the subject, and more importantly on the question of whether or not MSG causes or contributes to asthma attacks, as well as the validity of the research methods conducted in studies concerning asthma and MSG.
The hippocampus is a region of the brain and part of the limbic system associated with memory (Collison et al., 2010). Research has concluded that the hippocampus plays an important role in memory, specifically spatial memory (Frieder and Grimm, 1984). Animals used in MSG-induced obesity research have shown decreased efficiency in tasks testing spatial learning and memory. Research on the effects of MSG on memory and learning is primarily limited to animal studies involving rats, and much of this research focuses on the effects of MSG on spatial learning and memory as a result of the effects of MSG on the hippocampus and its neuronal processing. Animal studies show a clear relationship between MSG and spatial learning and memory; however, this study will explore the complexities of the underlying mechanism. Does MSG directly affect areas of the brain as the mechanism underlying weight gain and obesity in rats suggests? Or does MSG-induced obesity and weight gain affect mobility and physical activity to the detriment of rats’ performance in place learning tasks? The interaction of MSG and vision will also be a relevant consideration.

The United States Food and Drug Administration have deemed MSG a safe additive and ingredient in foods (Pepino et al., 2005). What this review ultimately seeks to assess is not the safety of MSG, but the varying degrees of negative health implications associated with MSG in both humans and animals. Considering the findings, this study asserts that MSG is a safe but relatively unhealthy food additive associated with increased body mass and adiposity in humans, as well as a possible connection to asthma in a small subset of the asthmatic population. The neurotoxic levels of MSG injected into rats results in not only increased body mass and adiposity, but also heightened diabetes
mellitus and degeneration of the liver. These neurotoxic effects have not been observed in humans. MSG is correlated to a decreased proficiency in spatial learning and memory tasks in rats, although the underlying mechanism causing this deficiency presents several possibilities.

**MSG, Obesity, and Health in Rats**

Research suggests a relationship between consumption of MSG and weight gain and obesity in humans, but the exact mechanism and level of neurotoxic activity underlying negative health implications is relatively unexplored (Collison et al., 2010). As in many cases involving human research, it is necessary to explore animal research with MSG, both orally and neonatally ingested, to understand the possible mechanisms of MSG-induced weight gain and the validity of previous studies’ claims that MSG consumption leads directly to weight gain and obesity. In order to more closely assess issues of obesity, weight gain, adiposity, leptin resistance, food consumption, and their interaction, this review presents studies that differ in their methods of inducing MSG consumption in animals.

**Oral Consumption**

The oral consumption of MSG leads to negative effects with regards to obesity and body mass in rats, but not at the level found in neonatal injection of MSG. In Collison et al. (2010) the effects of MSG on both weight gain and lipid adiposity were measured in addition to impairment of spatial memory. Subjects were presented with both MSG and Trans fatty acid (TFA) substances for ad libitum oral consumption, as
well as a combination of the two substances. Collison et al. (2010) note that leptin resistance caused by MSG ingestion and insulin resistance brought on by TFA consumption are both possible mechanisms of inducing obesity. Furthermore, TFAs and MSG are likely to be common ingredients in food. Rats orally consumed 0.24 g/L of MSG in water, 8.68 percent TFA substance, a combination of the two substances, or water. Both food and water were presented ad libitum daily over a two week period and monitored for consumption. The combined TFA and MSG group significantly increased central adiposity in the rats, while there was no significant increase in food and water intake or body weight for both control and experimental rats. The combined group also presented with greater leptin resistance. The TFA and MSG group showed greater adiposity than both the individual MSG group and TFA group. There were no significant differences between the individual MSG and TFA groups. Both the TFA group and MSG group demonstrated significantly more adiposity than the control group. Female rats weighted significantly more than male rats for both the MSG and MSG and TFA experimental groups (Collison et al., 2010).

Although findings show that MSG significantly increases food intake, the link between MSG and weight gain cannot be attributed fully to this increase in consumption. An increase in food consumption was not measured in Collison et al. (2010). According to a study by Leitner and Bartness (2008), rats that are deprived of food after neonatal injection of MSG exhibit changes in body fat mobilization. Leitner and Bartness (2008) assessed the effects of orally consumed MSG, considering the possible connection between leptin resistance and lesions in the arcuate nucleus, as well
as the role of body fat and lipid mobilization after MSG consumption. This study tested Siberian hamsters rather than rats and, although Leitner and Bartness (2008) do not mention this as a confound in comparing research with rats, the difference should be considered in interpreting the results. Hamsters orally ingested substances with 25 mM concentrations of MSG after 56-hour food deprivations. Controls consumed a placebo. Food intake was measured after each post-deprivation feeding, as well as body mass and leptin levels. Hamsters that consumed MSG had significantly increased body mass, specifically in white adipose tissue pads. Serum leptin levels were significantly higher in the experimental groups. According to Leitner and Bartness (2008), MSG deters lipid mobilization through and inhibition of glutamate synthesis, as well as metabolism through decreased thermogenesis. Growth hormone levels also decreased. MSG-treated animals still mobilize fat storages, but less efficiently than controls. Female hamsters exhibited heightened MSG sensitivity. Although MSG-treated rats presented with significantly greater body mass, as well as increased food consumption, Leitner and Bartness (2008) suggest that lipid mobilization is still active in MSG-treated rats, and that the combined effects of MSG on the arcuate nucleus and increase in food consumption account for not only the increase in body mass, but also other negative health effects found in rats and hamsters treated with MSG.

A study by Kreicheck et al. (2010) suggests that mobilization of fat bodies plays an important role in the weight gain associated with MSG consumption, but suggests an interaction between hydrochloric acid and the digestive system that could lead to MSG-induced obesity. Krycek et al. (1994) assessed the influence of MSG consumption on
basal gastric acid secretion, gastric mucosa, and body weight in rats. Rats were divided into three groups that were food for durations of 10, 20, and 30 days with daily oral doses of MSG that were randomized from 15 to 30 mg/kg of body weight. Rats were found to have ulcers and lesions of the gastric mucosa, as well as an increase in body weight. This study posits that the increase in body weight associated with MSG is a result of the increase in secretion of hydrochloric acid. The same secretion of hydrochloric acid could lead to gastritis, duodenal ulcers, and other acid-related diseases. Results showed that each MSG group demonstrated significantly more weight gain than the control groups (water). The 30-day feeding group demonstrated the most significant increase in weight gain. Krycek et al. (1994) suggest that the increased secretion of hydrochloric acid interferes with the digestion of MSG and the high fat foods that commonly contain MSG. Impaired digestion leads to a demobilization of metabolizing fat bodies. Consumption of high amounts of MSG is indicative of an excessive consumption of high fat foods that could also be correlated to an increase in weight gain.

An increase in food consumption after ingestion of MSG is a possible cause for increased weight gain and obesity in rats. In a study by Fernandez-Tresguerres Hernandez (2005), the effects of oral consumption of MSG in both pregnant female rats and subsequent administration of oral ingestion in new-born rats during the first week after birth on appetite and hormone levels were analyzed. Both pregnant mothers and offspring consumed 25 mg/kg of body weight of MSG on a daily basis. Some offspring were only given MSG through the mother’s ingestion, while others only received MSG after birth through oral dosages. Control groups drank water only. The pregnant mothers
consumed MSG during the last half of their pregnancy, while the offspring began consumption during the first week of life. At 30 and 90 days, the offspring were assessed for arcuate nucleus condition, plasma leptin levels, and food consumption. Rats born to mothers that consumed MSG during pregnancy and consumed MSG from postnatal day 1 demonstrated the highest levels of food consumption at days 30 and 90, as well as the highest plasma leptin resistance. Growth hormone levels were reduced at day 30 but recovered partially by day 90. Rats that consumed MSG through neonatal ingestion of oral consumption demonstrated significantly higher levels of food consumption than control rats. MSG rats showed increased adiposity but did not differ significantly in weight gain compared to control rats. This study suggests that rats affected by MSG consumption during pregnancy and early postnatal development have significantly affected hypothalamic functioning, resulting in altered hormone levels and an increase in voracity compared to control rats.

The increase in food intake and obesity observed in rats that have consumed MSG has been connected with an increase in leptin resistance in the arcuate nucleus; however, a study by Kondoh and Torii (1995) proposes that MSG suppresses weight gain, fat deposition, and leptin levels in Sprague-Dawley rats. Rats were divided into 4 groups for oral consumption: 1% MSG and water solution and high fat sucrose, 1% MSG and water solution and low fat sucrose, water and high fat sucrose, and water and low fat sucrose. Calorie, fat and carbohydrate content of the diet were considered in this study. MRIs were used to measure fat content over the course of 15 weeks. Rats with access to MSG solution consumed more of this solution than rats with only water. MSG-treated rats had
smaller weight gain and lower fat mass, and lower plasma leptin levels. There were no observed changes in lean mass, food and energy intake, blood pressure, or cholesterol. Plasma glucose levels were also maintained. Kondoh and Torii (1995) suggest that unlimited consumption of MSG actually increases energy expenditure and thermogenesis, specifically through activation of the glutamate receptors that are functionally linked to the vagus nerve. Energy expenditure is increased as a result of communication between the stomach and glutamate receptors via the vagus nerve. The decrease in leptin resistance surprisingly did not account for a change in food intake between the experimental and control groups. Kondoh and Torii (1995) suggest that decreased leptin resistance should result in some form of alteration in food consumption. This finding suggests a downplayed role of leptin in the interaction with MSG. Kondoh and Torii (1995) suggest that, contradictory to the findings of Collison et al. (2010) and Leitner and Bartness (1995), oral ingestion of MSG has more negative effects than neonatal consumption of the substance. Collison et al. (2010) and Leitner and Bartness (2008) found that MSG increased adiposity and body mass but did not produce a weight gain. Krycek et al. (1994) suggest that increased MSG consumption leads to an increase in weight gain. Both Leitner and Bartness (2008) and Collison et al. (2010) showed that MSG did not increase food consumption but increased leptin resistance, while Krycek et al. (1994) and Fernandez-Tresguerres Hernandez (2005) found that MSG consumption did increase voracity, with Fernandez-Tresguerres Hernandez (2005) pointing to hypothalamic degeneration as the result of MSG consumption and the reason for unregulated appetite in rats. Although Kondoh and Torii (1995) assessed the role of high
and low fat substances, while Collison et al. (2010) presented the combined effects of MSG and TFA, the high and low fat substances presented by Kondoh and Torii (1995) did not elicit the same weight gain and adiposity increases as Collison et al. (2010), suggesting that TFA could accentuate the obesity and adiposity measured in Collison et al. (2010) more than MSG. Furthermore, contradictory findings of increased and decreased leptin resistance by Kondoh and Torii (1995) bring the role of leptin into question. Krycek et al. (1994) also present a possible mechanism for MSG consumption inducing obesity: the interference of hydrochloric acid secretion resulting in inhibited digestion of MSG and high fats.

**Neonatal Injection**

While Collison et al. (2010) assessed spatial memory in addition to weight gain, Sasaki et al. (2009) sought to assess the effects of MSG consumption on diseases more closely linked to weight, such as diabetes mellitus and steatohepatitis of the liver. As MSG consumption has a possible connection to severe obesity, urinary glucose, hyperinsulinemia, and a decrease in both glucose tolerance and insulin sensitivity, Sasaki et al. (2009) looked to understand further the relationship between MSG consumption (at varying dosage levels), weight, and the aforementioned diseases.

Rats were injected neonatally during the second week after birth with 2mg/g of body weight MSG for 5 consecutive days, 4mg/g of body weight on one day, or 4 mg/g of MSG for 5 consecutive days. A saline control was also used for comparison. Rats injected with MSG all exhibited severe obesity at 29 weeks of age, as well as signs of diabetes mellitus and liver lesions before 54 weeks. The most severe lesions, diabetes,
and obesity were found in the rats administered the single 4mg/g injection of MSG. The most significant increase in body weight was also found in this group. In the 4 mg/g of MSG injected for 5 consecutive days, body length and weight were both inhibited. The MSG-injected groups also demonstrated significantly greater BMI at both 29 and 54 weeks. At 54 weeks only female rats in the 2 mg/g injected for 5 days and the 4 mg/g single injection had significantly different body weight as compared to the controls. The single injection of MSG group did show elevated food intake at 29 and 54 weeks, but there was no significant difference. This group also had a higher appearance of blood glucose and insulin tolerance at 29 and 54 weeks. Adiposity, as measured in white adipose tissue, was higher for MSG-injected rats but not significantly. In conclusion, Sasaki et al. (2009) suggest that MSG is toxic in higher dosages, though the effects of these injections over time require further exploration. Just as Collison et al. (2010) posit a relationship between weight gain and other negative health implications, the increase in weight and BMI found by Sasaki et al. (2009) appears connected to pronounced diabetes mellitus, increased blood glucose, and erosion of the liver. The increase in adiposity suggests an underlying mechanism for increases in BMI in Collison et al. (2010). While MSG and TFA combined did not affect food intake, the MSG ingestion in Sasaki et al.(2009) for single subcutaneous 4mg/g injections did increase food intake. The MSG only group in Collison et al. (2010) did not increase food intake. A possible explanation for this result is the difference between oral consumption and the heightened toxicity of neonatal injection.
The lesions found in the arcuate nucleus associated with MSG consumption and their relationship with food intake and metabolism led Dawson, Wallace, and Gabriel (2010) to further explore feeding in rats injected neonatally with MSG. Rats in one experimental group were injected on postnatal days 2 and 4 with 2.5 mg/g of MSG, while the other experimental group was injected with 2.5 mg/g of MSG on postnatal days 2, 4, 6, and 8. A control group was injected with sodium chloride. Rats fasted for 48 hours prior to injection and subsequent feeding. Unlike Sasaki et al. (2009) and the oral consumption studies, this study measured neuropeptide Y content, hypertension, and organ weight, in addition to food intake and body weight. Those rats injected with MSG for 4 days ate significantly more than controls during their dark cycle, while both experimental groups ate significantly more food than controls during the day cycle. Dawson et al. (2010) suggest that food intake regulation is affected by MSG consumption, and that both the reduction in neuropeptide Y and the increase in leptin resistance create a toxic interaction in the hypothalamus and circumventricular organs that leads to increased food intake in both low and high dosage injections of MSG.

The injection and oral consumption of MSG, when paired with varying amounts of TFA and fat diets, has demonstrated heightened adiposity and increases in body mass. Matyskova et al. (2007) present findings that address a wide range of aspects regarding MSG and its relationship to obesity and weight gain, including the presentation of high and low fat calorie diets. Comparing both male and female rats, with the experimental group receiving 4mg/g of body weight subcutaneous injections of MSG on postnatal days 2-8 and controls receiving saline injections on the same schedule, Matyskova et al.
(2007) measured adiposity, body weight, insulin resistance, glucose resistance, and other related aspects of MSG consumption. Both MSG and saline groups were further divided into high and low fat calorie diets. Rats were given food and water ad libitum.

Results showed that rats in both experimental and control groups did not differ in body weight, but that experimental groups in both diets had significantly increased fat to body weight ratios, with the high fat group having the most significant difference. Hyperleptinemia and hyperinsulinemia were found in both experimental groups, and the difference was more marked in females. Only female rats showed a significant increase in weight at 9 weeks, but both experimental groups overall did not demonstrate a significant difference in weight gain overall. The increase in obesity as a result of hyperleptinemia and neuronal damage to the arcuate nucleus is the most likely explanation of the effects seen in this study; however, the fact that only female rats showed any significant weight gain suggests an interaction in hormone levels such as Growth Hormone (GH) (Matyskova et al., 2007). The same liver weight loss and steatosis observed in Sasaki et al. (2009) was found in these experimental rats.

Leitner and Bartness (2008) cited a decrease in growth hormone as a result of MSG ingestion, which could possibly lead to increased adiposity and enhanced obesity. In a study by Hermanussen et al. (2006), the implications of MSG and its relationship with growth hormone, voracity, and stature were analyzed in Wistar rats utilizing both oral and neonatal consumption of MSG. Rats were divided into 4 groups. The first group was given a 4 mg injection of MSG once daily. The second and third groups consumed 2.5 and 5 grams of MSG with their daily meal. The fourth group was
the control group. Unlike the previous studies mentioned, in which rats were assessed after oral consumption of MSG and subcutaneous injection, this study assessed the effects of MSG consumption in the offspring of the pregnant mothers that comprised the aforementioned experimental and control groups. Mothers that consumed MSG either orally or through subcutaneous injection during their pregnancy were found to birth rats with reduced birth weights as compared to controls. The offspring of mothers that orally consumed MSG were found to have lower GH serum levels than the control and injected-MSG groups at both 30 and 90 days. Water and food consumption were both increased in the MSG-treated groups, with the 5g daily group having water consumption increase 3-fold and food consumption 2-fold compared to controls. Furthermore, the increases in voracity were accompanied by contrasting amounts of leptin in the offspring. Those rats born to mothers who consumed MSG orally showed increases in leptin resistance, while those rats in the neonatal injection group showed decreases in leptin. Both groups showed increases in food and water consumption, but the oral consumption group increased consumption more than both the injection group and controls. (Hermanussen et al., 2006) In contrast to previous studies, Hermanussen et al. (2006) found that oral consumption of MSG was more toxic than neonatal injection. Voracity increased and growth hormone secretion was impaired in both experimental groups. MSG clearly reduced birth weight, increased voracity, and affected leptin levels in both directions. The short stature measured in MSG-treated rats is also associated with obesity; however, this study suggests that the relationship between MSG and obesity is contingent on method of consumption.
Neonatal injection of MSG shows increases in adiposity, body mass, and leptin resistance. Oral consumption of MSG results in similar increases but not to the same degree as neonatal injection. The findings of Kondoh and Torii (1995) and Hermanussen et al. (2006) assert for different reasons that oral consumption is more neurotoxic and results in greater obesity and body mass in rats. The divergent leptin resistance demonstrated by the neonatal and oral injection groups as well as the increased voracity in both groups suggests that MSG’s interaction with leptin and food consumption is more complicated than previous studies assert. However, the heightened leptin resistance in the oral consumption group of Hermanussen et al. (2006) cannot negate the consistent findings that neonatal injection increases leptin resistance more than oral consumption in previous studies where body mass and fat deposits have significantly differed from control rats. Findings from Krycek et al. (1994) and Fernandez-Tresguerres Hernandez (2005) suggest that oral consumption of MSG leads to increased voracity and weight gain and obesity, and although the neuronal degeneration of the hypothalamus is cited as a possible inhibitor of appetite regulation, the relationship between leptin resistance and food consumption is not considered. The proposal of Krycek et al. (1994) that increases in hydrochloric acid secretion during digestion of MSG and foods containing MSG interfere with metabolism and could lead to weight gain suggests that MSG affects both the brain and the digestive system, and the chemical interaction of digestion and neuronal processing could further explain the increase in weight and food consumption observed in rats treated with MSG.

*MSG, Obesity, and Humans*
The effects of MSG on weight gain and obesity has been studied extensively in rats. MSG induces increased fat adiposity and BMI in rats while presenting conflicting results for weight gain. The research on MSG and its effects on weight gain and obesity in humans are relatively limited. Most of the research has focused on Asian populations, specifically Chinese, as there is a heightened consumption of MSG in Asian diets. The results are mixed and present both parallels and disconnects with research in rats.

The association of MSG with weight in Chinese populations was studied by He et al. (2008). He et al. (2008) propose that weight gain and obesity are function of energy balance. The composition of the diet affects energy balance and metabolism. Considering that both worldwide obesity and consumption of MSG have both dramatically increased during the last 50 years, this study sought to understand the relationship between MSG and Body Mass Index (BMI) in healthy Chinese adults. Compiling a data pool of 4600 subjects from 3 rural Chinese areas as well as Japan, the United States, and the United Kingdom, subjects were engaged in an intensive two-day consultation on the amount of MSG consumed in their diets. Multi-pass recalls to assess how much MSG was used in cooking, as well as investigation into recipes and nutritional facts of foods purchased at restaurants and grocery stores, determined the total amount of MSG consumed (He et al., 2008). Demographics such as smoking, age, heart conditions, and other health concerns were factored into analysis. Findings indicate that MSG users consume on average .35 grams of MSG daily. MSG users had higher BMI and were more likely to be overweight, though these were not significant differences. Furthermore, MSG consumers were also more likely to consume animal proteins,
cholesterol, and high calories, as compared to vegetable protein, starch and fiber (He et al., 2008). For every gram of MSG consumed on average daily, BMI rose an average of .61kg/m^2. These findings are consistent with those in rats. Unlike rats, humans cannot be assessed for hypothalamic scarring. Also, humans orally consumed MSG, while many rat studies utilize neonatal injections. The increase in leptin resistance and scarring in the hypothalamus are possible indirect mechanisms of increased BMI and weight gain. A decrease in thermogenesis and metabolism, regardless of the underlying mechanism, is the most likely explanation for why MSG leads to weight gain and BMI increases (He et al., 2008). The consumption of food did not significantly differ between those who consumed MSG and those who did not, which further suggests metabolism and decreased thermogenesis as possible reasons for weight gain.

The study by He et al. (2008) was designed based on an INTERMAP study performed by Zhou et al. (2003) that also assessed the Chinese population in rural villages; however, this study did not include American, Japanese, or British subjects. Also, the ages of the adults who participated in the study were limited to 40-59. Subjects were approximately half male and female. In addition to accounting for confounds such as smoking, vegetarianism, and other health issues, this study looked beyond the MSG consumption of subjects and determined whether or not subjects with diabetes and cardiovascular issues were on special diets as compared to healthy subjects. MSG consumption was measured in a multi-pass recall over 4 separate visits, similarly to the methods of He et al. (2008). MSG intake was found to correlate positively with BMI. MSG consumers had significantly higher BMIs than control subjects. Zhou et al. (2003)
assert that rural populations avoid commercially processed foods more than other populations, possibly reducing MSG consumption in these areas; however, the average consumption of .33 grams daily is consistent with the findings of He et al. (2008). Leptin resistance and hypothalamic lesions are considered likely results of MSG intoxication in rats, but it remains to be seen whether this mechanism is the underlying cause of BMI increase in humans. Zhou et al. (2003) point to increased adiposity as the most direct physical response to MSG consumption. Oral consumption of MSG is toxic in rats, and the increase in BMI in humans suggests that MSG is also toxic on some level. Although BMI was significantly higher in MSG consumers, this study posits that Asian populations engage in more physical activity and eat fewer calories, resulting in generally healthy populations with regards to weight. A more skewed population with greater amounts of obesity could yield further insights into the affects of MSG across weight ranges.

He et al. (2008) and Zhou et al. (2003) follow a nearly identical protocol with different subject sets. Their findings are remarkably similar, suggesting comparable mechanisms for MSG affecting BMI as well as reporting similar rates of consumption and increases in BMI for humans.

While the previous studies have addressed the effects of MSG on obesity, the interaction between taste, obesity, and weight has not been explored. In a study by Pepino et al. (2005), researchers looked to explore the interaction of taste and weight beyond sucrose and other sugars. Considering that umami and MSG serve as signals for protein and amino acid synthesis, as well as reinforcers for milk in baby formulas, Pepino et al. (2005) proposed that MSG and umami would not significantly affect obesity,
suggesting that only toxic levels would induce ARC damage and leptin resistance. Comparing approximately 60 women of normal and obese weights, subjects were given MSG and sucrose tastants of different molarities on consecutive days. For MSG, these molarities ranged from .005 to .064 mM. Tests of detection threshold, suprathreshold intensity, and preference were administered. MSG was presented in a vegetable broth, while sucrose was mixed in deionized water.

Obese women were found to significantly differ from normal weight women in preference for higher concentrations of MSG, as well as requiring higher concentrations for detection of MSG. This was not the case for sucrose. Pepino et al.(2005) concluded that elevated body weight leads to MSG sensitivity for taste detection, as well as a preference for high concentrations of MSG. However, Pepino et al. (2005) suggest that rather than MSG causing obesity and leading to higher preferences and detection thresholds, MSG and obesity likely have a cyclical interaction, with obesity leading to these increased thresholds and preferences, which subsequently leads to increased weight gain because of increased consumption of MSG, umami, and other food additives. Pepino et al.(2005)propose further neurochemical analysis to better understand toxicity, leptin resistance, and effects on areas of the brain.

Results from Zhou et al. (2003) and He et al. (2008) differ greatly from the findings of Shi et al. (2010). Using the same INTERMAP format for assessing MSG consumption, Shi et al. (2010) posit that MSG does not lead to obesity and weight gain in humans. Shi et al. (2010) acknowledge, as do Zhou et al. (2003) and He et al. (2008) the
association of MSG and the energy expenditure related to thermogenesis, specifically concerning glutamate receptors. This study looks to assess further the correlation between weight gain and MSG, as well as more closely look at the impact of appetite and consumption. Shi et al. (2010) also constructed a design with approximately 700 subjects from rural Chinese villages. The multi-pass recall system of inquiry and further investigation into amounts of MSG used in commercially processed foods and restaurant recipes were utilized to determine the amount of MSG consumed in subjects. MSG and total glutamate beyond MSG were calculated in Shi et al. (2010), while neither Zhou et al. (2003) or He et al. (2008) reference total glutamate consumption. In addition to BMI measurements, plasma glucose was analyzed in subjects. Confounds of health issues were considered. Shi et al. (2010) found that total MSG and glutamate consumption measured nearly 3.8 grams daily for subjects. This is almost 3.5 grams more than the average consumption found in previous studies. In addition to this contrast, Shi et al. (2010) found that MSG intake was neither associated with increased body mass nor weight gain. Food consumption was comparable between MSG consumers and non-consumers. Shi et al. (2010) assert that glutamate does not lead to weight gain. Regardless of the discrepancies in the amount of consumption of MSG and glutamate in Shi et al. (2010), He et al. (2008), and Zhou et al. (2003), the finding of Shi et al. (2010) that MSG and glutamate did not significantly increase weight gain and body mass is the most interesting. Shi et al. (2010) did note that the Asian diet is becoming increasingly westernized, and that weight gains observed in Asian populations could be a result of decreased exercise and overall changes in diet.
With the exception of Shi et al. (2010), this literature review points to MSG as a catalyst for weight gain and increased body mass and obesity. Upon review of a study by Muhilal et al. (1988), there is reason to question this finding. In a study seeking to assess the effects of Vitamin A-fortified MSG on malnourished children in rural Indonesian villages, results showed that MSG fortified with Vitamin A did not result in weight gain in subjects. Considering that vitamin A has been shown to significantly improve eyesight, mortality rates, and general growth and development, Muhilal et al. (1988) replaced MSG with Vitamin A-fortified MSG in 5 rural villages where they could control the distribution of the product. Baseline measurements were taken, including an assessment of hemoglobin levels, and compared with the post-intervention results in both the experimental and 5 control villages. Vitamin A was found to have significantly increased in both mothers’ breast milk and in children’s hemoglobin. There were significant improvements in both body growth and child survival. Measurements were made at 5 and 11 months after intervention. Bitot’s spots associated with Xerophthalmia, a dry eye syndrome produced by deficient tear ducts (Muhilal et al., 1988), were also found to have significantly reduced. While children significantly increased height, results showed no change in weight. Muhilal et al. (1988) suggest that weight gain would only be present at neurotoxic levels of MSG consumption. Essentially, the Vitamin A fortification of MSG did lead to an increase in the level of health, and there was no presence of weight gain. According to Muhilal et al. (1988), MSG can be an essential supplement when consumed in healthy doses. Considering that MSG consumption in control villages, where health problems remained stagnant, did not affect weight, it is
unlikely that Vitamin A somehow counterbalanced the possible negative effects of MSG consumption with regards to weight gain.

Rat consumption of MSG through oral administration and neonatal injection presents conflicting results, as do studies assessing the consumption of MSG and weight gain and obesity in humans. While there exists a clear correlation between increased adiposity and MSG consumption in rats, the relationship between MSG and humans is less defined. The levels of neurotoxicity in rats consuming MSG versus the apparent absence of neurotoxic effects in the oral consumption of MSG in humans suggests that animal studies do not present sufficiently applicable findings with regards to human weight gain and obesity and MSG consumption.

**MSG and Asthma**

The prevalence of MSG as a food additive worldwide has led to an assessment of its health implications beyond weight gain and obesity. Historically some food additives have demonstrated adverse effects concerning asthma, and an isolated number of reported asthmatic reactions occurring after consuming Chinese food have led to a continued debate over what is known as “Chinese-Restaurant Asthma” (Allen et al., 1987). Considering that MSG is the most widely used and predominant food additive in Chinese food, studies have attempted to understand the relationship between MSG and asthma.

**MSG leads to Asthma**

Allen and Baker (1981) presented the initial experimental findings linking MSG to asthma. In this study, which was reported in the New England Journal of Medicine in an abstract and letter form without specific description of the experimental parameters,
findings present a connection between MSG and asthma in two young women with chronic and unstable asthma. Both of these women are regimented on strictly additive free diets because of the severity of their reactions and the previously mentioned severity of their asthma. In single-blind challenges of orally consumed MSG, measuring 2.5 grams, these two women developed severe asthma between 11 and 12 hours after ingestion. Outside of the study, these women reportedly experienced similar delays in reaction of approximately 11 to 14 hours. Upon repeated presentation of the 2.5 gram challenge, both of these subjects also experienced asthmatic reactions, as was determined by unreported measurements in air flow reduction. Allen and Baker (1981) notes that between 2 and 5 grams of MSG are added in many Asian dishes, and while Western diets typically involve the consumption of .3 grams daily, approximately 3 grams are consumed on average in an individual Asian diet. Allen and Baker (1981) accounts for the long delay in asthmatic reaction by the explanation that the effects of glutamate on receptors in the hypothalamus require several hours to completely interact with the digestive system. The effects of MSG on glutamate synthesis and choline uptake will be further assessed in studies by Moneret-Vautrin (1987) and Nemeroff et al. (1978).

Six years after initially reporting the relationship between MSG and bronchoconstriction, Allen, Delohery, and Baker (1987) presented more detailed findings concerning the relationship between MSG and asthma. Looking within the asthmatic population and utilizing dosages ranging from .5 to 5 grams of MSG, Allen et al. (1987) challenged 32 subjects, all with either a history of delayed asthmatic reactions after eating either Chinese and spicy foods or chronically unstable asthma. No baseline
measurements of forced expiratory value (FEV), a measurement of lung capacity, or any other spirometric measurements either before or after the ingestion of MSG and placebo were detailed. The challenge was single blind and also presented a placebo for control measures. As in the previous study conducted by Allen Baker, subjects were deprived of their medication prior to challenges. The study found 13 subjects had asthmatic reactions to challenges. 7 developed these reactions approximately 1 to 2 hours after ingestion, while 6 developed asthma 6 to 12 hours after ingestion. Allen et al. (1987) defines an asthma attack as a fall of greater than 20% PEER (a measurement similar to FEV). In addition to asthma, subjects reported reactions of headache and nausea. The author cites the relationship between MSG and asthma as both dose-dependent and delayed; however, there is no mention of the dosages administered to subjects before their reactions, only that 5 to 10 grams of MSG could be highly toxic to those with asthma. Furthermore, half of the patients reacted approximately 1 to 2 hours after ingestion. As in the previous study, Allen et al. (1987) does not present the full parameters of his study. Allen et al. (1987) posits that MSG might cause allergic reactions in only a small subset of the asthmatic population.

**MSG and Asthma: Inconclusive**

In response to Allen and Baker (1981) and Allen et al. (1987), several studies have been conducted in an attempt to replicate the asthmatic reactions associated with MSG in the aforementioned study. Many of these studies cite the absence of concrete statistical data as well as the questionable validity of the experimental methods, including a lack of control, of Allen and Baker (1981) as shortcomings in the association between
MSG and asthma. In a study by Woods et al. (1998), asthmatics with the perception of intolerance to food additives such as MSG were challenged with 1 and 5 grams of MSG, as well as 5 grams of lactose and a saline solution as a controlled comparison. According to Woods et al. (1998), between 23% and 67% of asthmatics perceive that food additives heighten their asthma. After an overnight fast, 12 subjects were given single dosages of either MSG, lactose, or the placebo challenge. This process was repeated over several days until each challenge was administered to each subject. Before each challenge, baseline bronchial hyper-responsiveness was assessed using an FEV index. The average baseline responsiveness was 80.6%. An asthmatic reaction was defined as a greater than 20% drop from baseline, and while 8 subjects demonstrated drops between 1 and 20% across all conditions (2 placebo, 2 lactose, 4 MSG), no bronchoconstriction in the form of an asthma attack was recorded either in the MSG challenge or lactose and placebo challenges. Subjects were monitored for several hours after the challenge, but not to the extent of 10-12 hours, as was the delay reported by Allen and Baker (1981) before reactions. No subjects reported reactions during those intervals upon follow up assessment. This study also allowed for asthma prevention medication to be taken. Woods et al. (1998) concluded that, while MSG could possibly be linked to asthma in small subsets of the asthmatic population, a positive relationship between MSG consumption and asthma was not found.

The assertion by Allen and Baker (1981) that reactions to MSG occur at a delay of up to 14 hours does bring into question the official experimental results of Woods et al. (1998). Considering this aspect of the MSG and asthma relationship, a
study by Woessner, Simon, and Stevenson (1999) sought to assess asthmatics challenged with MSG between the 1 and 12 hour window after consumption. Considering that both Schwartzstein et al. (1987) and Germano et al. (1991) challenged patients with up to 6 grams of MSG, as well as the average daily consumption of MSG falling between 1 and 3 grams daily, Woessner et al. (1999) challenged subjects with 2.5 gram capsules of MSG, while also utilizing a placebo for control measures; however, Woessner et al. (1999) also presented 5 challenges over the course of 1 hour twice daily, both in the morning and afternoon. Baseline measurements of FEV response required a greater than 70% or greater predictive value, and no more than 10% variation on this baseline reading at the time of challenge. Unlike Woods et al. (1998), this study assessed asthmatic patients both with and without the perception of food additives causing changes in their bronchoconstriction. Subjects received either 2.5 gram capsules of MSG or placebo capsules on Day 1, and then subsequently were switched to the other group on Day 2. Any subject whose FEV dropped more than 20% during either day was challenged again on Days 4 and 5 with both placebo and MSG. Beyond FEV and other spirometric readings, levels of serum tryptase, an enzyme marker correlated with allergic reactions like those involved in asthma, were measured to assess further the pulmonary response. Results showed similar responses in both placebo and MSG challenges. Of 30 subjects tested, only 2 responded with a greater than 20% FEV drop when administered the placebo, while only one subject dropped below 20% in response to MSG. There was no significant difference in FEV readings for subjects who perceived themselves to be allergic to food additives and those who did not. 7 patients reported headaches, 4 within
the placebo group and 3 after consuming MSG. Unlike Allen and Baker (1981), subjects were allowed to continue their medication. Furthermore, 21 subjects did not qualify for the study because of the instability of their asthma. According to Woessner et al. (1999), these subjects would have qualified for Allen and Baker (1981). The only criterion used by Allen and Baker (1981) required that the patients have a history, or perceived history, of asthmatic reactions to MSG.

In response to Allen et al. (1987), a study by Schwartzstein et al. (1987) sought to challenge previous findings through assessing the MSG and asthma relationship while utilizing both controls and long-term observation. The study was both double blind and random, enlisting patients with asthma as defined by the American Thoracic Society; however, these subjects were not selected based on food sensitivity. They were given a questionnaire regarding their opinions concerning food additives. Subjects were challenged with either 25 mg/kg of body weight MSG or 25 mg/kg of body weight sodium chloride (control). Each subject was monitored for baseline FEV responses, averaging 88%, as well as monitored for FEV every 15 minutes for the first 2 hours after ingestion, and every 30 minutes for the next 2 hours. Any pulmonary irregularity, such as an FEV decline of more than 10%, registered during that 4-hour interval led to further analysis. Of the 12 subjects enlisted, 3 reported food allergies and one claimed to suffer from Chinese Restaurant Syndrome. There were no significant differences in FEV measurement for both MSG and the placebo, and only one subject challenged with MSG registered a greater than 10% FEV drop. Four subjects did measure approximately 10% FEV drops after consuming MSG. One subject measured a 17% FEV drop after
consuming the placebo. The subject who claimed to suffer from Chinese Restaurant Syndrome had no significant difference in his responses to MSG and the placebo. Subjects were monitored, but not critically assessed, over the next 24 hours after the challenges. This is one shortcoming noted by Schwartzstein et al. (1987), as well as the lack of variance in the MSG dosages (only 25mg/kg of body weight). Schwartzstein et al. (1987) conclude that there is no relationship between MSG consumption and asthma in the general asthmatic population, but do not rule out the possibility of an effect in a small subset.

While previous studies have looked to assess the link between MSG and asthma in asthmatics, a study by Germano et al. (1991) assessed MSG consumption in both asthmatics and non-asthmatics. Medication was withheld 8 hours prior to ingestion of MSG and placebo in asthmatics, and the challenge administered incremental dosages from 100 mg, 500 mg, 1 gram, and 6 grams, for a total of 7.6 grams of MSG over roughly 2 hours (doses administered 30 minutes apart). A single dose of 6 grams MSG was administered as another experimental group. Baseline measurements of FEV response showed that 9 of 30 asthmatics were averaged above 90%, while 18 were between 70% and 90%, and 3 were below 70%. Of all 30 asthmatics challenged, only 1 had a greater than 20% drop in FEV. When administered a double blind placebo challenge, the same subject did not have a change in FEV percentage response. As in previous studies, Germano et al. (1991) failed to monitor patients beyond the 2-4 hour window. Medication was withheld, and the overall dosages of between 6 and 7.6 grams of MSG are generally higher than several other experiments.
Of all the literature that criticizes the findings of both Allen and Baker (1981) and Allen et al. (1987), one of the major criticisms of the documented reactions to MSG is the delay in reaction. While several studies designed similar experiments with comparable levels of MSG and stronger internal validity, few studies have rigorously assessed and observed patients over the course of 12-14 hours. Moneret-Vautrin (1987) designed a study that challenges subjects with the approximate average MSG dosage consumed daily, 2.5 grams, assessing patients with a double blind placebo regimen. Of the 30 asthmatic patients challenged with both MSG and calcium carbonate placebo on successive days, only 2 reacted negatively to the MSG; however, both of these reactions were between 6 and 10 hours after the ingestion of MSG, with FEV drops of 23% and 30%. Neither subject reacted negatively to the control; furthermore, this study presents new reasons why MSG could lead to a delayed asthmatic attack: MSG could lead to an interaction of glutamate receptors and GABA, an inhibitor, which would cause a reaction (Moneret-Vautrin, 1987). However, the positive symptoms of MSG-induced asthma are not common reactions related to GABA. Secondly, MSG could interact with neurotransmission from glutamate fibers of the cortex, hippocampus, and olfactory tract, possibly leading to a cholinergic mechanism that would be attributed to long delays between ingestion and reaction. Lastly, increased synthesis of acetylcholine would not only result from MSG ingestion, but could be a dose-dependent response. Considering these assertions, the delayed reaction to MSG in asthmatics seems plausible (Moneret-Vautrin, 1987).
To further assess the implications of the cholinergic mechanism that Moneret-Vautrin (1987) suggests contributes to MSG-induced asthma, a study by Nemeroff, Lipton, and Kizer (1978) reveals a more in-depth analysis of the effects of MSG on neuroendocrine regulation. Nemeroff et al. (1978) assessed rats presented with between 15-30 mg/kg of MSG during the first two weeks of the postnatal period on a daily basis. These rats were assessed for hormone levels that included dopamine, serotonin, growth hormone, and acetylcholine. Considering the suggestion of the impaired synthesis of acetylcholine by Moneret-Vautrin (1987) as a possible catalyst for a delayed reaction to MSG in asthmatic patients, the finding of Nemeroff et al. (1978) that MSG reduced levels of choline acetyltransferase in the arcuate nucleus lends merit to this finding. While rats demonstrated normal diurnal rhythms of synthesis activity, the reduction in the level of acetylcholine transferase suggests that over a long-term period, choline uptake is taking longer to process in the hypothalamus. While this does not point to a direct causation with MSG and asthma, this finding does suggest that there exists a correlation between slowed synthesis of acetylcholine and a delayed reaction to MSG in asthmatics. As the hypothalamus neurons degenerate, acetylcholine deficiency occurs. However, this study did not consider the implications for MSG consumption in humans, such as MSG-induced obesity.

Considering the possible mechanisms of for MSG to induce asthma posited in the last study, the debate over MSG and its interaction with asthma has several layers. If MSG causes asthma, then what is the mechanism for this causation? Moneret-Vautrin (1987) and Nemeroff et al. (1978) both suggest that MSG interferes with the synthesis of
acetylcholine, and Moneret-Vautrin (1987) posits that the delay in choline uptake could correlate with the onset of asthma over the course of several hours. Although several studies appear to refute the findings of the flawed Allen and Baker (1981) and Allen et al. (1987), these studies also lack scientific consideration of several aspects in these studies that warrant further discussion. The discussion further explores the plausibility of MSG-induced asthma in a small subset of the asthmatic population.

**MSG, Memory and Learning**

Many of the studies pertaining to MSG and obesity, as well as those citing the cholinergic mechanism that could possibly lead to MSG inducing asthma, refer to the lesions of the arcuate nucleus of the hypothalamus. Recent studies have sought to explore the relationship between MSG, memory and learning, and another area of the brain: the hippocampus. Results demonstrate that MSG does lead to decreases in performance on spatial memory and learning tasks.

A study by Olvera-Cortes et al. (2005) studied the effects of MSG and place/spatial learning after neonatal injections of MSG were administered in newborn rats. Using a dosage of 4mg/g body weight of MSG, rats were neonatally injected daily for the first week after birth. At 4 months of age, the rats were challenged with place learning and acquisition-retrieval tests in a Morris Maze. Tests were performed at random before and after training. The results showed that MSG rats demonstrate significantly delayed entrances into the maze as well as significantly delayed escape latencies and did not improve over the course of testing. Velocity was significantly lower and distance traveled was significantly higher in MSG-treated rats. While control rats
improved performance after several days, the experimental rats remained consistently subpar in their performance. Considering that place learning is associated with the NMDA glutamate receptors in the hippocampus, Olvera-Cortes et al. (2005) assert that the MSG dosage interferes with stabilized glutamate synthesis in the hippocampus, resulting in the impaired spatial memory and learning. Short-term memory impairment as well as physical debilitations was cited as possible confounds, as well as glutamate’s degeneration of eyesight.

Another study by Frieder and Grimm (1984) cites MSG’s negative effect on eyesight and retinal degeneration as a possible confound in the spatial memory and place acquisition deficiencies observed in rats affected by MSG. Unlike the findings of Olvera-Cortes et al. (2005), Frieder and Grimm (1984) measured the behavioral deficits observed in rats whose mothers consumed MSG during the gestational period. These mothers consumed an MSG and water solution of 10mg/g of body weight from days 7 to 20 during pregnancy. These rats were run in a testing grid at postnatal days 20, 28, and 35, in exercises of place learning and acquisition that involved discriminating between alternating alleyways with water at the end of a single alley. The rats were given 10 second trials to locate water 4 times daily. Running speed was also timed. MSG rats had significantly longer latencies before entering the field, as well as significantly more errors in attempting to locate the water.

Control rats performed significantly better in tasks of visual discrimination between black and white alternating alleys as opposed to MSG-treated rats. Activity levels and running speed were significantly reduced in MSG rats. Because of the low
visual discrimination, as seen in Olvera-Cortes et al. (2005), these findings suggest a possible connection between impaired vision and the inability to discriminate between stimuli in MSG rats; however, the increased latencies and lack of mobility are not accounted for by visual deficits, or by physical impairment. While the effects of oral consumption of MSG in the mother as compared to neonatal injection in the offspring of Olvera-Cortes et al. (2005) suggest differences in the effects of MSG dosage, similar lesions of the arcuate nucleus was measured in this study as in other MSG-induced obesity studies. This study also references glutamate synthesis deficiencies in the hippocampus as the likely explanation for decreased spatial and place learning/memory, despite the possible confounds of impaired sight and movement.

Olvera-Cortes et al. (2005) looked at postnatal injection of MSG in days 7-20. The postnatal development of the brain in rats is highly sensitive, specifically within the first 10 days of growth. While days 7-20 are also vital, Hlinák, Gandalovicová, and Krejcí (2005) looked specifically at days 4-10 of postnatal development, neonatally injecting MSG during days 4-10, a time of high blood-brain barrier vulnerability. This is also a time in which NMDA receptors are highly sensitive, and a delay in glutamate synthesis could lead to both behavioral and cognitive deficits. Unlike the aforementioned studies, Hlinak et al. (2005) also examines the role of olfaction in learning and memory. While sight is an important sense, olfaction, the study claims, is the most relevant sense for understanding learning and memory in rats. The relationship between MSG, memory, and olfaction deserves a closer look. After neonatally injecting rats with 3-mg/g body weight of MSG from days 5-12, this study waited to perform behavioral tests during
adulthood at 120 days. MSG-treated rats demonstrated reduced locomotion and significantly delayed start and entrance latencies into the Morris Maze, as were observed in previous studies; however, during tests of olfactory-cued recognition and memory, rats also showed impaired sensitivity and reduced interest in normally potent stimuli (Hlinak et al., 2005). Habituation to stimuli in the Morris Maze over the course of testing was also significantly worse than in control rats, who learning to ignore irrelevant stimuli in pursuit of the escape platform. Body weight was significantly lower in MSG injected rats. Male rats showed greater behavioral deficits than females. This study cites cholinergic and glutamate mechanism deficiencies in the hippocampus as a likely explanation of reduced habituation and deficits in latency and spatially oriented tasks. Deficiencies in both olfaction and vision are offered as possible results of MSG ingestion that resulted in reduced proficiency but not necessarily with connection to spatial learning and memory (Hlinak et al., 2005)

The most common testing method for assessing spatial memory and learning in mice, as well as other general behavior deficits, is the water escape test of the Morris Water Maze. While Wong et al. (2005) also references visual impairment as a possible MSG-related deficit, this study also asserts the cholinergic mechanism’s inhibition, brought on by MSG, as the reason for deficient learning and memory in mice. More specifically, this study measured choline uptake in mice and found that it significantly reduced acetylcholine synthesis. As in other studies, Wong et al. (2005) subcutaneous injections ranging from approximately 2.5 to 4.2mg/g body weight MSG were injected during postnatal days 2-10. A saline control was also used. Results from testing in the
Morris Water Maze demonstrated a significantly increased latency for water maze entrance in MSG-treated mice, as well as a significant difference in overall efficiency, with MSG-mice requiring more travel time and longer durations of swimming to escape. MSG-treated mice were significantly heavier than controls at assessment at 6 and 16 weeks, but experimental rats only consumed a significantly greater amount of food than control rats at age 24 weeks, not at 6 and 16 weeks. With no evidence of slowness or physical defects, including impaired vision, poor spatial navigation skills appear to result from impaired spatial memory and learning in MSG-treated mice. Beyond the reduction in cholinergic action in the hippocampus, Wong et al. (2005) also posits that NMDA glutamate receptors have decreased efficiency, and the combined glutamate and cholinergic deficiencies could present the most convincing explanation for the disparity between MSG-treated mice and controls. Increased anxiety, without qualified explanation, is also a suggested reason for deficient performance.

While all previously explored studies have connected MSG with learning and memory deficiency, Collison et al. (2010) propose that central obesity, a result of MSG and high fatty acid diets, serves as the underlying catalyst for impaired learning and memory. The combination of insulin resistance, hypothalamic lesions, and fatty acid interference with both hippocampal and hypothalamic functioning, all by products of MSG consumption, lead to mental deficiencies. During early postnatal development, rats were treated with 0.24 g/L of water MSG, an 8.68% TFA substance, and a combination of the two substances. Spatial memory was assessed using the Morris Maze Test at 6, 16, and 32 weeks (Collison et al., 2010). While there was no significant increase in body
weight or food intake in both experimental groups, higher leptin levels were present in the combined MSG and TFA groups. This same group also had the highest failure rate on the Morris Maze test, and they were significantly slower than other groups. This study asserts that the central adiposity increase and accompanying impairment of the hippocampus and hypothalamus, as well as increased insulin resistance, led to decreased cognitive functioning. Impaired spatial reasoning and memory was more prominent, as well as weight gain, in females (Collison et al., 2010).

Deficits in behavior and performance in spatial memory and learning in MSG-treated mice have several possible explanations. The underlying thread of each possibility is that MSG, through some mechanism, impairs performance in memory and learning. Whether this impairment is a result of deficient NMDA glutamate receptors in the hippocampus, degenerative retinal function and impaired vision, cholinergic deficiency that leads to reduced acetylcholine synthesis, or a combination of one or all of these performance inhibitors, is the ultimate question. These studies present a unanimous assertion that MSG significantly effects spatial memory and learning in a negative manner, and MSG’s effect on the processes of the hippocampus appear to be the most likely cause. Also of interest are the significant differences in weight observed between the heavier MSG-treated mice and leaner controls. Although movement and weight were not correlated with poor performance, particularly in the Morris Maze, these deficiencies do not appear to be primary factors that account for significant differences between MSG and controls.

Discussion:
Animal studies have shown that MSG has a positive correlation with obesity. Even in subjects that do not show weight gain after consuming MSG or receiving it through neonatal injection, there is an increase in both adiposity and BMI in almost every reported study. The conflicting results concerning MSG and weight gain in rats appear to depend on the method of ingestion of MSG in the rat. While rats that orally consume MSG demonstrate increased adiposity as well as increased leptin resistance in both Collison et al. (2010) and Leitner and Bartness (2008), Kondoh and Torii (1995) argue that the decrease in leptin they observed, as well as reduced weight gain and obesity comparing MSG-treated rats and control rats, is a result of the increased energy expenditure and thermogenesis required to digest and process MSG; however, there was no measured difference in the amount of food consumption in MSG-treated versus control rats in Kondoh and Torii (1995), just as there was no measured decrease in Collison et al. (2010) and Leitner and Bartness (2008). Considering this finding, the assertion that rats have reduced weight gain because of increased thermogenesis resulting from MSG and food consumption lacks merit. There is no difference in the amount of metabolized food. This finding suggests that the leptin resistance and lesions observed in the arcuate nucleus, as well as the increased adiposity and BMI observed in Collison et al. (2010) and Leitner and Bartness (2008) has a more complicated interaction in leading to weight gain and obesity. The findings of Krycek et al. (1994) and Fernandez-Tresguerres Hernandez (2005) disregard the interaction of leptin resistance and food consumption, but in both studies rats that consumed MSG were found to significantly increase their levels of food consumption. While Fernandez-Tresguerres Hernandez
(2005) suggests that the degeneration of the hypothalamus after oral consumption of MSG leads to an interference in appetite regulation, whether this change is a result of a modification in leptin resistance is unexplored. Krycek et al. (1994) highlight the correlation between MSG consumption and high fat foods, which could lead to increases in weight gain and obesity in addition to the impairment of body fat mobilization caused by MSG consumption. The results of Kondoh and Torii (1995) cannot be disregarded. Knowing that leptin production depends on the amount of adiposity, and that adiposity is a function of the amount of fat consumed through MSG and other foods, the consumption of MSG, as posited by Pepino et al. (2005), is likely part of a cycle where increased adiposity, heightened leptin resistance, and voracity interact with metabolism and, depending on the dosage level of orally or neonatally consumed MSG, result in not only increased body mass but also the negative health effects seen in diabetes and steatosis of the liver.

In studies where rats were injected neonatally MSG, findings support the assertion that neurotoxic levels of MSG consumed neonatally both increase obesity and result in negative health effects. Sasaki et al. (2009) and Dawson et al. (2010) both showed that rats injected with MSG presented with increased adiposity and body mass, as well as heightened leptin resistance, yet unlike the oral consumption studies, the rats injected with MSG demonstrated increases in voracity and food consumption. Reductions in Neuropeptide Y, as well as pronouncement of diabetes mellitus, steatosis of the liver, hyperleptinemia, hyperinsulinemia, and scarring of the arcuate nucleus in the hypothalamus refute the assertion of Kondoh and Torii (1995) that neonatal injection of
MSG lead to less neurotoxicity than oral consumption of MSG. While the findings concerning body weight and MSG vary, results from Matyskova et al. (2007) suggest that MSG inhibits the mobilization of lipid processing, possibly leading to the increase in adiposity. Furthermore, with the exception of the single dosage of 4mg/g of body weight MSG in Sasaki et al. (2009), both neonatal and oral consumption of MSG shows that as dosage increases, levels of obesity and adiposity increase along with leptin resistance and marked changes in health of the liver, weight of organs, and food consumption. However, as noted earlier, the role of TFA and high and low fats in Collison et al. (2010), Matyskova et al. (2007), and Sasaki et al. (2009) suggests that MSG’s effects on weight gain and obesity, as well as negative health conditions associated with these effects, could be a result of the coinciding presence of MSG and high fat in many foods. MSG alone does not produce the combined effects of MSG and fat (Collison et al., 2010). The direct effects of neonatal injection of MSG seem to create more negative effects on health, whereas oral consumption of MSG has a similar but reduced effect. Hermanussen et al. (2006) studied the effects of both neonatal and oral consumption of MSG. This study assessed the effects of MSG on the offspring of rats that received both oral and neonatal MSG. The offspring were found to have reduced growth hormone and weight at birth, as well as increased food and water consumption. The effects on adiposity and BMI were not assessed over time; however, the most interesting result found by Hermanussen et al. (2006) was that the offspring of mothers that consumed MSG orally showed increases in leptin resistance, while those offspring of mothers that were injected with MSG showed decreases in leptin resistance. Considering that Hermanussen et al.
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(2006) assert that orally consumed MSG proved more toxic than neonatally injected MSG, the relationship between leptin levels and MSG consumption appears to have a direct effect on the level of neurotoxicity resulting from this consumption; however, this finding does not present any conclusive evidence regarding weight gain or weight loss and obesity. Lastly, females appear to respond with heightened sensitivity to MSG. Weight gain, adiposity and leptin levels are often slightly more pronounced in female rats compared to male rats. This finding suggests an interaction of differing hormone levels in males and females, such as human growth hormone, in the effects of MSG on obesity.

While MSG can be administered through both neonatal injection and oral consumption in rats, studies in this review have only administered MSG to subjects through oral consumption. Studies of MSG consumption in the human population using the INTERMAP system of multi-pass recall have generally demonstrated a positive correlation between MSG consumption and increased BMI and weight. He et al (2008) and Zhou et al. (2003) both suggest that the metabolic processing of foods containing MSG combined with the unknown relationship between leptin resistance and MSG consumption leads to increases in weight gain and obesity in those who consume MSG. For every gram of MSG consumed on daily, BMI is on average 0.61 kg/m^2 higher (He et al., 2008). However, these findings combined with the reporting of Pepino et al. (2005) suggest that MSG might be correlated with weight gain and obesity, but not necessarily connected with causality. Those people who consume MSG are more likely to consume animal protein and high fat foods, and the increasing westernization of Asian culture that leads to more commercially processed foods and reduced physical activity could mean
that MSG is part of a bigger picture of declining health (He et al., 2008). Pepino et al. (2005) suggests that MSG is part of cycle. Obese women are more likely to have reduced sensitivity and prefer higher quantities of MSG than normal women. MSG consumption could both lead to and be heightened by MSG consumption. Furthermore, all of these studies except for Shi et al. (2010) fail to account for total glutamate consumption in comparison to only MSG consumption. And that same study by Shi et al. (2010) suggests that MSG is not correlated to weight gain and obesity. These results are not confirmed by any other study of obesity and MSG in humans. Muhilal et al. (1988) showed that MSG consumption with and without Vitamin A fortification not only did not contribute to obesity, but also did not lead to any weight gain. This finding highlights that in addition to MSG’s part in the bigger picture of unhealthy eating, the food additive likely is only neurotoxic when administered through neonatal injection. Although leptin resistance has been observed in humans, the lesions of the arcuate nucleus commonly found in rats after injection with MSG cannot be detected in humans. Outside of a positive correlation with increased body mass index and some weight gain, MSG does not appear toxic to humans.

While Hermanussen et al. (2006) posit that oral consumption of MSG is more neurotoxic than neonatal injection, all other studies suggest that MSG is not as toxic after oral consumption than when received through neonatal injection. The 2-5 grams of MSG consumed daily in humans does not show neurotoxic effects, but it is reasonable to expect that rats are negatively affected by oral consumption of MSG with regards to obesity and body mass.
MSG and Asthma

The findings of both Allen and Baker (1981) and Allen et al. (1987) are suspect but not implausible. The method for reporting their findings such as the letter and abstract in Allen and Baker (1981) does not strengthen their findings. Although Allen et al. (1987) report that an asthma attack is regarded as a drop in FEV and PEER value of greater than 20%, neither study explicitly details what constitutes an asthma attack, how this is measured, and what constructs were developed. Furthermore, Allen and Baker (1981) and Allen et al. (1987) fail to administer any baseline readings to determine the initial levels of bronchoconstriction in subjects. Their subjects also present with chronic unstable asthma, a history of food additive sensitivity, or the belief that food additives such as MSG affect their asthma. Allen et al. (1987) also stop the medication regimen of patients. Considering all the flaws in Allen and Baker (1981) and Allen et al. (1987), their reporting does suggest a possible agitation of asthma after MSG ingestion, brought on in delays of 10-14 hours in asthmatics with heightened sensitivity to additives. The question remains: how can chronic unstable asthmatics deprived of their medication during a 24-hour period solely attribute their asthma attack to the ingestion of MSG? A control utilizing the same subjects without MSG consumption during the same time period could either strengthen or weaken Allen et al. (1987)’s findings, depending on whether or not the same subjects experience asthma attacks.

Studies like those of Woods et al. (1998) present subjects with between 1 and 5 grams of MSG, as well as lactose and a placebo control. Their findings reject the results of Allen and Baker (1981) and Allen et al. (1987) overwhelmingly. Using baseline FEV
measurements to compare reactions after MSG ingestion to initial bronchoconstriction, the controlled environment and protocol lend greater internal validity to the study; however, this study fails to monitor patients for the long-term 10-12 hours needed to reject completely the findings of Allen et al. (1987). And while allowing patients to maintain their asthma medication increases the external validity of the findings, Allen et al. (1987) asserts that a small percentage of the asthmatic population with heightened sensitivity to additives like MSG can, at vulnerable moments (such as when not taking medication), be at risk for an asthma attack.

Woessner et al. (1999) also support the findings of Woods et al. (1998), as well as monitoring patients over the course of several days to see if a delayed reaction occurs in subjects. Only 2 subjects experienced a greater than 20% drop in FEV compared to baseline readings. In addition to the long-term observation employed in Woessner et al. (1999), subjects were selected that presented with and without the perception and/or history of food additives relating to asthma attacks. Perhaps most importantly, 21 subjects failed to qualify for this study that would have been enlisted in Allen et al. (1987). On the one hand, this exclusion strengthens the external validity of Woessner et al. (1999), yet it fails to account for Allen et al. (1987) claiming that a small vulnerable subset of the population is prone to MSG-induced asthma attacks.

Both Germano et al. (1991) and Schwartzstein et al. (1987) failed to monitor patients for the long-term 12 hour window suggested by Allen et al. (1987), and their findings are controlled and comparable to those of Woessner et al. (1999) and Woods et al. (1998). The responses of those few subjects who do react are equally divided between
MSG and placebo challenges. Germano et al. (1991) presented dosages of over 6 and 7 grams to subjects, with no reactions measured.

While all of the aforementioned asthma-related studies present findings either in support of or against the relationship between MSG and asthma, the potential underlying mechanism of MSG-induced asthma remains relatively unexplored. Although Moneret-Vautrin (1987) presents similar negative findings to Woods et al. (1998), Woessner et al. (1999), Schwartzstein et al. (1987) and Germano et al. (1991), the study suggests that a delayed reaction to MSG between 6 and 10 hours after ingestion, which is the time frame for the two reactions found in the study, is a possibility. The combined effects of glutamnergic and cholinergic mechanisms leading to long delays in the processing of MSG and the synthesis of acetylcholine could lead to an adverse digestive reaction that exacerbates the pulmonary rhythm of an asthmatic.

A study by Nemeroff et al. (1978) further describes the effects of MSG consumption on the inhibition of choline uptake and synthesis. While the study does not assess the effects of MSG on asthma, the mechanism suggested by Moneret-Vautrin in which the delayed reaction to MSG in asthmatics is correlated with an interaction between the digestive system and acetylcholine uptake remains plausible.

Results show that MSG does not lead to adverse reactions in the general asthmatic population, but there is no evidence that overwhelmingly disproves the assertion that MSG could cause delayed reactions in small subset of the asthmatic population with unstable asthma and a heightened sensitivity to food additives like MSG.
The study of MSG and asthma is an entirely human-based research effort. The study of MSG’s effects on memory learning is an almost entirely animal-based effort. The findings of Olvera-Cortes et al. (2005), Frieder and Grimm (1984), Hlinak et al. (2005) Wong et al. (2005) and Collison et al. (2010) demonstrate a clear connection between the neonatal injection of MSG and the impairment of learning and memory, specifically with regards to spatial reasoning. The uncertainty surrounding these results involves the mechanism of MSG. These studies demonstrate that increases in adiposity and weight gain do no lead to slowness or impaired mobility. The controversy is whether or not the visual degeneration measured in rats after MSG injection is leading to a false positive of impaired spatial memory and learning. Although impaired vision might enhance poor performance, the delays in latency and entrance into the maze as well as discrimination in black and white visual tasks where escape is not contingent upon sight as much as memory of navigated space suggests a more complicated explanation; nonetheless, MSG’s effect in sight in rats cannot be excluded as a possible detraction from performance in spatial memory tasks. These studies cite the interaction of glutamate NMDA receptors and the cholinergic uptake involved in acetylcholine synthesis creating some kind of interference with cells in the hippocampus as the likely impairment of spatial memory and learning. There was no marked difference between the effects of oral consumption of MSG and neonatal injection of the additive. Further studies should demonstrate that the increase in dosages, particularly in neonatal injection, would lead to greater delays and latencies and higher numbers of errors. Also of interest is the period of injection in the rats. Many rats were injected in a vital period of biological
and cognitive development. The neonatal injection of MSG could have varying levels of neurotoxicity in and beyond studies of memory and learning depending on the time frame in which rats are injected. Also, injecting adult rats after full development or giving them oral dosages could better reflect the effects of MSG on humans who consume MSG after their full development.

When assessing the holistic effects of the food additive MSG on health, the results in both animals and humans must be compared and contrasted. For humans, the oral consumption of MSG likely leads to increased adiposity and body mass index, suggesting the possibility of a link between obesity and MSG. There is only correlative evidence that links MSG with weight gain, and this is more likely a result of the comorbidity of MSG and TFAs and other high fat substances as ingredients in common foods. The increase in obesity and weight is likely correlated with an increase in MSG in the world diet. Food additives like MSG could lead to adverse reactions in a small subset of asthmatics, but the experimental research suggests that asthmatics, even those who perceive themselves to be MSG-sensitive, do not have asthma attacks as a result of consuming MSG. Within rats, the neonatal injection of MSG leads to toxic levels of the substance that not only lead to induced obesity but also scarring of the hippocampus, exacerbation of diabetes and liver steatosis, and impairment of spatial memory and learning. Oral consumption of MSG can lead to these effects, but the neonatal injection is consistently more devastating to the rat’s overall health. Results suggesting that oral consumption of MSG are as great or greater a threat than neonatal injections in rats are inconsistent and lack replication.
If humans could ethically receive injections of MSG, the effects of increased adiposity and body mass index would likely be observed. Future research should seek to follow human subjects longitudinally while manipulating diets in the short term to consume different levels of MSG. It is unlikely that MSG would ever be neurotoxic in humans, but the food additive contributes to and is associated with varying levels of negative health implications.
References


