

ORIGINAL ARTICLE

Obesity, voracity, and short stature: the impact of glutamate on the regulation of appetite

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Background: World-wide obesity has risen to alarming levels. We present experimental support for a new and very challenging hypothesis linking obesity, voracity, and growth hormone (GH) deficiency, to the consumption of elevated amounts of the amino-acid glutamate (GLU). Supraphysiological doses of GLU are toxic for neuronal cells.

Methods: Human data were obtained from 807 592 German conscripts born between 1974 and 1978, and from 1 432 368 women of the German birth statistics (deutsche Perinatalerhebung) 1995–1997. The effects of orally administered monosodium glutamate (MSG) were investigated in 30 pregnant Wistar rats and their offspring. Pregnant animals either received no extra MSG, or 2.5 g MSG, or 5 g MSG per day, up to the end of the weaning period. In all, 2.5 g, respectively 5 g, MSG accounted for some 10%, respectively 20%, of dry weight of the average daily food ration. After weaning, MSG feeding was continued in the offspring.

Findings: Morbid obesity associates with short stature. Average stature of conscripts progressively declines when body mass index increases above 38 kg/m². Also morbidly obese young women are shorter than average though to a lesser extent than conscripts. Oral administration of MSG to pregnant rats affects birth weight of the offspring. Maternal feeding with 5 g MSG per day results in severe birth weight reduction ($P < 0.01$). Weight increments remain subnormal when MSG feeding to the mothers is maintained during weaning ($P < 0.01$). GH serum levels are affected in animals that received MSG during prenatal life via maternal feeding. Animals that are kept on high MSG diet (5 g MSG per day) continue to show serum GH levels that are as low or even lower than those of MSG injected animals ($P < 0.05$), both at day 30 and at day 90 of life. Animals that were kept on medium MSG diet (2.5 g MSG per day) showed low serum GH levels at day 30 of life ($P < 0.01$), but seemed to partially recover before day 90. Almost identical results were observed in IGF-1 serum levels. Oral MSG resulted in dose dependent voracity. The animals fed 5 g MSG per day increased water uptake by threefold ($P < 0.01$), and food uptake by almost two-fold ($P < 0.01$). The influence of MSG is in general more marked in males than in females.

Interpretation: GLU is a widely used nutritional substance that potentially exhibits significant neuronal toxicity. Voracity, and impaired GH secretion are the two major characteristics of parenterally administered GLU-induced neuronal damage. GLU maintains its toxicity in animals even when administered orally. Males appear to be more sensitive than females. The present study for the first time demonstrates, that a widely used nutritional monosubstance – the flavouring agent MSG – at concentrations that only slightly surpass those found in everyday human food, exhibits significant potential for damaging the hypothalamic regulation of appetite, and thereby determines the propensity of world-wide obesity. We suggest to reconsider the recommended daily allowances of amino acids and nutritional protein, and to abstain from the popular protein-rich diets, and particularly from adding the flavouring agents MSG.

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Introduction

World-wide obesity has risen to alarming levels (McLellan, 2002). The average weight of German conscripts now increases by almost 400 g/year. Similar data were obtained in Austria, Norway, and the UK. Obesity is not a separate

problem of only the obese people but appears to be a characteristic feature of modern populations as a whole (Hermanussen *et al.*, 2001).

Much effort has been spent to understand the pathophysiology of obesity. Apart from the rare monogenic causes for severe disturbances of the eating regulation – genetic alterations of the *ob* gene (leptin) (Zhang *et al.*, 1996; Strobil *et al.*, 1998), the leptin receptor (Clement *et al.*, 1998), a mutation of the melanocortin 4 receptor (MC4R) gene (Farooqi *et al.*, 2000), and mutations in the pro-opiomelanocortin (POMC) gene (Krude *et al.*, 1998) – obesity appears to show a multifactorial aetiopathogenesis. Disadvantageous dietary habits, such as overconsumption of fat-rich diets, excessive use of modern media, in particular television viewing (Robinson, 2001), a sedentary lifestyle (Votruba *et al.*, 2000), and many other exogenous factors, have been made responsible for the development of obesity already in early childhood. And recently, a new and very challenging hypothesis has been added linking obesity, voracity, and growth hormone (GH) deficiency to the consumption of elevated amounts of the amino-acid glutamate (GLU) (Hermanussen and Tresguerres, 2003a, b). Supraphysiological doses of GLU are toxic for neuronal cells.

The arcuate nucleus is the major site of GLU-induced neuronal damage in the hypothalamus. It is situated close to the bottom of the third ventricle, and is a potent site of leptin action. Leptin is produced in the adipose tissue, crosses the blood-brain barrier by active transport systems, and stimulates a specific signalling cascade (Jequier, 2002): it downregulates the orexigenic neuropeptides NPY, agouti gene-related protein, melanin-concentrating hormone, and orexins, and upregulates POMC and cocaine- and amphetamine-regulated transcript (CART) mRNA (Elmqvist, 2001). POMC and its post-translational product, alpha-MSH, stimulate melanocortin receptors (MC3R, MC4R), and thereby downregulate appetite. Arcuate nucleus damage disrupts the signalling cascade of leptin action, thereby impairs the regulation of appetite, and causes voracity (Fan *et al.*, 1997; Lu, 2001).

GLU toxicity is mediated either by inhibiting cystine uptake (Murphy *et al.*, 1990) or receptor-mediated. The *N*-methyl-D-aspartate receptor (NMDA-R) is fully functional in the rat early in embryogenesis. Xue *et al.* (1997) found that GLU- and aspartate-immunoreactive neurones were completely absent in the monosodium glutamate (MSG)-lesioned arcuate nucleus as well as the ventromedial nucleus lateral to the arcuate nucleus, in mice treated neonatally with MSG. Similarly, NMDA-R1-immunoreactive neurones were mostly absent in the MSG-lesioned arcuate nucleus but remained intact in the ventromedial nucleus. There was also a substantial loss of NMDA-R2 immunoreactivity within the arcuate nucleus. Beas-Zarate *et al.* (2001) measured changes in gene expression of the NMDA-R subunits: NMDA-R1, NMDA-R 2A, and NMDA-R 2B in the cerebral cortex, striatum and hippocampus in the brains of rats treated neonatally with MSG. The authors showed increases in GLU

levels and activation of GLU-receptors after neonatal s.c. administration of MSG at doses of 4 mg/g body weight and an increase in glial cell reactivity and important changes in NMDA-R molecular composition, with signs of neuronal damage. Kaufhold *et al.* (2002) were able to prevent the adverse effects of neonatal MSG treatment by concurrent administration of a selective and highly potent noncompetitive NMDA-R antagonist of GLU.

Administering GLU to newborn rodents not only destroys arcuate nucleus neurones, it also damages other hypothalamic areas. Bloch *et al.* (1984) showed that MSG treatment results in the complete loss of growth hormone releasing factor (GRF)-immunoreactive cell bodies within this nucleus and provokes a selective disappearance of GRF-immunoreactive fibres in the median eminence of rats. This technique has routinely been practised to produce functionally hypopituitary animals (Lima *et al.*, 1993) for studies of short-term growth (Hermanussen *et al.*, 1996).

That is, GLU-induced neuronal damage results in voracity and subsequent excessive weight gain, and impaired GH secretion, the two major characteristics of human obesity.

The present study was undertaken to further investigate the links between obesity, voracity, and GH deficiency. We present novel human data supporting evidence that morbid obesity not only associates with GH secretory dysfunction, but also with short stature, and animal data supporting evidence that GLU toxicity is not limited to parenteral administration of this amino acid, but that oral administration of GLU also causes voracity and GH deficiency. The similarity between clinical findings in human obesity, and effects of oral administration of MSG in laboratory animals strongly support the view that supraphysiological oral loads of the amino-acid GLU play a key role in human obesity.

Material and methods

Human data

Body height and body mass index (BMI) were obtained from 807 592 German conscripts born between 1974 and 1978, aged 19–20 years. BMI ranged between 14 and 48 kg/m². In all, 4.7% of the young men were obese with BMI ≥ 30 kg/m², and some 20% overweight with BMI ≥ 25 kg/m². The data were given to us by courtesy of the Institut für Wehrmedizin-statistik und Berichtswesen, Remagen, Germany. All conscripts had either completed high school (A-level, German: Gymnasium), secondary school (O-level, German: Realschule), or 9-year elementary school (German: Hauptschule). We excluded persons who were chronically ill, or lived under the care of a guardian, and conscripts who did not complete school education (less than 10%). This was performed on purpose in order to exclude mentally handicapped subjects suffering from Down's Syndrome, Prader-Willi-Syndrome, and other syndromes with short stature and obesity. We assumed that very obese young men had also been obese during the final period of adolescent growth.

Maternal data on body height and weight at the beginning of pregnancy from 1 432 368 women were obtained from the German birth statistics (deutsche Perinatalerhebung) 1995–1997 (Voigt *et al.*, 2001). BMI ranged between 12 and 59 kg/m². A 10.4% of the young women were obese with BMI ≥ 30 kg/m², and some 35% overweight with BMI ≥ 25 kg/m². We rejected adolescent mothers (<18 years of age), in order to exclude those who had not yet reached final height, and restricted the sample to persons below the age of 30 years. We assumed that very obese young women had also been obese during the final period of adolescent growth. We are aware that data obtained from birth statistics are not representative for women in general. Pregnancy provides evidence for unimpaired hypothalamic-pituitary-gonadal function. However, large samples of unselected young women are not available in Germany.

Animal data

The effects of oral administration of GLU were investigated in 32 pregnant rats and their offspring up to day 90 of life, in the animal facilities of the Department of Physiology, Medical School, Universidad Complutense, Madrid, Spain. The study was conducted in accordance with the principles and procedures outlined in the NIH Guide for the Care and Use of Laboratory Animals. Pregnant Wistar rats were kept under controlled conditions of light (12 h light/12 h darkness) and temperature ($21 \pm 2^\circ\text{C}$), and were fed with tap water and rat chow (Panlab, Barcelona, Spain) *ad libitum*.

At day 14 of pregnancy, the animals were divided into four groups ($n=8$), and either received no extra MSG (control, group 1), or 2.5 g MSG (group 2) or 5 g MSG per day (group 3), up to the end of the weaning period. 2.5 g, respectively, 5 g MSG accounted for some 10%, respectively, 20% of dry weight of the average daily food ration. After weaning and gender separation, MSG feeding was continued in the offspring at the same concentrations.

Group 4 was not given MSG with the chow, and thus exactly resembled the control group 1, but their offspring was injected with MSG 4 mg/g body weight s.c., on alternate days from day 1 to day 10 of life. Injecting MSG 4 mg/g body weight s.c. at neonatal age, is known to deplete the arcuate nucleus of GHRH neurons (Bloch *et al.*, 1984) thus leading to GH deficiency. Also, our group had previous experience with this model when investigating the growth process in GH deficient animals (Hermanussen *et al.*, 1996). Four mg/g correspond to 1 g in a 250 g rat, That is, the s.c. dose was kept a little lower than the dose range of the orally treated groups. The bioavailability of s.c. administered MSG might be higher, and also different in terms of GLU/glutamine conversion. The offspring of group 4 was important in order to compare the effects of s.c. vs orally administered MSG.

Owing to the existence of two gender groups a total of eight experimental groups were obtained with $n=6-9$ for each group of females and males. All litter was weighed at weekly intervals, and the amount of food consumed was

registered daily. Offspring was killed half at day 30 and the rest at day 90 of life.

Tissue preparation

Half of the animals were killed by decapitation at day 30 and the other half at the end of the observation period at day 90. Anterior pituitaries were removed, and trunk blood was collected. Serum samples and anterior pituitaries after being weighted were kept at -80°C , for hormonal determinations by specific radioimmunoassays (RIA). Pituitary homogenates were obtained by manual glass homogenisers, and processed in saline after thawing in the moment of the measurement.

Radioimmunoassays

Plasma GH levels and pituitary GH content were determined by RIA as previously described (Lima *et al.*, 1993). Pituitary homogenates were diluted 1:5000 for determination. Reagents were kindly provided by the National Institute of Diabetes, Digestive, and Kidney Diseases (NIDDK). The standard used was rat GH RP2. The sensitivity of the curve was 2 ng/ml and the Intraassay coefficient of variation was 5.7%.

Plasma IGF I concentrations were measured using a commercially available rat RIA kit (DSL-2900, Diagnostic Systems Laboratories, Inc.). The sensitivity of the assay was 20 ng/ml, and the intraassay coefficients of variation for mean serum concentrations of 323, 772, and 1604 ng/ml were 5.9, 6.1, and 3.8%, respectively.

Leptin levels were determined by RIA using a commercial kit (RL-83 K, LINCO RESEARCH), with a sensitivity of 0.5 ng/ml, and intra-assay coefficients of variation of 2.4% (1.6 ng/ml), 4.1% (3.3 ng/ml), 2% (6.8 ng/ml), and 4.6% (11.6 ng/ml).

Statistical analysis

Values are expressed as mean \pm s.e.m. In some cases data were subject to log transformation since variances showed a log-normal distribution. To determine differences in final weight or hormonal levels a two-way ANOVA test was performed. Differences among groups were subjected to a *post hoc* comparison by using Tukey HSD for unequal N -test. Statistics were executed using Statistica program. The significance level was determined to be $P < 0.05$.

Results

Human data

Morbid obesity associates with short stature. Regardless of school education, average stature of conscripts progressively declines when BMI increases above 38 kg/m². The same applies for fertile women. Morbidly, obese young women are shorter than average (Figure 1) though to a lesser extent than conscripts.

Animal data

Oral administration of MSG to pregnant Wistar rats affects birth weight of the offspring (Figure 2a). Maternal feeding

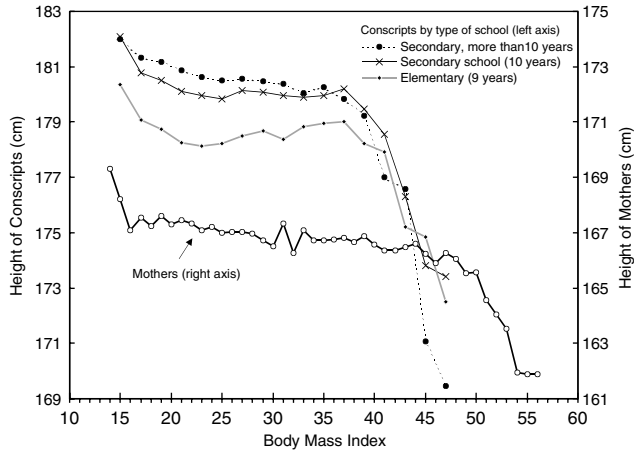


Figure 1 Average body height of 807 592 German conscripts born between 1974 and 1978, aged 19 years, and 1432 368 young German women at the beginning of pregnancy (deutsche Perinatalerhebung) 1995–1997 (Voigt *et al.*, 2001), vs BMI.

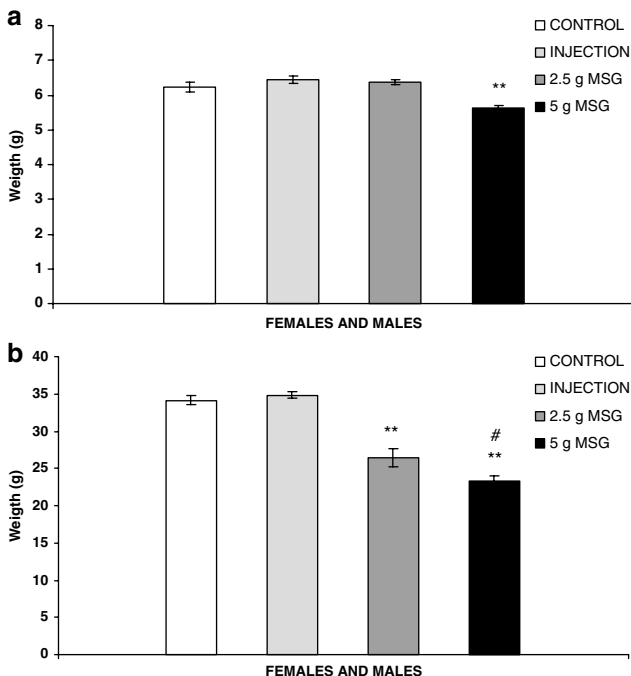


Figure 2 Mean (\pm s.e.m.) birth weight (a) and weaning body weight (b) in normal rats (control), neonatally MSG-treated rats (injection) and 2.5 g (2.5 g MSG) and 5 g (5 g MSG) MSG oral administered rats ($n=12-18$). Each group includes male and female data since statistical analysis showed no gender differences. $**P<0.01$ vs other groups (a), $**P<0.01$ vs CONTROL + INJECTION groups and $\#P<0.05$ vs 2.5 g MSG group (b).

with 2.5 g MSG per day (group 2) results in no birth weight modification as compared to controls, whereas maternal feeding with 5 g MSG per day (group 3) results in severe birth weight reduction ($P<0.01$). Weight increments remain subnormal when MSG feeding to the mothers is maintained during weaning (Figure 2b) ($P<0.01$).

Figure 3a, b shows GH plasma levels of the offspring. As expected, GH plasma levels were low in animals that were neonatally injected with MSG, both at day 30 and at day 90 of life ($P<0.05$). However, GH serum levels were also affected in animals that had received MSG during prenatal life via maternal feeding. Figure 3b illustrates that animals kept on high MSG diet (5 g MSG per day) show serum GH levels that are as low or even lower than those of MSG injected animals ($P<0.05$), both at day 30 and at day 90 of life. The influence of MSG is in general more marked in males than in females.

Animals that were kept on medium MSG diet (2.5 g MSG per day) showed low-serum GH levels at day 30 of life ($P<0.01$), but seemed to partially recover before day 90. Almost identical results were observed in IGF-1 serum levels (Figure 4a, b).

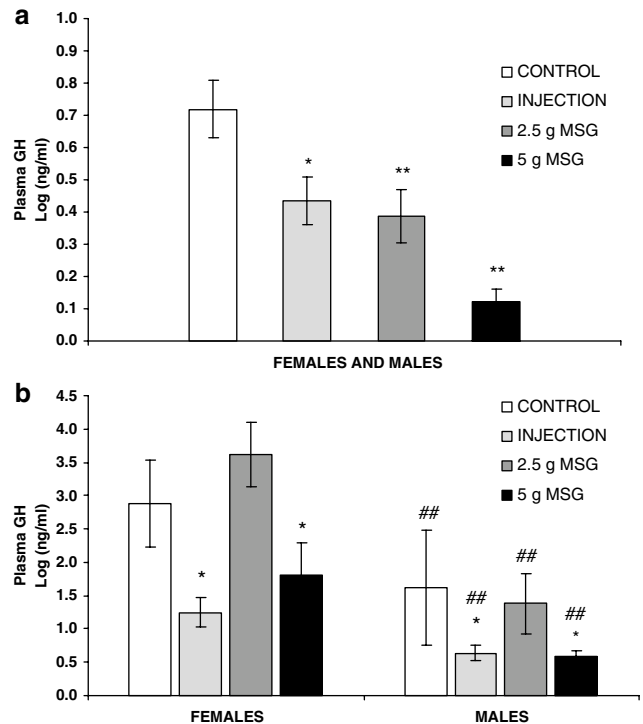


Figure 3 Mean (\pm s.e.m.) plasma concentration of GH at 30 days (a), and at 90 days (b) of life in normal rats (control), neonatally MSG-treated rats (injection) and 2.5 g (2.5 g MSG) and 5 g (5 g MSG) MSG oral administered rats ($n=12-18$ (a), $n=6-9$ (b)). Each group includes male and female data since statistical analysis showed no gender differences. $**P<0.01$ vs CONTROL group and $*P<0.05$ vs CONTROL group (a), $*P<0.05$ vs CONTROL + 2.5 g MSG and $\#\#P<0.01$ vs the corresponding FEMALE group (b).

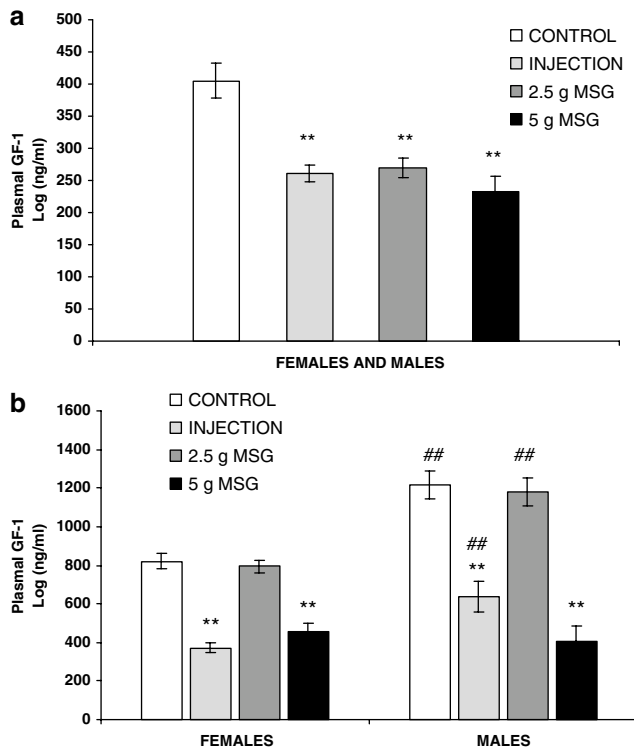


Figure 4 Mean (\pm s.e.m.) IGF-1 plasma concentration at 30 days (a) and at 90 days (b) of life in normal rats (control), neonatally MSG-treated rats (injection) and 2.5 g (2.5 g MSG) and 5 g (5 g MSG) MSG oral administered rats ($n=12-18$ (a), $n=6-9$ (b)). Each group includes male and female data since statistical analysis showed no gender differences. ** $P<0.01$ vs CONTROL group (a), ** $P<0.01$ vs CONTROL + 2.5 g MSG and ## $P<0.01$ vs the corresponding FEMALE group (b).

Figure 5a, b shows the influence of MSG on appetite. Whereas – in contrast to previous findings (Fan *et al.*, 1997) – MSG-injected animals of this investigation did not show significantly increased appetite compared to controls, the animals kept on medium MSG diet (2.5 g MSG per day), and particularly those kept on high MSG diet (5 g MSG per day) demonstrated marked voracity. The animals fed 5 g MSG per day increased water uptake by threefold ($P<0.01$), and food uptake by almost two-fold ($P<0.01$). Voracity seems to be MSG-dose-dependent and the increase was identical in both genders.

Leptin values were significantly increased in animals that were neonatally injected with MSG, both at day 30 and at day 90 of life ($P<0.05$), we found reduced leptin levels in the two orally treated groups.

Rats orally treated with MSG are smaller and have lower body weight, than control animals. The gravity index (specific weight, measured in air and water) that provides a relative information about the fat content of animal carcasses, however, indicated that MSG fed animals contained significantly more body fat both at day 30 and at day 90 than controls ($P<0.05$).

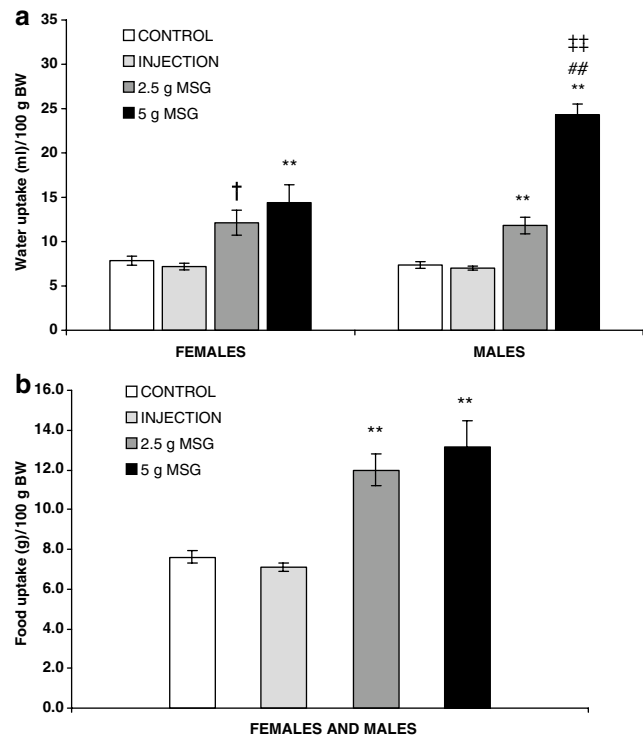


Figure 5 Mean (\pm s.e.m.) water (a) and food (b) uptake at 90 days of life in normal rats (control), neonatally MSG-treated rats (injection) and 2.5 g (2.5 g MSG) and 5 g (5 g MSG) MSG oral administered rats ($n=6-9$). ** $P<0.05$ vs CONTROL + INJECTION groups; † $P<0.05$ vs INJECTION group; ‡ $P<0.01$ vs 2.5 g MSG group and ## $P<0.01$ vs the corresponding FEMALE group (a), ** $P<0.01$ vs CONTROL + INJECTION group (b).

Discussion

Glutamic acid (GLU) is the most common amino acid in animal protein, and accounts for some 16% of meat protein, and some 20% of milk protein weight. That is, infants who daily consume up to 5 g/kg body weight of protein (Koletzko, 2002), consume as much as 1 g/kg body weight of GLU. GLU is also the physiological ligand of the taste receptor umami, the dominant taste of food containing L-GLU, like chicken broth, meat extracts, ageing cheese. Umami is responsible for the immediate sensory effect of MSG on the palatability of food. MSG is used as flavouring agent.

However, it has long been known that MSG can also intoxicate arcuate nucleus neurons. In 1969, Olney and Sharpe reported on brain lesions, obesity, and other disturbances in mice (Olney, 1969), and in an infant rhesus monkey (Olney and Sharpe, 1969) treated with MSG. In 1976, Holzwarth-McBride *et al.* (1976) investigated the effect of the MSG induced lesion of the arcuate nucleus by measuring catecholamine content in this nucleus and the median eminence of the mouse hypothalamus. The two major characteristics of MSG-induced arcuate nucleus

damage hitherto described, are voracity, and impaired GH secretion. However, all of these studies focussed on parenterally administered MSG. We demonstrated that MSG maintains its toxicity even when administered orally.

The influence of MSG is in general more marked in males than in females. Since MSG has excitotoxic activities and implies oxidative stress, the gender difference may be explained by to the antioxidant activity of estrogens (Ruiz-Larrea *et al.*, 1997; Cuzzocrea *et al.*, 2001). Estrogens have a very important neuroprotective activity (Azcoitia *et al.*, 1999).

The present investigation was performed in animals not older than 90 days. Although at this age, the animals are still too young to exhibit obvious signs of obesity, MSG fed animals contain more body fat than controls, and show impaired glucose tolerance and insulin resistance (Hirata *et al.*, 1997). Macho *et al.* (2000) found a shift in glucose metabolism towards lipid synthesis in fat tissue, in 3-month-old rats treated with MSG during the postnatal period, and demonstrated an attenuation of insulin effect on glucose transport due to a lower insulin binding and lower content of GLUT4 protein. They concluded that early postnatal administration of MSG exerts an important effect on glucose metabolism and insulin action in adipocytes of adult animals, indicating that apart from excitotoxic effects in the central nervous system, MSG treatment appears to also exert peripheral metabolic effects.

The present findings are alarming, and throw doubts upon the unscrupulousness of current use of the flavouring agent MSG. L-Glutamic acid was evaluated by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 1988. The JECFA allocated an 'acceptable daily intake not specified' to glutamic acid and its salts with no additional risk to infants. The Scientific Committee for Food (SCF) of the European Commission reached a similar evaluation in 1991. The conclusions of a subsequent review by the Federation of American Societies for Experimental Biology (FASEB) and the Federal Drug Administration concurred with the safety evaluation of JECFA and the SCF (Walker and Lupien, 2000). MSG can be added at concentrations of up to 10 g per kg food (European Parliament and Council Directive 95/2/EC). Ca. 3 g MSG are added per kg potato chips (Greiff, Bahlsen-Lorenz company, personal communication, 2002), ca. 3–6 g are added per kg meat products (Kasch, Dölling company, 2002, personal communication).

We used a medium (2.5 g per day per adult animal) and a high (5 g per day per adult animal) MSG diet, accounting for some 10%, respectively, some 20% of the daily amount of food. Yet, rat chow is dried food. Assuming a water content of some 70% in an ordinary breakfast sausage, 6 g MSG per kg meat product equals some 2% MSG in the dry product. That is, the medium concentrations of GLU used in our animals, surpassed the concentration that is currently added to modern industrial food, by only the factor five!

The present study for the first time demonstrates, that a widely used nutritional monosubstance – the flavouring agent MSG – at concentrations that only slightly surpass

those found in everyday human food, exhibits significant potential for damaging the hypothalamic regulation of appetite. Although the experimental part of this study was performed in rodents, and though it remains to be elucidated whether rodents are more sensitive to MSG than humans, uneasiness remains when considering that world-wide MSG production has increased from 200 000 (1969), to 270 000 (1979), to 800 000 tons/year in 2001 (Schmid, 2002) (Schmid, 2002, personal communication). First, clinical evidence in the treatment of very obese subjects further stresses the importance of GLU in the regulation of appetite: Blocking GLU action by antagonising GLU-gated Ca^{2+} ion channels with memantine normalises binge-eating disorders within a few hours (Hermanussen and Tresguerres, 2005).

Other questions remain: is obesity the disease that we are interested in? Obesity results from a nutritional imbalance. That is, in view of the present findings, we rather have to consider if not voracity is the disease that needs to be addressed in the first place. It has been shown that obesity associates with GH secretory dysfunction. A 24 h integrated concentrations of GH were lower in young, obese subjects than in young subjects who were lean (Meistas *et al.*, 1982). Veldhuis *et al.* (1991) examined the mechanisms underlying the reduced circulating GH concentrations in obese subjects. Obese men had fewer GH secretory bursts, and both GH secretion rate and GH burst frequency were negatively correlated with the degree of obesity (Veldhuis *et al.*, 1991). However, since obesity results from a nutritional imbalance, that is, obesity results from voracity – we are now concerned that both the damage in the regulation of appetite, and the impaired GH secretion, result from world-wide supraphysiological GLU consumption. The fact that large BMI associates with short stature, indicates towards the possibility that both excessive appetite and growth failure, may have a common cause.

If this be the case, many more questions arise: Do other amino acids metabolise into GLU, do other amino acids lead to similar toxic effects when fed at supraphysiological doses? Is GLU the only ligand that causes NMDA-R-mediated neuronal damage, or do elevated levels of glycine produce similarly deleterious effects when binding to the glycine site of the NMDA-R (the NMDA-R has a glycine-binding site (Huggins and Grant, 2005))? Is the NMDA-R the only receptor that mediates arcuate nucleus damages? Do oral loads of GLU exhibit the same effects than parenteral loads of this amino acid? Much work is still to be performed, but good reasons have already been accumulated to reconsider the recommended daily allowances of amino acids and nutritional protein, and to abstain from the popular protein-rich diets, and particularly from adding the flavouring agents MSG.

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