European Journal of Clinical Nutrition (2006), 1–10
 0954-3007/06 $30.00
www.nature.com/ejcn

ORIGINAL ARTICLE

Consensus meeting: monosodium glutamate – an update

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Objective: Update of the Hohenheim consensus on monosodium glutamate from 1997: Summary and evaluation of recent knowledge with respect to physiology and safety of monosodium glutamate.
Design: Experts from a range of relevant disciplines received and considered a series of questions related to aspects of the topic.
Setting: University of Hohenheim, Stuttgart, Germany.
Method: The experts met and discussed the questions and arrived at a consensus.
Conclusion: Total intake of glutamate from food in European countries is generally stable and ranged from 5 to 12 g/day (free: ca. 1 g, protein-bound: ca. 10 g, added as flavor: ca. 0.4 g). L-Glutamate (GLU) from all sources is mainly used as energy fuel in enterocytes. A maximum intake of 16.000 mg/kg body weight is regarded as safe. The general use of glutamate salts (monosodium-L-glutamate and others) as food additive can, thus, be regarded as harmless for the whole population. Even in unphysiologically high doses GLU will not trespass into fetal circulation. Further research work should, however, be done concerning the effects of high doses of a bolus supply at presence of an impaired blood brain barrier function. In situations with decreased appetite (e.g., elderly persons) palatability can be improved by low dose use of monosodium-L-glutamate.
European Journal of Clinical Nutrition advance online publication, 6 September 2006; doi:10.1038/sj.ejcn.1602526

Keywords: monosodium glutamate; CNS; breast milk; food safety; toxicology; human nutrition

Background

The 1997 Hohenheim consensus talk has dealt with aspects of metabolic and safety aspects of monosodium glutamate (Biesalski *et al*., 1997). In the meantime, new data including results of an 'International Symposium on Glutamate' (Fernstrom and Garattini, 2000) were published. Consequently, it was decided to update results of the 1997 concensus conference considering the available new information with a special focus on safety aspects.

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Received 21 December 2005; revised 14 June 2006; accepted 6 July 2006

Physiology of glutamate

Definitions
Consensus. To clarify that added monosodium-L-glutamate (MSG) and all other glutamate salts dissociate in aqueous solutions and therefore are identical with free glutamic acid, only the term L-glutamate (GLU) should be used in the following statements.

Background. GLU is part of many food proteins (bound GLU) but it appears as well in its free form in certain foods (free GLU). To this food derived GLU adds GLU salts (e.g.,

MSG) that are used as food enhancer in instant products such as soups, sauces or pizza. Presently, six additives are admitted in the European Union (EU): GLU (E620) and its sodium (E621), potassium (E622), calcium (E623), ammonium (E624) and magnesium (E625) salt. These food enhancers are not allowed to be added to milk, emulsified fat and oil, pasta, cocoa/chocolate products and fruit juice. Following the compulsory EU-food labeling law the use of 'enhancer' has to be declared and the name or E-number of the salt has to be given. GLU salts dissociate in the neutral area so that independent from origin and salt species free GLU is formed.

Estimated intake of GLU from natural sources (European diet, Asian diet) and as food additive

Consensus. In Germany average intake of native GLU (as protein constituent or in free form in foods) can be calculated to about 10 g/day (range: 4.6–12 g/day). The use of new technologies in food processing (e.g., microwave technology) does not influence native GLU content.

With respect to added GLU, only limited data are available. In EU countries the mean intake ranges from 0.3 to 0.5 g/day; in Asian countries people consume in average 1.2–1.7 g/day. It is, however, to mention that the individual GLU intake from food additives shows broad variations; high consumers in Europe may reach up to 1 g/day, in Asian countries 4 g/day. Average intake in EU countries might only be slightly increased since 1997.

The amount of GLU added to a specific product is limited by the fact that increasing amounts of GLU will not increase but decrease palatability. When specific nucleotides are added as flavors to the products GLU content can be lowered due to 'synergisms' of taste.

Background. With respect to the amount of protein bound GLU in a mixed diet only limited data are available. This is due to the fact that the amino-acid composition of a food protein is commonly assessed after acid hydrolysis and that glutamine residues are decomposed to GLU during this process. In consequence, most of the amino-acid composition data published only include the percentage of 'GLX' per 100 g of protein/16 g of nitrogen reflecting the sum of GLU plus glutamine (Kuhn *et al.,* 1996). With the assumption that ca. 40% of GLX are native GLU residues, the amount of protein bound GLU can be estimated to 4–12 g/100 g food protein (Anderson and Raiten, 1992). Considering an average protein intake of 90 g/day for young adults (German Nutrition Society 2004), GLU intake from intact protein approached 3.6–10.8 g/day.

In addition to bound GLU, some products like fresh fruits, vegetables and cheese contain various amounts of free GLU (unprocessed potatoes: 50–80 mg/100 g, tomatoes: 200–300 mg/100 g, tomato products: up to 630 mg/100 g, long matured cheese like Parmesan: up to 1200 mg/100 g). Based on a mixed diet, intake of free GLU can be presently estimated to 1 g/day. As the consumption of tomatoes/tomato products and cheese consistently increased in Germany during the last years (German Nutrition Society 2004), a further increase in free GLU intake from food can be expected.

Within the last couple of years, 'low-carb diets' were heavily promoted in western societies (Berkowitz, 2000). Energy deficits due to low carbohydrate intake are generally compensated by a quantitatively higher protein, which may slightly increase GLU intake.

As food enhancer GLU is preferably used in form of MSG. The concentration in convenience foods adds up to 0.1–0.8% of weight which is similar to the concentration of native free GLU in tomatoes or parmesan. Based on measured added GLU content of over 500 MSG-containing food items obtained from the grocery, Rhodes *et al*. (1991) calculated daily added GLU intake in the United Kingdom (UK). These are: whole population, 586 mg/day; households buying foods in each category examined (likely to be maximum intake), 1560 mg/day; extreme users (97.5th percentile consumers), 2330 mg/day (likely to be maximum intake); children, 10–11 and 14–15 year, 1300 mg/day (if 40 kg body weight, 33 mg/kg/day; if 60 kg body weight, 22 mg/kg/day). If extreme consumption group weighs 70 kg (adults), daily dose is about 30 mg/kg/day; if whole population averages 50 kg (all ages), daily dose is about 12 mg/kg/day (Rhodes *et al.,* 1991).

In Western societies, there is a general trend to an increased consumption of flavored convenience food. Theoretically, this change in behavior might lead to an increased GLU intake, which is used in these products as flavor. On the other hand, the food industry steadily increases the number of MSG-free products due to an enhanced reservation of the consumer against food additives (Dillon, 1993). Consequently, overall intake of added GLU might not be significantly altered.

In Asia, especially in Japan and Korea MSG and other GLU salts are used more intensively than in Europe. In these countries the intake of added GLU is estimated to 1.2–1.7 g/day (for details see Biesalski *et al*. (1997)). In a highly seasoned restaurant meal, however, intake as high as 5000 mg or more may be possible (Yang *et al.,* 1997).

What is the role of GLU in biochemical and metabolic processes?

Consensus. Most of GLU (up to 95%) derived from food (bound and added) is used as energy source by the enterocytes of the intestinal mucosa.

Background. In healthy adults, GLU can be endogenously synthesized in adequate amounts and, thus, is qualified as a nonessential (dispensable) amino acid (Fürst and Stehle, 2004). The daily GLU turnover is calculated to about 48 g (Garattini, 2000). GLU liberated from food protein is quantitatively absorbed from the lumen. Absorption kinetics is influenced by the retention time in the stomach and the surrounding matrix in the gut.

Studies over the last two decades have demonstrated extensive catabolism of nonessential amino acids in intestinal mucosa (Burrin and Reeds, 1997). In recent years, there has been growing recognition that catabolism also dominates the first-pass intestinal utilization of dietary essential amino acids (Stoll *et al.,* 1998). The major objective of current views of intestinal mucosal amino acid catabolism and its implications for protein and amino acid nutrition is the role of nonessential (indispensable) amino acids like GLU. Current studies of Reeds *et al.* (2000) demonstrated that GLU is the most important oxidative substrate for the intestinal mucosa. In addition, GLU (via glutamine) appears to be a specific precursor for the amino acids arginine and proline as well as for the tripeptide glutathione by the small intestinal mucosa. Glutathione clearly plays an important role in the protection of the mucosa from peroxide damage and from dietary toxins. These results raise the intriguing questions whether dietary GLU is an indispensable factor for the maintenance of mucosal health.

Intestinal metabolism of GLU derived from natural sources or food additives and its function: are there differences?
Consensus. Food-derived protein-bound and free GLU and GLU derived from food additives are similarly metabolized in the human body.

Background. It is well known that GLU penetrates carrier-mediated but largely Na(+)-independent through the cell membranes. There are no differences in luminal uptake between GLU liberated from proteins, natural free GLU and additive GLU. All GLU taken up is used for the diverse synthesis processes in intracellular compartments (Kovacevic and McGivan, 1983; Hundal *et al.,* 1986; Low *et al.,* 1992).

Fetal development: does the placenta barrier control GLU transfer?
Consensus. The placenta barrier controls GLU transfer even in situations of elevated maternal plasma levels. The limitation of transplacental transfer is due to placental metabolism of GLU.

Background. The early non-human primate studies of Stegink *et al.* (1975) in pregnant females showed that even very large, intravenously infused doses of GLU penetrate only to a minor extent into the fetal circulation. A biochemical explanation is offered by the recent studies in sheep, in which the placenta was shown to extract GLU from both the maternal and fetal circulations for use as a principal energy source (Battaglia, 2000).

Up to which maternal plasma level this may be applicable has been also tested in rhesus monkeys their placenta being morphologically and functionally the most similar to human placenta (Stegink *et al.,* 1975). Pregnant females received during 1 h intravenous drip containing 0.15, 0.17–0.19, 0.22 or 0.40 g MSG/kg bw, respectively. Infusions with 0.15–0.22 g/kg bw increased the maternal plasma level from a baseline value (50 μmol/l) to about 500–1000 μmol/l; GLU concentration in fetal plasma was thereby, however, not affected. Only at the highest exposure (0.40 g/kg bw) associated with a maternal plasma level of about 2800 μmol/l there was an increase of the fetal plasma level up to 440 μmol/l. A plasma level between 2000 and 2500 μmol/l was identified as barrier for the GLU transfer to the fetus. It is therefore concluded that a transfer of GLU from mother to fetus is highly unlikely even with the highest oral intake (see above).

Umami receptor and transduction mechanism: is it a selective taste? Umami perception-recognition and palatability: nutritional aspects
Consensus. The Umami receptor is present in humans and gives rise to a selective taste. The Umami receptor is specific for GLU but might also detect other free amino acids.

Background. Considerable behavioral and electrophysiological evidence already existed in the 1980s supporting the notion that GLU (umami) represents a fifth basic taste, separate from sweet, sour, salty and bitter or combinations of these tastes. For example, in human taste testing studies, subjects could differentiate umami tastes from those of the other basic tastes, in both simple and complex food matrices (Yamaguchi, 1987). In electrophysiological studies, recording from afferent chorda tympani fibers in dogs, taste cells were found that responded to GLU application to the tongue independent of sodium receptor stimulation (sodium receptors were blocked with amiloride) (Nakamura and Kurihara, 1991). In addition to these earlier results, glossopharyngeal afferent fibers were identified in mice that responded to GLU (and mononucleotide) applications to the tongue, but not to the other basic tastants (Kurihara and Kashiwayanagi, 2000).

More recently, attempts have been made to identify the specific type of receptor on the tongue that mediates umami taste. One approach has been pharmacologic, and it was examined in rats and humans whether agonists at known neuronal GLU receptors are perceived as having umami taste. In rats, studies have focused on taste preference and taste synergy studies, and evidence was found for an umami taste receptor that shares pharmacologic similarities with the metabotropic GLU receptor 4-subtype (mGLU-R4) (Delay *et al.,* 2000). In human studies, subjects reported the presence and intensity of umami taste for a variety of GLU receptor agonists. The result was that the umami taste receptor is probably a metabotropic, but not an ionotropic GLU receptor, perhaps somewhat similar to, but not identical with the metabotropic GLU receptor subtype-4. Kurihara and Kashiwayanagi (2000) concluded from their human studies that the umami taste receptor may be a unique GLU receptor subtype.

A second approach has been to use molecular techniques to identify candidate umami taste receptors. One strategy,

based on earlier work suggesting that the mGLU-R4 might function as an umami taste receptor, has been to search for the expression in taste tissue of the mGLU-R4. A gene expressing an N-terminal truncated version of the mGLU-R4 has been found in rat taste buds; this receptor elaborates umami taste receptor-like properties (Chaudhari *et al.,* 2000). Another strategy has been to use novel screening strategies to create a taste-bud enriched cDNA library from rats, and use it to search for candidate taste receptors. This approach has led to the identification of a set of G-protein-coupled receptors, organized into two receptor families (taste receptor 1 (T1R) and taste receptor 2 (T2R)) that elaborate the basic taste modalities, including umami (Hoon *et al.,* 1999; Nelson *et al.,* 2002; Zhao *et al.,* 2003). Umami taste receptors fall into the T1R family of receptors, and recent studies in knockout mice suggest that a particular member of the T1R family (the T1R1 + 3 variant) serves as an L-amino-acid receptor in rat taste buds (Zhao *et al.,* 2003), and an umami-specific taste receptor in humans (Li *et al.,* 2002).

Finally, a recent report has identified in humans a specific ageusia for GLU, suggesting that such individuals may lack an umami taste receptor (Lugaz *et al.,* 2002).

Does GLU improve palatability and does it have nutritional impacts on certain subjects?

Consensus. Added GLU improves food palatability and taste. Sodium or calcium salts of GLU increases acceptability of new flavors. Liking of GLU-enriched foods may contribute to maintain nutrient intake in subjects with reduced chemosensory sensitivity, for example institutionalized elderly persons.

Background. Taste and smell losses can reduce appetite and may lead to inadequate dietary intake, a situation frequently occurring in elderly. Most of these chemosensory deficits are not reversible. Symptomatic treatment including intensification of taste and odor can compensate in part for perceptual losses. One method for treatment involves a sensory enhancement of foods with flavors and MSG. Several studies showed that amplification of flavor and taste can improve food palatability, increase salivary flow and local immunity and thereby at least acceptance of food (Schiffman, 2000; Mojet *et al.,* 2003).

In institutionalized elderly persons and in hospitalized diabetic patients, the addition of MSG to specific foods in a lunch meal induced an increased intake for those foods with a subsequent decreased intake of foods presented later in the meal. In both populations only food selection was affected by MSG but meal size remained the same (Bellisle, 1998).

With the idea to reduce sodium intake studies have been performed to exchange sodium salts in foods with calcium salts, for example calcium diglutamate. Addition of calcium diglutamate raised liking of fried sausages (Bratwurst) similar to the corresponding sodium salt-enriched products (Woodward *et al.,* 2003).

Based on broad range of experimental data and human studies, MSG or calcium diglutamate can be used cautiously by the consumer in order to increase palatability and can also be used selectively by nutrition experts in order to influence food selections towards a healthy diet composition specifically in individuals with either a low food intake or disturbance of taste and smell.

GLU safety in food supply

General aspects

Food has to be safe. This statement is of paramount meaning in the legislation of virtually all countries and governs the work of international bodies dealing with food and/or health. However, inappropriate eating habit, or individual predisposition (e.g. idiosynkrasie, metabolic disorders) show that it is not possible to make food absolutely safe for every person and under all circumstances. Therefore, the definitions of food safety take these restrictions into consideration.

According to the general principles of Codex alimentarius (1995) food safety is the assurance that food will not cause harm to the consumer when it is prepared and/or eaten according to its intended use. Several other definitions are published:

- ISO 8402: Food safety means the state in which risk of harm to persons or damage is limited to an acceptable level
- ISI/CEI Guide 2: Food safety means freedom from unaccepted risk of harm
- OECD, 1993: 'A food is safe if there is a reasonable certainty that no harm will result from its consumption under the anticipated conditions of use'.

Thus, one is aware that virtually no food can be described to which a zero-risk may apply. This background leads to the question as to the 'acceptable level of risk' or 'the reasonable certainty'. It is commonly accepted that this limit rests on social consensus.

Whereas it is still a problem to assess the safety of a complex food, the assessment of a distinct compound that may be employed as a food additive is a well established procedure. The principles of which follow the recommendations of FAO/WHO Expert Committees and base on testing all toxicological endpoints as well as the definition of acceptable daily intake amounts that take into account a safety margin of a factor 100. This experimentally determined amount is defined as the 'no observed adverse effect level' (NOAEL).

Can we define a safe level of intake regarding added GLU?

Consensus. Based on dietary animal studies (metabolic control), a NOAEL of 16 000 mg/kg body weight was calculated in weaning animals, on parenteral supply 500–1000 mg/kg body weight.

Background. There is an early literature showing that free GLU can be administered chronically to humans in very large doses with no ill effect. An example of this is the study of Bazzano *et al*. (1970), in which doses up to 147 g/day GLU were given for 30 days or more, with no adverse effects reported (147 g/day in a 70 kg male would be about 210 mg/kg bw/day). Other studies date even earlier that is from the 1940s through the 1960s, for the most part. In animals, there is the multigenerational study performed by Anantharaman in the 1970s (Anantharaman, 1979) using doses of 6000–7000 mg/kg bw/day into male and female mice and generations of offspring with no ill effects whatsoever. But, no LOAEL or NOAEL has been set for added GLU, at least by the US Committee on Dietary Reference Intakes (Panel on Micronutrients, 2002).

Do we have additional knowledge on the effect of added GLU on lung and immune system since 1997 until now?
Consensus. Two new studies showed that there are no adverse effects on the lung. Other new data derived from *in vitro* studies show differing results but these cannot be transferred to the situation of GLU derived from food. The existence of GLU-induced asthma, even in history-positive patients, has not been established firmly.

The information on the effects of high GLU concentrations on immunological parameters is scarce.

Background. In 1981, two experiments were described in which asthma attacks could be provoked by ingesting 2.5 g GLU (Allen and Baker, 1981). Recently, GLU receptors of the NMDA subtype have been identified in the lungs of rats, which might be responsible for the hypersensitivity of asthmatics (Dickmann *et al.,* 2004). A survey of Schwartzstein (Schwartzstein, 1992) documented 19 cases of asthma attacks induced by GLU dosages (as MSG) in the gram range. Here, the design of the study has to be criticized: under double-blind conditions only a single attack could be provoked.

Concerning lungs in relation to asthma two studies have appeared since 1997. Woods (Woods *et al.,* 1998) examined a group of asthmatic subjects who believed that added GLU was a cause of their asthma. They conducted a double-blind, placebo-controlled, crossover study ($n=12$); subjects ingested placebo (lactose), 1 or 5 g MSG on separate test days, and lung function was followed for 12 h. They observed no significant effect of MSG on lung function at either dose, relative to placebo. Woessner *et al*. recruited groups of asthmatic patients who reported (a) sensitivity to added GLU ($n=30$) and (b) no GLU sensitivity ($n=70$). Subjects received, single-blind, on separate days either placebo or 2.5 g MSG, and were followed for 12 h. All subjects were tested for aspirin sensitivity. Subjects who reported sensitivity to GLU showed no difference in response to placebo and MSG. Twelve of these subjects demonstrated aspiring sensitivity (a positive control). Subjects who reported no GLU sensitivity also showed no response to MSG; 80% of this group demonstrated aspiring sensitivity. The investigators concluded that MSG does not provoke bronchospasm (Woessner *et al.,* 1999).

In a survey of Stevenson (Stevenson, 2000) a total of 45 patients out of four studies cited are listed. The survey was on patients who reported asthma attacks after the consumption of meals in oriental restaurants. None of the patients showed reactions on orally applied GLU *per se*. In contrast there are two former studies (Allen *et al.,* 1987; Moneret-Vautrin, 1987) reporting GLU provoking a reaction – under simple blind conditions after discontinuing the antiasthma-medication – in 16 out of 62 high-risk patients. Out of a total of 109 asthmatics tested none showed reactions on oriental food and none reacted on oral GLU.

An inquiry brought only one study up in which high-dose GLU supplementation (up to 8% in the diet) improved significantly the immune status of rats recovering from chemotherapy. The immune-enhancing effect of dietary GLU was dose-dependent and more pronounced after a longer duration of dietary GLU intake (Lin *et al*., 1999).

Can groups sensitive to GLU (derived from either natural food or food additives) be defined? Are there at present placebo controlled studies available sufficiently to either exclude or promote side effects of added GLU?
Consensus. No, there is no clear description of a sensitive phenotype. One multicenter study with real placebo did not find any effect of GLU when MSG was given with food. Another study did not show reproducible effects.

Background. Regarding GLU sensitivity, two articles are relevant since 1997 (Yang *et al.,* 1997; Geha *et al.,* 2000). Yang *et al*. conducted a double-blind study in self-identified, GLU-sensitive subjects. They received placebo or 5 g MSG in liquid in random order, and those showing a response to one of the treatments were retested with 1.25, 2.5 and 5 g MSG. A response was defined as any two of a list of 10 symptoms listed in a recent expert panel-government report (Raiten *et al*., 1995) Subjects reported any symptoms, and were unaware of the index symptoms being followed. In the first trial, 22 of 61 subjects responded to 5 g MSG, but not placebo (18 responded to neither treatment, six responded to both and 15 responded to placebo). When analyzed for order effects of treatment (an assessment of subject bias), positive responses to placebo were greater when it was administered during the first, rather than the second challenge. Subjects showing a response to one treatment only ($n=37$:22 MSG + 15 placebo; the study was double-blind) were then retested. An analysis of total occurrences in all subjects of the 10 index symptoms revealed that headache, muscle tightness, numbness, weakness and flushing were increased when MSG was ingested, and a dose-effect was evident.

The Yang study evaluated the total occurrence of all index symptoms of GLU, and did not require that subjects

show reproducibility of symptoms with retesting, a key issue of a recent US expert panel review (Raiten *et al*., 1995). Another recent study addressed the issue of symptom reproducibility among subjects who identified themselves as GLU sensitive.

The Geha study (Geha *et al*., 2000) had four sequential tests, the first two being identical to those in the Yang study (above). A total of 130 subjects entered the first phase of the study, in which they received, double-blind, placebo or 5 g MSG in liquid in random order on separate days, and symptoms were recorded for 2 h. Fifty subjects reported two or more index symptoms following MSG ingestion, and 0 or 1 following placebo, 19 reported two or more symptoms with MSG and placebo, 17 two or more symptoms with placebo, and 0 or 1 with MSG, and 44 0–1 symptoms with either MSG or placebo. Phase two (the dose–response study using 0, 1.25, 2.5 and 5.0 g MSG) entered 86 subjects (they included all subjects who had two or more responses to either *or both* treatments) and completed 69. In this phase, when total symptom occurrence was analyzed, the outcome was similar to that observed by Yang *et al*. (1997): more subjects reported index responses as MSG dose increased. However, the responses were then analyzed for reproducibility across both trials. As the MSG dose in the first trial was 5 g, the reproducibility of response to the 5 g dose was assessed over both trials. The criterion of symptom reproducibility was met by only 14 of the subjects (a total of 19 responded to MSG but not placebo, but only 14 had reproducible symptoms to MSG). Based on the expert panel report (Raiten *et al*., 1995) the next phase of the study, which included 12 of the 19 subjects who responded to MSG but not placebo (only 12 agreed to participate further), involved administering MSG (5 g) or placebo in capsules (to prevent their tasting the test substance) twice, each on separate occasions. Only two of the subjects reported two or more symptoms after MSG, but not placebo. However, neither subject reported the same symptoms following each MSG challenge. A final phase assessed symptom occurrence following the ingestion of *food* containing MSG (or placebo) on three separate occasions. Even though no subjects remained that had proven MSG-sensitivity, the two that responded to MSG, but not placebo, were invited to participate in this phase. Both subjects reported two or more symptoms in one of the three MSG trials, and the symptoms were not the same as reported in previous MSG challenges.

The study of Geha *et al*. demonstrates that when a group of self-identified, GLU sensitive individuals is asked to show reproducibility in symptoms, none can do so.

The conclusions of a subsequent review by the Federation of American Societies for Experimental Biology (FASEB) and the Federal Drug Administration (FDA) did not discount the existence of a sensitive subpopulation but otherwise concurred with the safety evaluation of JECFA and the SCF (Walker and Lupien, 2000).

The trend is going to exclude GLU from food additive intolerance list because of uncertainty (Young, 1997). In addition, hard clinical criteria are requested when testing patients with food additives (Asero, 2004).

Central nervous system

General aspects

In cases of an impaired blood/brain barrier (BBB) GLU from blood might cross the barrier and might cause toxic effects even at physiological plasma levels.

As the gastrointestinal tract has a very high capacity for using GLU, dietary intake (free and bound GLU) has a minor impact on plasma levels. Only high concentrations (as bolus) (e.g. 550 μmol/l) may lead to a transient increase of plasma level. Consequently food-derived GLU (including added GLU as food additive in normal amounts of <1 g/day) does not further increase the risk for toxic effects in cases of an impairment of BBB because plasma levels do not rise.

Does the BBB control the GLU transfer under normal conditions?
Consensus. As long as BBB is intact there is no risk for GLU transfer across BBB.

Background. The BBB restricts and regulates the flux of substrates between the circulation and the central nervous system. To cross the barrier substances must either cross the lipoid cellular membranes or be transported by selected BBB carriers. GLU is a polar solute, thus the passive influx is limited to $<1\%$ of that occurring at the blood vessels of other tissues (Smith, 2000).

Are there conditions where this barrier function regarding GLU might be impaired?
Consensus. Several common brain pathologies are known to be associated with BBB disruption. There is no assured research data available whether augmented plasma levels in this situation influence synaptic GLU concentrations.

Background. There is evidence that a doubling of plasma GLU, for example after infusion of GLU containing parenteral nutrition augments brain edema in conditions with a lesioned BBB (Stover and Kempski, 1999). Elevated plasma GLU may also occur during anesthesia with isoflurane (Stover *et al*., 2004; Stover and Kempski, 2005).

Do we have data that might promote a relationship or role of added GLU in the development of neurological degenerative diseases under in vivo *conditions?*
Consensus. At present there is no scientific data available supporting the presumption of an involvement of added GLU in the development of human neurological disease.

Background. GLU functions in the CNS as excitatoric transmitter. Therefore, high intracellular GLU concentrations

concurrently with low extracellular concentrations have to be maintained. This will be reached on the one hand by a fast elimination of the released GLU by surrounding astrocytes and on the other hand by an active transport mechanism provided at the BBB which ensures that the spinal fluid (CSF)-GLU level is kept lower than the concentration in blood.

In the brain, GLU binds to the NMDA-receptor and controls the intra- and extracellular (synaptic) calcium levels. In times of overactivation there is a reinforced calcium influx into the cell leading finally to apoptosis. After ischemia in definite brain sections neurons will be destroyed. Out of these damaged cells GLU will be released and the CSF GLU level will increase. Therefore, primarily not infarcted brain sections will probably also be affected.

Basal synaptic concentrations of GLU are estimated to be in the 2–5 μmol/l range, and rise to 50–100 μmol/l following release (Daikhin and Yudkoff, 2000; Meldrum, 2000). Plasma GLU concentrations are typically 50–100 μmol/l under normal conditions (Tsai and Huang, 1999; Fernstrom *et al.,* 1996) and do not rise significantly even in the presence of sizable oral doses of MSG (Tsai and Huang, 1999). Plasma GLU concentrations appear to rise only when pharmacologic doses of MSG are administered. Hence, if the BBB were to become permeable (for review see Ballabh *et al.,* 2004; Neuwelt, 2004), or BBB GLU transporters were to become compromised (they normally function to transport GLU out of the brain (O'Kane *et al*., 1999), one might imagine that synaptic GLU concentrations could rise, which would be sufficient to stimulate GLU receptors.

Few studies to date have searched for changes in BBB GLU transport in physiologic and pathophysiologic settings. However, a growing body of evidence addresses alterations in BBB permeability (typically to large molecules). For example, increases in BBB permeability have been reported to accompany aging (Shah and Mooradian, 1997), Alzheimers dementia (Skoog *et al.,* 1998; Ujiie *et al.,* 2003), type II diabetes (Starr *et al.,* 2003), and hypertension (Mooradian, 1988; Mayhan, 1990; Ueno *et al.,* 2004). BBB permeability also increases with increasing plasma osmolarity (Tamaki *et al.,* 1984), and after the administration of certain drugs (Boertje *et al*., 1992). Presumably, increases in BBB permeability would permit increased entry of all molecules from the plasma, including molecules such as GLU. However, most studies that have specifically examined GLU transport (penetration) into the brain, deal with aging, in which GLU transport appears to be not different in adult and aged animals (Shah and Mooradian, 1997), and with hypertension, in which GLU uptake into brain may be increased (Tang *et al.,* 1993; Al-Sarraf and Philip, 2003).

However, there is evidence that a doubling of plasma GLU, e.g. after infusion of GLU-containing parenteral nutrition augments brain edema in conditions with a lesioned blood brain barrier (Kempski *et al.,* 1990). In those experiments the BBB of rats was focally destroyed by a freezing lesion, and water content of the brain was measured a day later. In animals that had received a continuous infusion of GLU water content (edema) was significantly higher than in rats without GLU infusion. A doubling of plasma GLU concentrations was sufficient to cause this effect, and brain edema only worsened in those animals, which had elevated plasma GLU concentrations. GLU increases brain water content most likely as a consequence of glial GLU uptake systems, which eliminate extracellular GLU together with sodium ions and – osmotically obliged – water. The deterioration of brain edema hence was a direct consequence of homeostatic mechanisms that prevent interaction of extracellular GLU with neuronal receptor sites.

However, several caveats should be noted: (1) The GLU transporters at the BBB appear to be on the abluminal membrane, and function to transport GLU out of the brain (O'Kane *et al*., 1999). These transporters presumably would still function in situations in which BBB permeability has increased; (2) Glial and neuronal GLU transporters (Goldsmith, 2000; Meldrum, 2000) would also presumably remain functional under conditions of increased BBB permeability (except if the brain is ischemic, and thus oxygen deprived, such as during a stroke/vascular occlusion or under conditions of increased intracranial pressure), and help to keep brain ECF and basal synaptic GLU concentrations low; and (3) Dietary GLU and MSG, even at a very high dose in the daily diet (Tsai and Huang, 1999), do not raise plasma GLU concentrations (MSG intake is self-limiting, since it is not palatable at high concentrations in foods (Yamaguchi, 1987)); hence, dietary GLU or MSG should not influence synaptic GLU concentrations, *per se*, if BBB permeability were to be increased.

Are toxicological data derived from animal experiments (dose–effect-relations) directly transferable to humans?

Consensus. Comparative functional and metabolic studies in a variety of animals including primates and human studies provide a rational safety evaluation for human beings.

Background. Relevant literature has already been summarized and listed (Biesalski *et al.,* 1997; Walker and Lupien, 2000). Briefly, the toxicologic database available for review includes acute, subchronic and chronic toxicity studies as well as studies on reproductive toxicity and teratology in rats, mice and dogs. GLU has a very low acute toxicity under normal circumstances; the oral dose that is lethal to 50% of subjects (LD_{50}) in rats and mice is 15000–18000 mg/kg bw, respectively. Subchronic and chronic toxicity studies of up to 2 years duration in mice and rats, including a reproductive phase, did not reveal any specific adverse effects at dietary levels of up to 4%. Reproduction and teratology studies using the oral route of administration have been uneventful indicating that the fetus and suckling neonate was not exposed to toxic GLU levels from the maternal diet through transplacental transfer. Based on these results from mammals

authoritative organizations have affirmed the safety of added GLU at levels normally consumed by the general population.

Large doses of dietary GLU: do they have an impact on endocrine parameters?
Consensus. Very high doses of GLU influence the insulin reaction induced by an unphysiologically high glucose load.

Background. Recently, Chevassus *et al*. (2002) gave 10 g MSG or placebo in capsules orally to fasted human subjects at the time they received a 75 g glucose load, and followed the plasma insulin changes over time. There was a significant positive correlation between plasma insulin area-under-the-curve and peak plasma GLU concentrations, suggesting to the authors that GLU enhanced glucose-induced insulin secretion, consistent with the existence of stimulatory GLU receptors on pancreatic beta cells (Hinoi *et al.,* 2004). In this study, peak plasma GLU concentrations were about doubled over baseline and placebo values. Studies of similar design have also been conducted by Graham and associates, but administering MSG (or a placebo) by itself to fasting subjects; with this design, significant increases in plasma insulin concentrations are clearly evident (Graham *et al.,* 2000; Mourtzakis and Graham, 2002).

Are there any effects of GLU on neonatal development?
Consensus. Even in unphysiologically high doses GLU will not trespass in fetal circulation. Therefore, orally applied GLU is not expected to influence neonatal development.

Background. There is a single study on this topic by Anantharaman (1979), who conducted a multi-generation study in male and female mice exposed to MSG in a standard diet (at 1 or 4%). The average daily MSG intake at the higher dose was calculated to be 6000 mg/kg/day in males and 7200 mg/kg/day in females, extremely high doses. Animals were exposed to MSG at all ages and at all stages of development. No developmental or reproductive effects were noted. No histological incidences of brain lesions or brain abnormalities were noted.

Do babies fed with breast milk consume free GLU?
Consensus. Breast milk contains measurable amounts of free GLU with great individual variations. Babies, thus, consume higher amount of free GLU per kg body weight than during their later life.

Background. Free amino acids are constituents of the so-called nonprotein nitrogen fraction of human milk (Rudloff and Kunz, 1997; Agostoni *et al.,* 2000). The total amount of free amino acids is around 3 mmol/l plasma with great variations (association with the nutritional behavior of the mother). GLU, glutamine and taurine are the prevalent amino acids accounting for around 50% of total free amino acids (Agostoni *et al.,* 2000; Ramirez *et al.,* 2001). Actual analyses of free GLU in milk samples of mothers delivered on time revealed 827 ± 342 μmol/l for transitional milk and 868 ± 462 μmol/l for mature milk (Meinardus *et al.,* 2004; Jochum *et al.,* 2006). Considering a daily feeding of 600 ml, a 4-kg-infant would ingest around 130 μmol/kg (19 mg/kg) free GLU. Moreover, the intake of bound GLU would reach ca. 1.3–1.5 g/day depending of the protein content of the milk. The role of free amino acids in breast milk is still under debate. It is, however, speculated that especially free GLU and glutamine might have a double role of protecting the intestinal growth while supplying functional substrates to the nervous tissue (Agostoni *et al.,* 2000; Jochum *et al.,* 2006). Consequently, the intake of free GLU in suckling babies is seen as a useful physiological support of growth and metabolic development. In addition, GLU is seen as a rapidly available nitrogen donor in growing mammals due to its central role in transamination processes.

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