MNF Report

The potential involvement of glutamate ingestion in chronic neurodegenerative diseases

Opinion of the Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG) – (shortened version)***

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The Senate Commission on Food Safety (SKLM) of the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation), in consultation with external experts, discussed the potential involvement of glutamate ingestion in chronic neurodegenerative diseases, evaluating data on concentrations in foods, exposure, kinetics and neurotoxicity. The german version of the opinion was adopted on 08th April 2005, the english version was agreed on 28th September 2005.

1 Introduction

Glutamic acid and its salts, the glutamates, occur naturally and are also used as an additive for enhancing the flavour of food. The general public and scientific committees have, from time to time, debated a potential connection between a higher consumption of glutamate and chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. The SKLM was asked to reassess the safety of glutamate, particularly monosodium glutamate (MSG), which is used as a flavour enhancer, with respect to a potential neurotoxicity. [The hotly debated issue of hypersensitivity reactions from eating foods containing glutamate (Chinese restaurant syndrome) is not subject of this opinion.]

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2 Occurrence and natural concentration in foods

Glutamic acid occurs naturally in almost all foods (see Table 1). As an amino acid it is a component of most proteins, up to 20% in animal protein and up to 40% in plant protein.

[…]

3 Utilization and contents in processed foods

Because of its flavour enhancing properties ("umami"), free glutamate, *i.e.* not bound in protein, is added to foods as a salt, *e.g.* monosodium glutamate (MSG), or in the form of hydrolyzed vegetable protein.

In the European Union, glutamic acid and glutamates are approved for use as food additives (E 620–625) according to EU Directive 95/2/EC, for foodstuffs in general up to a

* The Senate Commission on Food Safety (SKLM) of the German Research Foundation (DFG) advises authorities and the government on the safety for health of foodstuffs. Further information on the SKLM activity profile, see *Mol. Nutr. Food Res.* 2005, *49*, 285 – 288.
Detailed information on the work of the DFG-Senate Commission on Food Safety can be provided by Professor Dr. Gerhard Eisenbrand or by the Scientific Office of the SKLM: S. Guth, M. Habermeyer and D. Wolf; e-mail: sklm@rhrk.uni-kl.de and also by Dr. H. Strelen, DFG-administrative headquarters; e-mail: Heike.Strelen@dfg.de.

** Deletions in the original text are labelled by "[…]". Original references are omitted throughout. The original version of this opinion can be obtained through the Scientific Office (sklm@rhrk.uni-kl.de).

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Table 1. Typical contents of naturally occurring glutamate in foods

Food	Glutamate bound in peptides (mg/100 g)	Free glutamate (mg/100 g)
Cow's milk	819	2
Human breast milk	229	22
Eggs	1583	23
Beef	2846	33
Salmon	2216	20
Peas	5583	200
Carrots	218	33
Spinach	289	39
Potatoes	280	180
Tomatoes	238	140

Table 2. Amount of free glutamate in seasonings, sauces and restaurant meals

Food	Concentration (g/100 g)
Hydrolyzed vegetable protein – HVP (USA)	approx. 8
Typical meal seasoned with HVP	approx. 0.05
Seasonings and sauces	0.02–1.9
Soy sauce	0.4–1.3
Parmesan cheese	1.2
Restaurant meals	<0.01–0.71
Chinese restaurant meals	<0.01–1.5

total amount of 10 g/kg, or according to the "quantum satis" principle for condiments and seasonings. Various processed foods such as seasonings, sauces and restaurant meals prepared with glutamate can contain considerable amounts (see Table 2) of free glutamate, from natural sources as well as added glutamates.

4 Exposure

[…]

In European countries, the average consumption of added glutamate is estimated to be 0.3–0.6 g/day, *i.e.* 5–10 mg/kg bw/day at a body weight of 60 kg. According to estimates for the United Kingdom, the average consumption is 0.6 g MSG/day, extreme consumption (97.5th percentile) is up to 2.3 g MSG/day.

[…]

A strongly seasoned restaurant meal may contain 5 g of MSG, *i.e.* a consumption of approx. 83 mg/kg bw (60 kg bw).

The exposure in Asian countries is estimated to be on average 1.2–1.7 g added glutamate/day, with a 97.5th percentile of approx. 4 g/day.

In comparison, the total glutamate consumption with a normal mixed diet is estimated to be 10–20 g/day, of which approx. 1 g is assumed to be free glutamate. In the US, the mean total consumption from foods and food supplements is estimated at 15–16 g/day and the highest consumption (men 31–50 years of age; 99th percentile) at 33–34 g/day.

At approx. 36 mg free glutamate/kg bw/day and approx. 360 mg protein-bound glutamate/kg bw/day, breast-fed babies have the highest total glutamate consumption relative to body weight.

The Senate Commission has no further information at this time concerning the content of free glutamate in processed foods or the scope of use of glutamate as an additive and the resulting exposure.

5 Metabolism and kinetics

5.1 The role of glutamate in intermediary metabolism

Glutamate occupies a central position in human intermediary metabolism (Fig. 1).

[…]

Glutamate is also a precursor of glutamine. This reaction catalyzed by glutamine synthetase has a central function in amino acid metabolism. It is the main pathway to transform free ammonium into glutamine for transport in the blood stream. Glutamate acts as an excitatory neurotransmitter in the central nervous system (CNS) and is the precursor of the neurotransmitter γ-aminobutyric acid (GABA).

[…]

5.2 Factors that affect kinetics and the plasma level

The kinetics of glutamate absorption strongly depend on whether the compound is consumed as free glutamate or bound in protein as well as on the presence of other food components. Glutamic acid bound in protein is only absorbed after enzymatic hydrolysis, and hence more slowly. In several animal species, the administration of MSG in water resulted in higher plasma levels and a shorter period of time until the maximum value was reached compared to administration in the feed. The simultaneous administration of metabolizable carbohydrates results in a

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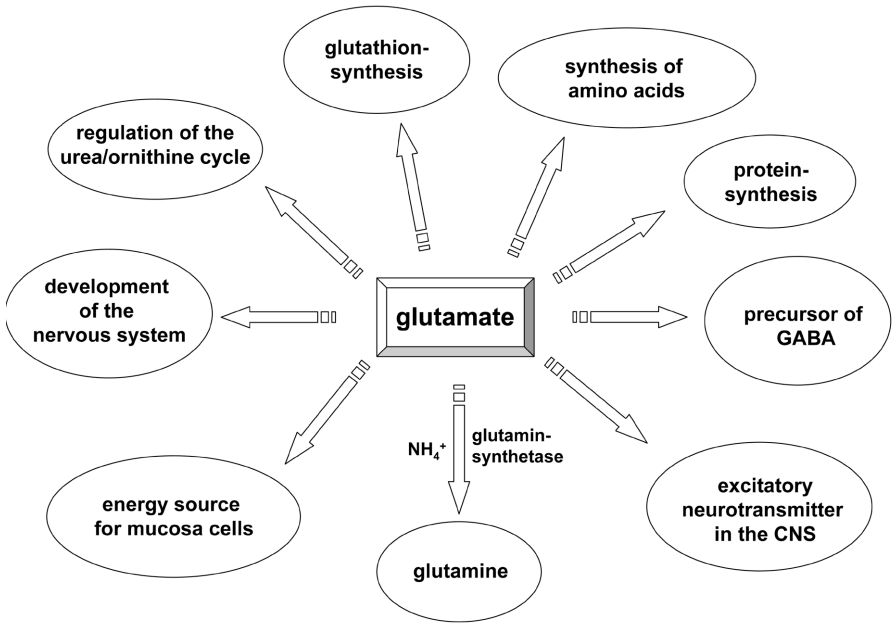

Figure 1. The multiple functions of glutamate in the intermediary metabolism

lower rise in the plasma level because of the increase in glutamate catabolism. Compared to using a stomach tube, administration of MSG in the feed (ad libitum) only results in minor increases in the plasma levels.

Furthermore, the results vary depending on age and species.

[…]

Infants, including premature babies, are able to metabolize orally administered glutamate as efficiently as adults, which leads to the conclusion that there is no increased risk of a greater rise in glutamate plasma levels.

The placenta is regarded as an effective metabolic barrier for glutamate. After the administration of very high doses of glutamate to pregnant rats (8 g/kg bw orally) and monkeys (infusion of 1 g MSG/h), despite a ten- to twenty-fold rise in the plasma levels of the mothers there was no increase in that of the fetuses. In pregnant sheep, it was shown that the fetal liver produces glutamate and releases it into the fetal circulation, of which a large part is removed by the placenta. The human placenta also eliminates glutamate from the fetal circulation, whereas it provides large quantities of glutamine.

In humans, the normal plasma level of free glutamate is in the range of 30–60 μmol/L and 4.4–8.8 mg/L.

In a study, an average free glutamate plasma level of approx. 40 μmol/L was measured after several hours of fasting. After eating a protein-rich meal (1 g protein/kg bw/day), there was a transient rise in the mean maximum plasma level to about 90 μmol/L. When the meal also had MSG added to it in an amount equivalent to a dose of 34 mg/kg bw, *i.e*. about three times the average daily intake of added glutamate in Europe and the US, there was no further rise.

With a dose of 150 mg MSG/kg bw, almost twice the amount of a strongly seasoned restaurant meal, there was a greater rise than with a protein-rich control meal (see above) without added glutamate. After a protein-rich control meal without added glutamate the plasma levels rose from about 50 to about 120 μmol/L and reached about 200 μmol/L with added glutamate. After administering 150 mg MSG/kg bw in a typical Chinese meal to Taiwanese adults, there was a transient rise in the mean plasma level from 95 to 125 μmol/L, which is about 1.3 times the base value. After administering 150 mg MSG/kg bw in a liquid formula meal, the equivalent of a carbohydrate administration of 1.1 g/kg bw, the glutamate plasma level rose from approx. 35 μmol/L to approx. 70 μmol/L.

In comparison, however, after ingesting 150 mg MSG/kg bw in water, there was a more rapid and higher rise in the plasma concentration, from approx. 40 to 600 μmol/L.

[…]

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) concluded that compared with ingestion of food without metabolizable carbohydrates, administration in foods providing metabolizable carbohydrates significantly attenuates the rise in plasma levels at doses up to 150 mg MSG/kg bw (9 g/60 kg person).

In humans, plasma concentrations of 0.8–1.0 mmol/L (12–15 mg/100 mL) caused nausea and vomiting in 50% of the

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test subjects. These plasma levels were reached after intravenous administration of a dose of 100 mg/kg bw.

6 Neurotoxicity

6.1 Endogenous glutamate

Glutamate is an important excitatory neurotransmitter in the central nervous system. Glutamate plays a role in learning and memory processes, evidenced by the fact that the highest density of glutamate receptors is in the hippocampus. After release, glutamate diffuses across the 15–30 nm wide synaptic cleft in less than one millisecond, binds to specific glutamate receptors (GluR) and activates the postsynaptic neuron. Termination of the glutamatergic transmission occurs primarily via neuronal and glial glutamate transporters, namely the excitatory amino acid transporters (EAAT) 1–5. These transporters are critical for transporting glutamate back to the neuronal or glial cytoplasm. In both cell types, glutamate reaches the amino acid pool, which is freely available in the cytoplasm. If the physiological concentration in the glia cell is exceeded, glutamate is converted to glutamine or, if the concentration is too low, regenerated from it. The vesicular transporter in the neuron pumps glutamate from the cytosol into the vesicles. If the physiological concentration in the amino acid pool is exceeded, glutamine can also be generated in the neuron.

In certain cases the glutamate concentration in the neuronal cytosol may rise and cause a reversal of the direction of transport of the EAATs. This is possible in the case of a stroke, for instance. Due to the lack of oxygen caused by a vascular occlusion, all the ATP-related processes fail within a short period of time resulting in a rise in the glutamate concentration. The cell primarily attempts to compensate for this by removing it via the EAATs. If the extracellular glutamate exceeds a narrow concentration range, the result is excitotoxic damage. The term excitotoxicity refers to neuron damage caused by toxic concentrations of excitatory neurotransmitters such as glutamic acid or aspartic acid. It is based on excessive stimulation of NMDA receptors (N-methyl-D-aspartate) and the subsequent opening of Ca^{2+} channels. The elevated cystolic Ca^{2+} concentration results in cell death. Furthermore, in the case of a stroke, because of the impaired Na/K-ATPases, a massive influx of water occurs which finally leads to the destruction of the cell and the release of the entire glutamate reservoir. Because of the high density of the receptors, the hippocampus is more sensitive than other areas of the brain when glutamate is released endogenously.

Elevated endogenous glutamate concentrations are related to slow progressive neurodegenerative diseases such as Alzheimer's dementia, multiple sclerosis (MS), Parkinson's disease, Huntington's chorea and amyotrophic lateral sclerosis (ALS).

6.2 Exogenous glutamate

The situation described above refer to glutamate of endogenous origin.

Glutamate ingested with food is virtually completely absorbed from the intestine by means of a specific active transport system. During absorption, most of the glutamate is transaminated and transformed into other compounds of intermediary metabolism by the formation of α-ketoglutarate. When large amounts of glutamate are consumed, the concentration in the portal vein rises, which results in an increased metabolism of glutamate in the liver and the release of glucose, lactate, glutamine and other amino acids into the systemic circulation. Because of the extensive metabolism of the glutamate ingested with food in the intestinal mucosa cells and the liver, the glutamate level in the plasma is relatively stable.

In healthy adults, the blood-brain barrier very effectively prevents the passive influx of glutamate from the plasma. Changes in plasma levels, *e.g*. as a consequence of absorbing exogenous glutamate, cause little change in concentrations in the brain. This applies even when taking into account that the endothelial blood-brain barrier function is suspended in the area of the circumventricular organs (subfornical organ, subcommissural organ, area postrema and organum vasculosum laminae terminalis), the choroid plexus and the hypothalmic-pituitary system. A brisk substance exchange with the blood must occur in these organs, which is apparent from the high permeability of the endothelial cells (fenestration). For this reason, in this case the blood-brain barrier is shifted to the plexus epithelial cells and/or to specialized ependymal cells (tanycytes) as a blood-liquor barrier. The endothelial blood-brain barrier as well as the epithelial (glial) blood-liquor barrier are represented by impermeable cell-cell contacts (tight junctions).

It is highly unlikely that there is a causal link between ingested MSG and Parkinson's disease or Alzheimer's disease. Parkinson's disease is due to cellular degeneration in the substantia nigra, which results in a lower dopaminergic innervation of the corpus striatum. The areas that are affected first in Alzheimer's disease are the hippocampus and the cholinergenic neurons in the nucleus basalis Meynert. However, the circumventricular organs, in which damage might be expected after ingesting large amounts of exogenous glutamate, are not affected in both diseases.

If serious diseases of the central nervous system already exist, the barrier function of the blood-brain barrier may be impaired with a loss in selectivity of the barrier. It is not

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known whether ingested MSG increases the risk of damage to the central nervous system in persons suffering from these diseases.

7 Summary of the evaluation

Previous assessments have shown that there is no risk of neurotoxic effects with the usual amounts of glutamate in foods. The Senate Commission agrees with this opinion for the following reasons: Damage in certain areas of the central nervous system, particularly in the circumventricular organs, could only be reproducibly induced in animal experiments after parenteral administration or administration of very high doses using a stomach tube (ED_{50} in the most sensitive species, newborn mice: 500 mg/kg bw), but not after administration in the feed or drinking water. The only exception was in newborn mice who, after deprivation of feed and water, received drinking water with 5% or 10% MSG. There are species, strain and age-related differences with respect to sensitivity to neuronal damage. Newborn mice are the most sensitive; rats, guinea pigs and primates are less sensitive. The threshold plasma levels for neuronal damage observed in newborn mice were 1–1.3 mmol/L, in weaned and adult animals 3.8 and >6.3 mmol/L, respectively.

All data indicate that, even in the case of extreme conditions of ingestion, plasma levels in humans do not reach the values at which neuronal damage were observed in the most sensitive species (newborn mice). Even after oral administration of a single dose of 150 mg/kg bw in water (9 g/60 kg bw), the maximum values found did not exceed 600 µmol/L in plasma. The peak value was reached after 30 minutes and then dropped rapidly. When the same dose was administered in a meal, the rise was significantly lower (200 µmol/L compared to 120 µmol/L after a meal without added glutamate). Because of the very effective metabolism of glutamate in the intestine and liver, the plasma level remains relatively stable under normal circumstances.

In studies on reproductive toxicity and teratogenicity, there was no evidence of harmful effects after oral administration, even when high doses of MSG were administered to the parent generation. This indicates that the fetus is protected against high doses by the mother's metabolism and the placenta. In babies, it was shown that glutamate is important in postnatal development for forming the plastic connection of neurons in the brain. Studies of the concentration in human milk show a relatively high amount of free glutamate, about 15–30 mg/100 mL. The total daily intake for breast-fed babies in relation to body weight was estimated at about 36 mg free glutamate/kg bw, *i.e.* relatively large amounts of glutamate are absorbed through breast milk.

There are indications that disorders of the endogenous glutamate metabolism are associated with chronic diseases such as Alzheimer's, Parkinson's, chorea Huntington and amyotrophic lateral sclerosis. However, there are no indications that glutamate ingested exogenously with food plays a role in the etiology or the clinical progression of such chronic diseases. In particular, a causal link between exogenously ingested MSG and Parkinson's or Alzheimer's disease is not very likely for the following reasons: In the case of Parkinson's and Alzheimer's disease, it is a matter of cell degeneration: in the former case in the substantia nigra, in the latter case in the hippocampus and the nucleus basalis Meynert. In both cases the circumventricular organs, in which damage might be expected after ingesting large amounts of exogenous glutamate, are not affected.

8 Research needs

The SKLM concludes that there is a need for more research in the characterisation of potential risk groups. For instance, it would be worthwhile examining whether people with limited intestinal function, *e.g.* with inflammatory intestinal diseases or liver diseases such as hepatitis, have higher plasma levels after consuming glutamate than healthy people. Furthermore, human data is desirable for the detailed monitoring of plasma levels after absorption of various amounts of glutamate in various foods.

The high glutamate concentrations in human breast milk raise questions about absorption, distribution, metabolization and excretion in infants, the answers to which might also clarify questions with respect to possible protective mechanisms in infants. Comparison of breast-fed infants with those that are not breast-fed might provide more information with respect to beneficial as well as adverse effects.

The data base upon which the assumptions for the current assessment of consumer exposure were based should be updated. In particular, data are required on the amounts of glutamate used in foods and the resulting exposure. This data update must also include the actual use of glutamate as a household seasoning in order to ensure the most topical and reliable consumption data.

9 Conclusion

Since the earlier assessments by national and international panels of experts there have been no new findings that make it necessary to re-evaluate glutamate with respect to a potential neurotoxicity. The SKLM concludes that these assessments are still valid.

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