# Getting to the root of infertility

NOTE: Studies confirming that the free glutamate in MSG caused brain damage, intractable obesity, infertility and more were done before it was understood that excitotoxic free glutamate would be found in ingredients other than MSG.

### Abstract

Submissions to medical journals traditionally offer cutting edge research that throws new light on a subject of interest, either presenting a solution or encouraging/stimulating meaningful research for the future.

In contrast, this submission draws from a number of seemingly unrelated subjects as Albert Einstein suggested in what he called Combinatory Play: taking two or more unrelated things and putting them together to generate new ideas. Einstein did not invent the concepts of energy, mass, or speed of light for the equation,  $E=mc^2$ . Rather, he combined these concepts in a novel way which restructured the way he looked at the universe.

Drawing from what is known about glutamate-induced brain damage, nourishment of fetuses and neonates by pregnant and lactating women, and the availability of free glutamate in processed foods, snacks, dietary supplements, pharmaceuticals and more for uptake by the human body, we propose to establish that ingestion of free glutamate by humans 1) can cause infertility following brain damage to the arcuate nucleus of the hypothalamus (AN), and 2) that ingestion of free glutamate by humans lies at the root of the fertility crisis.

## Introduction

In the 1970s it was demonstrated by Olney and others that reproductive dysfunction follows glutamate-induced brain lesions in the arcuate nucleus of the hypothalamus (AN), and that monosodium glutamate fed to laboratory animals was an excellent source of free glutamate.

It is the purpose of this paper to establish that ingestion of free glutamate by humans 1) can cause infertility following brain damage to the AN, and 2) that ingestion of free glutamate by humans lies at the root of the infertility crisis.

#### This is what we know:

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

- There must be a vulnerable brain (immature or damaged)
- There must be a sufficient quantity of excitotoxic free glutamate to enable that free glutamate to become excitotoxic.

(Glutamate is an excitotoxic amino acid. When present in controlled quantities it is essential to normal body function. When accumulated in excess, in amounts more than needed for normal body function, glutamate neurotransmitters fire non-stop until the brain cells targeted by those neurotransmitters die) (1-6).

• There must be a way for that excess of glutamate to be delivered to the vulnerable brain.

2. Glutamic acid (free glutamate) fed to infant animals causes brain lesions in the arcuate nucleus of the hypothalamus (7-16).

3. Today there is sufficient excitotoxic free glutamate in processed foods, dietary supplements, snacks, protein powders and protein drinks, protein substitutes, enteral care products, and pharmaceuticals for a person to consume the quantity necessary for that free glutamate to become excitotoxic.

In 1957, bacterial fermentation was introduced as a new and improved method for production of free glutamic acid for use in food. From that point forward, the genetically modified bacteria used to secrete free glutamic acid through their cell walls guaranteed virtually unlimited production of free glutamic acid (17).

It wasn't long before competing manufacturers added dozens more excitotoxic food additives to the American diet. Following MSG's surge in production and its manufacturer's aggressive advertising, there was broad recognition that profits could be significantly increased if a company produced its own flavor-enhancing additives. Since that time, the market has been flooded with flavor enhancers and protein substitutes that contain manufactured free glutamate (MfG) such as hydrolyzed pea protein, yeast extracts, maltodextrin and soy protein isolate, as well as MSG. To that has been added the toxic load contributed by excitotoxic aspartic acid, approved by the FDA for use in aspartame, equal, and related products starting in 1974

Since the 1957 change in method of MSG production, there are so many products that contain excitotoxic ingredients that it is easy for a consumer to ingest an excess of excitotoxic material during the course of a day (18- 23). Thus, a pregnant woman could easily become a vehicle for delivering brain-damaging free glutamate to her fetus and neonate.

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

In children and adults, delivery of free glutamate to a vulnerable brain can be achieved simply through the subject's consuming a sufficient quantity of free glutamate to cause the free glutamate to be excitotoxic.

Delivery of excitotoxic free glutamate to the vulnerable brain of a fetus and/or neonate will be achieved when a pregnant or lactating female passes excess free glutamate to a fetus or neonate through the placenta or in mothers' milk. Once it is understood that excitotoxins are readily available, it is easy to grasp how these toxins are transported to the fetus and newborn where they cause brain damage which in turn causes infertility.

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

MSG can cross the placenta during pregnancy (24-26), can cross the blood brain barrier (BBB) in an unregulated manner during development (27), and can pass through the five circumventricular organs which are leaky at best at any stage of life (28-29).

Glutamate is an ingredient that passes to the fetus. The placenta does not filter out glutamate (24). Moreover, the BBB is easily damaged by fever, stroke, trauma to the head, seizures, ingestion of MSG, and the normal process of aging (30-31). And the fetus will be more vulnerable to glutamate-insult than the newborn.

Similar to drugs and alcohol, free glutamate can also be passed to infants through mothers' milk. Newborn humans will receive glutamate through mothers' milk or through infant formula, both of which routinely contain free glutamate (32).

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

#### Discussion

With the first suggestion that MSG might have toxic potential, those with financial interest in promoting MSG as a valuable flavor-enhancer launched a well-funded, well-articulated campaign to promote their product, and deny any hint of toxicity. That included rigging studies to come to the foredrawn conclusion that MSG is a harmless food additive and securing the active cooperation of regulators as well as the help of medical professionals, many of whom appeared to be more than happy to look the other way. (33).

That might account for the fact that to date, the role of MSG and MfG in the fertility crisis has been overlooked.

## Conclusion

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

The onset of the infertility crisis can be traced to the introduction of excessive amounts of MfG being made available to humans following the modernization of MSG manufacture in 1957.

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

Recognition of the fact that glutamate-induced brain damage in fetuses and neonates lies at the root of the fertility crisis, would be of immediate benefit to both patients and their health care providers, and serve as a valid starting point for ground-breaking research.

## References

1. Excitotoxicity and cell damage

https://www.sciencedaily.com/terms/excitotoxicity.htm (accessed 7/3/2021)

2. Belov Kirdajova D, Kriska J, Tureckova J, Anderova M. Ischemia-Triggered Glutamate Excitotoxicity From the Perspective of Glial Cells.

Front Cell Neurosci 19,14:51 (2020). doi: 10.3389/fncel.2020.00051.

3. Hernández DE, Salvadores NA, Moya-Alvarado G, Catalán RJ, Bronfman FC, Court FA. Axonal degeneration induced by glutamate excitotoxicity is mediated by necroptosis. *J. Cell Sci.* 131(22):jcs214684. (2018)

4. Garzón F, Coimbra D, Parcerisas A, Rodriguez Y, García JC, Soriano E, et al. NeuroEPO preserves neurons from glutamate-induced excitotoxicity *J. Alzheimers Dis.* 65, 1469-1483 (2018)

5. Zárate SC, Traetta ME, Codagnone MG, Seilicovich A, Reinés AG. Humanin, a mitochondrial-derived peptide released by astrocytes, prevents synapse loss in hippocampal neurons. *Front Aging Neurosci* 11,123 (2019)

6. Plitman E, Nakajima S, de la Fuente-Sandoval C, Gerretsen P, Chakravarty MM, Kobylianskii J, et al. A Glutamate-mediated excitotoxicity in schizophrenia: a review. *Eur Neuropsychopharmacol* 24,1591-1605 (2014)

7. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science*. 164, 719-721, (1969)

8. Olney JW. Glutamate-induced neuronal necrosis in the infant mouse hypothalamus. *J Neuropathol Exp Neurol* 30, 75-90 (1971)

9. Burde RM, Schainker B, Kayes J. Acute effect of oral and subcutaneous administration of monosodium glutamate on the arcuate nucleus of the hypothalamus in mice and rats. *Nature(Lond)* 233, 58-60 (1971)

10. Olney JW, Sharpe LG, Feigin RD. Glutamate-induced brain damage in infant primates. *J Neuropathol Exp Neurol* 31, 464-488 (1972)

11. Burde RM, Schainker B, Kayes J. Monosodium glutamate: necrosis of hypothalamic neurons in infant rats and mice following either oral or subcutaneous administration. *J Neuropathol Exp Neurol* 31, 181 (1972)

12. Olney JW, Ho OL. Brain damage in infant mice following oral intake of glutamate, aspartate or cystine. *Nature(Lond)* 227, 609-611 (1970)

13. Lemkey-Johnston N, Reynolds WA. Incidence and extent of brain lesions in mice following ingestion of monosodium glutamate (MSG). *Anat Rec* 172, 354, (1972)

14. Takasaki Y. Protective effect of mono- and disaccharides on glutamate- induced brain damage in mice. *Toxicol Lett* 4, 205-210 (1979)

15. Takasaki Y. Protective effect of arginine, leucine, and preinjection of insulin on glutamate neurotoxicity in mice. *Toxicol Lett* 5, 39-44 (1980)

16. Lemkey-Johnston N, Reynolds WA. Nature and extent of brain lesions in mice related to ingestion of monosodium glutamate: a light and electron microscope study. *J Neuropathol Exp Neurol* 33, 74-97 (1974)

17. Khan IA, Abourashed EA. Leung's Encyclopedia of common natural ingredients used in food, drugs, and cosmetics. 3<sup>rd</sup> edn. (New Jersey: Wily, 2010) 452-455.

18. Hashimoto S. Discovery and History of Amino Acid Fermentation. *Adv Biochem Eng Biotechnol* 159,15-34, (2017) https://pubmed.ncbi.nlm.nih.gov/27909736/

19. Sano C. History of glutamate production. *Am J Clin Nutr*. 90, 728S-732S (2009) https://pubmed.ncbi.nlm.nih.gov/19640955/

20. Market Research Store. Global Monosodium Glutamate Market Poised to Surge from USD 4,500.0 Million in 2014 to USD 5,850.0 Million by 2020. https://www.globenewswire.com/newsrelease/2016/03/17/820804/0/en/Global-Monosodium-Glutamate-Market- Poised-to-Surge-from-USD-4-500-0-Million-in-2014-to-USD- 5-850-0- Million-by-2020-MarketResearchStore-Com.html (Accessed 5/29/2020.)

21. Open PR Worldwide Public Relations for Verified Market. Global Flavor Enhancers Market.

https://www.bccresearch.com/partners/verified-market-research/global-flavor-enhancers-market.html (Accessed 5/29/2020.)

22. Dataintelo. Global Food Flavor Enhancer Market Report, History and Forecast 2014-2025, Breakdown Data by Manufacturers, Key Regions, Types and Application. https://dataintelo.com/report/food-flavor-enhancer- market (Accessed 5/29/2020)

23. Onaolapo AY, Onaolapo OJ. Dietary glutamate and the brain: In the footprints of a Jekyll and Hyde molecule. *Neurotoxicology* 80, 93-104 (2020) doi: 10.1016/j.neuro.2020.07.001.

24. Frieder B, Grimm V E. Prenatal Monosodium Glutamate (MSG) Treatment Given through the Mother's Diet Causes Behavioral Deficits in Rat Offspring. *Int. J. Neurosci.* 23, 117–126 (1984) DOI: 10.3109/00207458408985353.

25. Gao J, Wu J, Zhao XN, Zhang WN, Zhang YY, Zhang ZX. [Transplacental Neurotoxic Effects of Monosodium Glutamate on Structures and Functions of Specific Brain Areas of Filial Mice.] Sheng Li Hsueh Pao. *Acta Physiologica Sinica*. 46, 44–51 (1994)

26. Yu T, Zhao Y, Shi W, Ma R, Yu L. Effects of Maternal Oral Administration of Monosodium Glutamate at a Late Stage of Pregnancy on Developing Mouse Fetal Brain. *Brain Res* 747, 195–206 (1997) DOI: 10.1016/S0006-8993(96)01181-X.

27. Skultetyova I, Tokarev D, Jezova D. Stress-induced Increase in Blood- brain Barrier Permeability in Control and Monosodium Glutamate-treated Rats. *Brain Res. Bull* 45, 175–178 (1998) DOI: 10.1016/S0361- 9230(97)00335-3.

28. Price MT, Olney JW, Lowry OH, Buchsbaum S. Uptake of Exogenous Glutamate and Aspartate by Circumventricular Organs but Not Other Regions of Brain. *J Neurochem* 36, 1774–178 (1981) DOI: 10.1111/jnc.1981.36.issue-5.

29. Broadwell RD, Sofroniew MV. Serum Proteins Bypass the Bloodbrain Fluid Barriers for Extracellular Entry to the Central Nervous System *Exp Neurol* 120, 245–263 (1993) DOI: 10.1006/exnr.1993.1059.

30. Blaylock RL. *Excitotoxins: The Taste That Kills*; Health Press: Santa Fe, New Mexico, 1994.

31. Nemeroff CB, Crisley FD. Monosodium L-glutamate Induced Convulsions: Temporary Alteration in Blood-brain Barrier Permeability to Plasma Proteins. *Environ Physiol Biochem* 5, 389–395 (1975)

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

33. Samuels A. The toxicity/safety of processed free glutamic acid (MSG): a study in suppression of information. *Account Res.* 6, 259-310 (1999) doi: 10.1080/08989629908573933. PMID: 11657840.

Adrienne Samuels, Ph.D. Chicago, IL 60611 USA questionsaboutMSG@gmail.com