

Olney J W. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science* 164:719-21, 1969.

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This paper showed that glutamate, when administered subcutaneously to infant mice, destroys neurons in certain regions of the brain, including the endocrine hypothalamus, and that this caused animals to grow up with obesity and multiple endocrine abnormalities. [The SCF® indicates that this paper has been cited in over 470 publications.]

Trying to Get Glutamate out of Baby Food

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In addition to the disturbances in mice, I discovered in 1969 that glutamate (Glu) damages the infant brain when administered orally, that several species, including monkeys, are susceptible, and that large amounts of Glu were being added to baby foods. These findings, when conveyed to a US Senate Investigating Committee, persuaded the baby food industry to "voluntarily" quit adding Glu to baby foods. However, they did not really even reduce the amount of added Glu; they merely started adding it in a different form—hydrolyzed vegetable protein. I and others protested for seven years before industry officials abandoned the subterfuge and really quit adding Glu to baby foods. The problem is not fully resolved today, since Glu is still being added heavily to many foods (not designated as baby foods) that are fed to infants and children.

In 1971 I published two papers of fundamental significance, one showing that the neurotoxic action of Glu impinges upon dendritic and somal (but not axonal) membranes,¹ and

the other showing that specific structural analogs of Glu that possess Glu-like neuroexcitatory properties also mimic its neurotoxic effects and have the same order of potencies for the two effects.² These observations prompted me in the early 1970s to propose the now well-accepted excitotoxic hypothesis^{2,3} attributing the neurotoxic effects of Glu to an excitatory action at Glu receptors on dendrosomal membranes resulting in disruption of transmembrane ion homeostasis. I also proposed^{2,3} that endogenous excitotoxins might play a role in neurodegenerative disorders and that potent excitotoxic analogs of Glu might serve as useful axon-sparing lesioning tools.

Soon thereafter, J. Coyle, R. Schwarcz, E. McGeer, P. McGeer, and others began applying excitotoxins as lesioning tools for studying central nervous system structure/function relations and for developing animal models of human neurodegenerative diseases (e.g., Huntington's and Alzheimer's). Simultaneously, J.C. Watkins and colleagues spearheaded studies resulting in the identification of three Glu receptor subtypes and in the discovery of Glu antagonists with anti-excitotoxic actions. Finally, evidence for the complicity of both endogenous and exogenous excitotoxins in human neurodegenerative disorders, in both youth and old age, is gradually unfolding, and there is hope that anti-excitotoxic drugs may be therapeutically useful in clinical neurology.

Interesting new findings include: L-DOPA and an ortho-hydroxylated derivative have excitotoxic activity that could possibly have pathophysiological significance in Huntington's or Parkinson's diseases.⁴ L-cysteine is an excitotoxin that causes widespread brain damage resembling that associated with cerebral palsy,⁵ and M.T. Heafield and associates⁶ have found an apparent error of cysteine metabolism causing abnormally high cysteine/sulfate ratios in the blood of patients with motor neuron, Parkinson's, and Alzheimer's diseases. Thus, a role for L-cysteine excitotoxicity in either developmental or adult neuropathological processes is possible.

1. Olney J W. Glutamate-induced neuronal necrosis in the infant mouse hypothalamus: an electron microscopic study. *J. Neuropathol. Exp. Neurol.* 30:75-90, 1971. (Cited 200 times.)
2. Olney J W, Ho O L & Rhee V. Cytotoxic effects of acidic and sulphur-containing amino acids on the infant mouse central nervous system. *Exp. Brain Res.* 14:61-76, 1971. (Cited 295 times.)
3. Olney J W, Sharpe L G & deGubareff T. Excitotoxic amino acids. *Neurosci. Abstr.* 1:371, 1975. (Cited 70 times.)
4. Olney J W, Zorumski C F, Stewart G R, Price M T, Wang G & Labruyere J. Excitotoxicity of L-DOPA and 6-OH-DOPA: implications for Parkinson's and Huntington's diseases. *Exp. Neurol.* (In press.)
5. Olney J W, Zorumski C, Price M T & Labruyere J. L-cysteine, a bicarbonate-sensitive endogenous excitotoxin. *Science* 248:596-9, 1990.
6. Heafield M T, Fearn S, Stevenson G B, Waring R H, Williams A C & Sturman S G. Plasma cysteine and sulphate levels in patients with motor neurone, Parkinson's and Alzheimer's disease. *Neurosci. Lett.* 110:216-20, 1990.