

This Week's Citation Classic®

Rothman S M & Olney J W. Glutamate and the pathophysiology of hypoxic-ischemic brain damage. *Ann. Neurol.* 19:105-11, 1986. [Depts. Pediat., Anat. and Neurobiol., and Psychiat., Washington Univ. Sch. Med., St. Louis, MO]

This brief review summarized experimental data linking excessive extracellular glutamate accumulation and ischemic neuronal injury. The last part of the article speculated on the value of glutamate antagonists as neuroprotective agents in the treatment of acute stroke. [The *SCC*® indicates that this paper has been cited in more than 745 publications.]

and H. Benveniste et al.⁴ showed that glutamate accumulates extracellularly in the *in vivo* ischemic rat hippocampus. Robert Collins, who was then in the Department of Neurology at Washington University, encouraged us to write a brief synthesis focusing on the clinical implications of these observations.

Excitotoxicity Comes of Age

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It is perhaps not surprising that this paper has been frequently cited. Stroke, a common cause of brain damage, had long been considered hopelessly untreatable, and glutamate excitotoxicity had been considered a mere curiosity. We proposed a novel mechanism by which this mere curiosity could be held responsible for mediating intracranial disasters numbering in the billions throughout the world and the millennia. Better yet, the primary basis for linking these two phenomena was evidence suggesting a simple method by which the disaster could be prevented or, at least, ameliorated—administering a glutamate receptor antagonist. Finally, the fact that glutamate in the mid-1980s was just beginning to be recognized as the major excitatory transmitter in the mammalian CNS gave the story an ironic twist. An abundant neurotransmitter having vitally important functions in the CNS need only be translocated from an intracellular to extracellular locus to become a monster molecule that can destroy many of the neurons in the CNS.

in the spring of 1985, when we wrote this review, glutamate neurotoxicity (excitotoxicity) was an enigma still waiting to be deciphered. It had been known for decades that central nervous system (CNS) neurons contain large amounts of glutamate and that experimental application of small amounts to a neuron's external surface excites it either reversibly or unto death, depending on the duration of the stimulus. In the 1960s and 1970s, the majority of neuroscientists rejected glutamate as a transmitter and, therefore, deemed the molecule of limited interest. A few true believers¹ reasoned as follows: Transmitter or not, glutamate is of considerable interest as an endogenous excitotoxin that might play a role in neurodegenerative diseases. However, translocation of glutamate from the intracellular to the extracellular compartment was the most likely mechanism by which its excitotoxicity might be unleashed,¹ and there was no evidence for a disease process involving extracellular accumulation of glutamate.

It is gratifying that many aspects of the glutamate hypothesis we proposed have been borne out and that ramifications of the hypothesis which we could not have specifically anticipated in 1985 are now emerging as important new hypotheses. For example, evidence is accumulating² for R.L. Henneberry's proposal³ that defective intracellular energy metabolism may activate a mechanism (relief of Mg²⁺ blockade) which, even without abnormal glutamate accumulation, might unleash low grade excitotoxic processes that could occultly underlie chronic neurodegenerative disorders. If this concept holds up, it would signify that a single unifying mechanism—energy-linked excitotoxicity—may be a common denominator of a wide spectrum of neurological disorders ranging from acute brain injury to chronic neurodegenerative diseases.

In 1984, this situation was remedied by three independent findings. S.M. Rothman² discovered that glutamate antagonists could protect neurons against anoxic degeneration *in vitro*, R.P. Simon et al.³ demonstrated similar protection against ischemic neurodegeneration *in vivo*.

1. Olney J W. Toxic effects of glutamate and related amino acids on the developing central nervous system. (Nyhan W H. ed.) *Heritable disorders of amino acid metabolism*. New York: Wiley, 1974. p. 501-12.
2. Rothman S M. Synaptic release of excitatory amino acid neurotransmitter mediates anoxic neuronal death. *J. Neurosci.* 4:1884-91, 1984. (Cited 370 times.)
3. Simon R P, Swan J H, Griffiths T & Meldrum B S. Blockade of N-methyl-D-aspartate receptors may protect against ischemic damage in the brain. *Science* 226:850-2, 1984. (Cited 865 times.)
4. Benveniste H, Drejer J, Schousboe A & Diemer N M. Elevation of the extracellular concentrations of glutamate and aspartate in rat hippocampus during transient cerebral ischemia monitored by intracerebral microdialysis. *J. Neurochem.* 43:1369-74, 1984. (Cited 750 times.)
5. Beal M F, Hyman B T & Koroshetz W. Do defects in mitochondrial energy metabolism underlie the pathology of neurodegenerative diseases? *Trends Neurosci.* 16:125-31, 1993
6. Henneberry R L, Novelli A, Cox J A & Lysko P G. Neurotoxicity at the N-methyl-D-aspartate receptor in energy-compromised neurons: an hypothesis for cell death in aging and disease. *Ann. NY Acad. Sci.* 568:225-33, 1989

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