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 SCI® indicates that this paper has been cited in more than 745 publications.)

Excitotoxicity Comes of Age

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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 extracellular 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.

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 ischemia in vivo, 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.

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.

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 accumulating5 for R.L. Henneberry's proposal6 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.


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