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NEWS AND VIEWS

TRPM4 and the Emperor

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One of the great discoveries of the last half-century was that of neuronal "excitotoxicity". In 1969, John Olney coined the term excitotoxicity to describe the finding that an injection of sodium glutamate could destroy neurons throughout the brain.[1] Moreover, Olney found that cell death was restricted to postsynaptic neurons, that glutamate agonists were neurotoxic in direct proportion to their ability to activate glutamate receptors, and that glutamate antagonists could prevent neurotoxicity. Glutamate signaling is, of course, a normal and important physiological process but, in the context of CNS injury, this normal process is highjacked – excitotoxicity is the term used to refer to the pathological process by which neurons are damaged or killed by the overactivation of NMDA or AMPA receptors, the receptors for the excitatory neurotransmitter, glutamate.

Over the years, excitotoxicity has attained the lofty recognition as the dominant mechanism involved in "accidental", i.e., not programmed, death of neurons. Excitotoxicity has been shown to play a key role in all sorts of CNS injuries, ranging from stroke to traumatic brain and spinal cord injury, neurodegenerative diseases, and others. Not surprisingly, excitotoxicity has been the subject of innumerable publications, grants and clinical trials. A quick search of PubMed reveals over 7300 titles linked to excitotoxicity that date back to 1983. A quick search of NIH RePORTER retrieves 224 "hits" of grants awarded with excitotoxicity as a key term. A quick search of ClinicalTrials.gov identifies 16 clinical trials related to excitotoxicity. Many millions of dollars have been spent elucidating this phenomenon of excitotoxicity, the mechanism that determines, or commands, neuronal survival or death. In Latin, "to command" is "*imperare*", the etymological root of the word Emperor. However, the Emperor had something missing.

It has been known for some time that excitotoxicity is self-limited, and terminates naturally when synaptic vesicles are depleted.[2] Nevertheless, even though excitotoxicity is self-limited, neurons remain depolarized due to a poorly understood mechanism involving an inward sodium current activated by elevated intracellular calcium and low ATP.[3,4] Thus, neuronal death is comprised not of one but of two components – a glutamate-dependent and a glutamate-independent mechanism. One might think that this critical observation of the existence of a glutamate-independent mechanism would have threatened the supreme dominance of excitotoxicity as *the* mechanism of accidental neuronal death. Historically, however, glutamate-independent mechanisms of neuronal death have received scant attention.[5]

In their new study published in *Channels (Austin)*, Andrés Stutzin and colleagues.[6] make important progress on this front, building on their previous work.[7] Using murine cortical neuron cultures and ischemia-reperfusion protocols, they show that TRPM4 is fundamental for glutamate-independent neuronal damage. TRPM4 is a monovalent cation channel activated by intracellular calcium and ATP depletion. TRPM4 previously was implicated in glutamate-dependent axonal degeneration.[8] but its role in the sustained depolarization during reperfusion had not been characterized. Now, Stutzin and colleagues show that the continuous activation of TRPM4 during reperfusion leads neurons to a state of sustained depolarization that results in their death. Both pharmacological inhibition

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(glibenclamide and 9-phenanthrol) and shRNA-based silencing of TRPM4 renders neurons resistant to reperfusion damage, and increases their survival. Furthermore, Stutzin and colleagues report that neuronal protection induced by TRPM4 inhibition becomes evident once the glutamate-induced damage, i.e., excitotoxicity, is blocked, consistent with TRPM4 being critical for the glutamate-independent neuronal damage observed with ischemia-reperfusion injury.

This newly emerging link between excitotoxicity and TRPM4, as advanced by Stutzin and colleagues, is an important advance in understanding accidental neuronal death. At last, the Emperor now appears to be more fully clothed.

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