FAST MOVING FRONTS - 2009

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Michael Tymianski talks with *ScienceWatch.com* and answers a few questions about this month's Fast Moving Front in the field of Molecular Biology & Genetics. The author has also sent along an image of his work.

Article: A key role for TRPM7 channels in anoxic neuronal death
Authors: Aarts, M;Iihara, K;Wei, WL;Xiong, ZG;Arundine, M;Cerwinski, W;MacDonald, JF;Tymianski, M
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SW: Why do you think your paper is highly cited?

This paper is of interest to a wide audience. Most importantly, it provides the first strong evidence that excitotoxicity, the process by which the excitatory neurotransmitter glutamate causes neuronal cell death in stroke, is not the chief mechanism responsible for anoxic neuronal death. The findings provide mechanistic evidence which demonstrates that treating exictotoxicity is insufficient to prevent the death of anoxic neurons because TRPM7, a member of the Transient Receptor Potential superfamily of proteins, triggers parallel death mechanisms that occur independently of excitotoxicity.

The results may explain why attempts at treating stroke solely using anti-excitotoxic strategies (glutamate receptor antagonists) have failed. Moreover, the results provide a new target, TRPM7, which may be a key to treating to anoxic death. Furthermore, although TRPM7 can trigger anoxic neuronal death, it is also expressed in other tissues. Consequently, TRPM7 may participate in broader ischemic mechanisms, in tissues both within and outside the CNS. Thus TRPM7 may be of interest to all those interested in tissue ischemia.

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

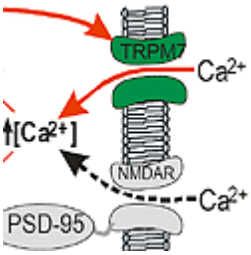
To our knowledge, ours was the first paper to use RNA interference in fully differentiated non-dividing postmitotic neurons to suppress the expression of a protein.

SW: Would you summarize the significance of your paper in layman's terms?

The paper describes a previously unappreciated cell death mechanism

caused by a protein, TRPM7, which triggers brain cell death when the cells are deprived of oxygen and glucose. The lack of oxygen and glucose is what happens in strokes, a leading cause of death and disability in Western society. The discovery of the importance of TRPM7 is causing the death of brain cells may explain why previous attempts at preventing the damaging effects of strokes was unsuccessful, and provide a potential target for future drug treatments of strokes.

Figure 1:



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SW: How did you become involved in this research and were any particular problems encountered along the way?

I am a stroke researcher. When clinical trials of anti-excitotoxic strategies uniformly failed in the late '90s, I began to re-examine potential causes for this, including the possibility that other key mechanisms of ischemic damage might have been overlooked. We began by reproducing the original experiments which demonstrated that blocking excitotoxicity in cultured neurons inhibited cell death caused by oxygen-glucose deprivation (OGD). We then extended the duration of OGD and found that, even when excitotoxicity was blocked, the neurons still died (in prolonged OGD). The challenge was to discover why.

We performed various experiments for about two years, but with little success in narrowing down the mechanism, other than to discover that it involved an unknown ion conductance (as determined using electrophysiological techniques). Then, TRPM7 was cloned, and its electrophysiological properties resembled very much the cation conductance (i.e., the ion channel) that we were observing in ischemic neurons.

All we had to do was to find a way to block TRPM7. However, there are no drugs to do so, and no knockout animals. Therefore, we developed a method to knock down the expression of TRPM7 using RNA interference, a technique which had just recently been published. When we did so, the neurons became very resistant to prolonged OGD, confirming a key role for TRPM7 in anoxic neuronal death.

SW: Where do you see your research leading in the future?

Our research defines TRPM7 as an important protein which triggers anoxic death in cultured neurons. Its role in intact animals is as yet uncertain when it comes to stroke or to other ischemic problems. There are no viable knockout animals and no drugs to selectively block TRPM7 in order to test its relevance *in-vivo*. Our lab is currently carrying out experiments in which we are suppressing TRPM7 expression *in-vivo* in order to determine its importance in stroke. We are also developing small molecule inhibitors of TRPM7.

Do you foresee any social or political implications for your research?

If TRPM7 is the key to treating ischemic brain damage, then our discovery may lead to better treatments for one of the major causes of death and disability worldwide.

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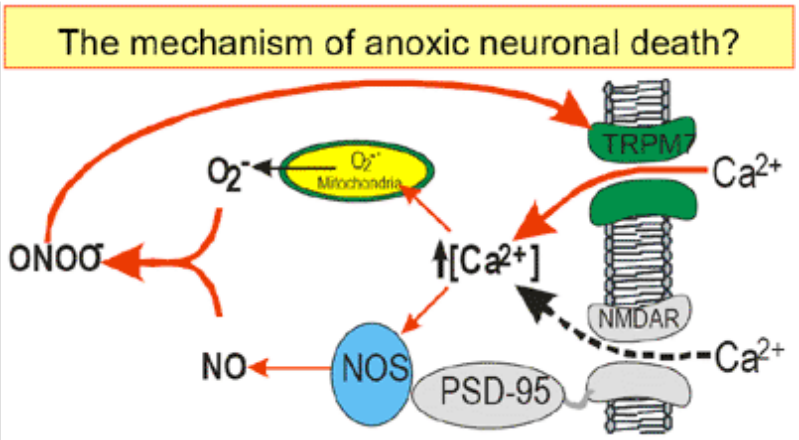
Figure 1:



KEYWORDS: METHYL-D-ASPARTATE; CORTICAL CELL-CULTURE; CATION CHANNEL; CALCIUM NEUROTOXICITY; RECEPTOR ACTIVATION; RNA INTERFERENCE; CLINICAL-TRIALS; BRAIN INJURY; NITRIC-OXIDE; ACUTE STROKE.

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