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Targeting Kv2.1 Channels as a Neuroprotective Strategy ID: 03203

Featured Innovator: Elias Aizenman, PhD

Stroke — the sudden death of brain cells due to blockage or rupture of an artery — kills nearly 140,000 Americans each year. That's 1 out of every 20 deaths. It is also the leading cause of long-term disability, with survivors often facing a devastating reduction in their independence and quality of life. Acute stroke treatment involves surgery or clot-dissolving agents, which — if applied quickly — can improve the odds of survival and reduce complications. Our novel peptide could work in conjunction with these treatments to extend the window for treatment and further reduce the lasting effects of a stroke by preventing neuron loss. Since many modes of neuronal cell death share the same mechanism of action, this peptide could also be applied to traumatic brain injuries (TBI) or neurodegenerative diseases.

Technology Description

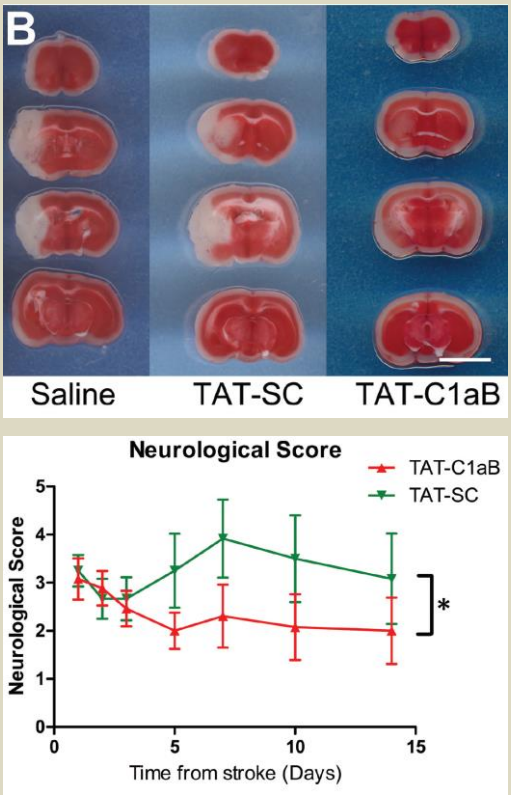
The apoptotic cell death pathway following neuronal injury requires insertion of the Kv2.1 channel into the cell membrane, causing a massive loss of intracellular potassium. Binding of the SNARE protein, syntaxin, with Kv2.1 is a necessary step in this pathway. We have demonstrated that overexpression of the SNARE-binding intracellular Kv2.1 domain alone is neuroprotective *in vitro*. Our novel peptide (TAT-C1aB) — derived from the C-terminal SNARE-binding region of Kv2.1 — disrupt the insertion of Kv2.1 channels to prevent neuronal death upstream of the potassium current surge. In mice, this peptide significantly reduced stroke damage and improved neurological outcomes. As the apoptotic action of Kv2.1 is involved not only in stroke, but also in several neurodegenerative diseases, our novel peptide could prove to be useful for neuroprotection in many different contexts.

Advantages

- Neuroprotective — prevents further loss of neurons
- Disrupts a universal cell death pathway without affecting properties of viable neurons

Applications

- Treatment of acute CNS insult — stroke, ischemia, or traumatic brain injury
- Potential for neuroprotective treatment of chronic disease — Alzheimer's, Parkinson's, and other neurodegenerative diseases



TAT-C1aB reduces ischemic stroke damage and improves neurological deficits in mice. TAT-SC indicates scrambled control.

Stage of Development

in vivo

IP Status

US patent 9,932,382

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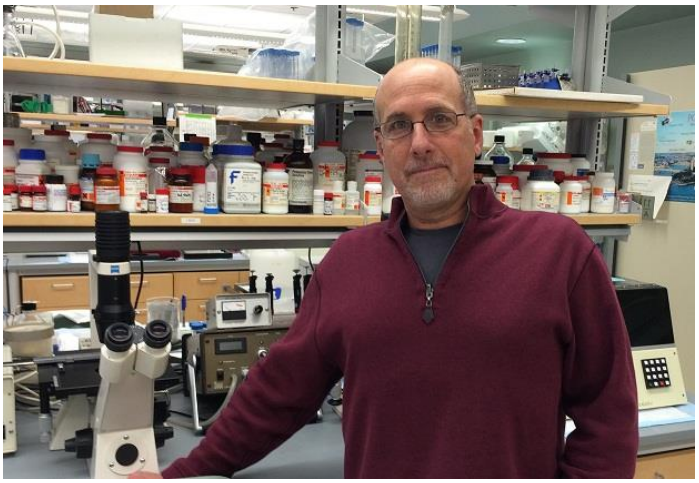

Elias Aizenman, Ph.D.

Professor
Neurobiology
University of Pittsburgh

Research in Dr. Aizenman's laboratory is directed towards investigating cellular signaling processes leading to neuronal cell death and devising novel approaches to neuroprotection. He uses molecular dissection of cellular pathways to discover novel therapeutic targets for neuronal cell death. This work is primarily focused on acute neuronal injury, such as stroke, although the results obtained from these studies could have broader applications to more chronic neurodegenerative conditions. Over the last several years, the laboratory has investigated redox and photic regulation of NMDA receptors, excitotoxicity, dopamine oxidation pathways, zinc-mediated neurotoxicity, zinc signaling and epilepsy, and Kv2.1 potassium channel facilitated forms of neuronal apoptosis. The laboratory uses a wide range of techniques that include cellular electrophysiology, molecular biology, protein biochemistry, cell culture, cell imaging, gene-expression assays, toxicity assays, pharmacological screening and, in vivo ischemia models.

Education

PhD in Toxicology
The Johns Hopkins University, Baltimore

BA in Biology
Boston University

Publications

- Justice JA, Schulien AJ, He K, Hartnett KA, Aizenman E, Shah NH (2017). Disruption of KV2. 1 somato-dendritic clusters prevents the apoptogenic increase of potassium currents. *J Neurosci*, 354, 158-167.
- Yeh CY, Bulas AM, Moutal A, Saloman JL, Hartnett KA, Anderson CT, Tzounopoulos T, Sun D, Khanna R, Aizenman E. (2017). Targeting a Potassium Channel/Syntaxin Interaction Ameliorates Cell Death in Ischemic Stroke. *J Neurosci.* 37(23):5648-5658. doi: 10.1523/JNEUROSCI.
- McCord MC, Kullmann PH, He K, Hartnett KA, Horn JP, Lotan I, Aizenman E. (2014). Syntaxin-binding domain of Kv2.1 is essential for the expression of apoptotic K+ currents. *J Physiol*. 592(16):3511-21. doi: 10.1113/jphysiol.

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