Zinc plays important role in brain circuitry

November 22 2006

To the multitude of substances that regulate neuronal signaling in the brain and spinal cord add a new key player: zinc. By engineering a mouse with a mutation affecting a neuronal zinc target, researchers have demonstrated a central role for zinc in modulating signaling among the neurons. Significantly, they found the mutant mouse shows the same exaggerated response to noise as children with the genetic disorder called "startle disease," or hyperekplexia.

The findings shed light on a nagging mystery in neurobiology: why the connections among certain types of neurons contain considerable pools of free zinc ions. And even though many studies had shown that zinc can act toxically on transmission of neural impulses, half a century of experiment researchers had not been able to show conclusively that the metal plays a role in normal nerve cell transmission.

However, in an article in the November 22, 2006, issue of the journal Neuron, published by Cell Press, Heinrich Betz and colleagues conclusively demonstrate just such a role for zinc.

In their experiments, the researchers produced mice harboring a mutant form of a gene for a receptor for zinc in neurons--thereby compromising the neurons' ability to respond to zinc. The mutation in the receptor, called the glycine receptor, targets the same receptor known to be mutated in humans with hyperekplexia. The receptor functions as a modulator of neurons in both motor and sensory signaling pathways in the brain and spinal cord.

The genetic approach used by the researchers was a more targeted technique than previous experiments in which researchers reduced overall neuronal zinc levels using chemicals called chelators that soak up zinc ions.

The resulting mutant mice showed tremors, delayed ability to right themselves when turned over, abnormal gait, altered transmission of visual signals, and an enhanced startle response to sudden noise.

Electrophysiological studies of the mutant animals' brain and spinal neurons showed significant zinc-related abnormalities in transmission of signals at the connections, called synapses, among neurons.

Betz and his colleagues wrote that "The data presented in our paper disclose a pivotal role of ambient synaptic [zinc ion] for glycinergic neurotransmission in the context of normal animal behavior." They also concluded that their results implied that manipulating synaptic zinc levels could affect the neuronal action of zinc, but that such manipulation "highlights the complexity of potential therapeutic interventions," which could cause an imbalance between the excitatory and inhibitory circuitry in the central nervous system.

In a preview of the paper in the same issue of Neuron, Alan R. Kay, Jacques Neyton, and Pierre Paoletti wrote "Undoubtedly this work is important, since it directly demonstrates that zinc acts as an endogenous modulator of synaptic transmission." They wrote that the findings "will certainly revive the flagging hopes of zincologists. This work provides a clear demonstration that interfering with zinc modulation of a synaptic pathway leads to a significant alteration in the phenotype of the animal." The three scientists added that the finding "puts a nice dent in the zinc armor, which held firm for more than 50 years."

Source: Cell Press