Researchers add to understanding of how brain cells communicate

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An hour from now, will you remember reading this? It all depends on proteins in your brain called NMDA receptors, which allow your neurons to communicate with each other.

Jon W. Johnson, University of Pittsburgh associate professor of neuroscience, and former Pitt graduate student Anqi Qian, now of Carnegie Mellon University in Qatar, have discovered how different types of NMDA (N-methyl-d-aspartate) receptors perform varied functions. Their findings are published in the current issue of the Journal of Neuroscience in a paper titled "Permeant Ion Effects on External Mg2+ Block of NR1/2D NMDA Receptors."

Communication between cells in the brain depends on specialized molecular receptors that conduct charged particles, or ions, between the outside and inside of cells. Ions also modify how receptors work. In this paper, Johnson and Qian studied the effects of ions on receptors and found them to vary between different types of receptor molecules. They used computer modeling to show that variation in how ions interact with receptors combined with variation in the structure of receptors is responsible for specialization of receptor function.

"This research helps explain how evolution accomplished a critical goal: producing receptor proteins with finely tuned properties that help optimize brain function," said Johnson.

NR1/2D receptors may be the least-studied of the major NMDA receptor subtypes, but there is increasing evidence that they play important roles in the brain, including the process of long-term depression (which, like long-term potentiation, is thought to be essential for learning and memory) and disease. A better understanding of how NMDA receptors work could lead to better treatments for schizophrenia, Alzheimer's disease, and stroke, said Johnson.

Memories are formed by strengthening the connections between brain cells, known as synapses. If you touch a hot stove, the pain signal from your hand and the visual signal from your eyes reach the brain at about the same time, forging a memory. Specifically, memory requires the coordinated activation of many types of receptors at synapses. The flow of calcium ions through a channel in NMDA receptors plays a central role.

Neurons "talk" to each other by releasing glutamate at a synapse that binds to NMDA receptors on the surface of the "listening" neuron. If the listening neuron is strongly excited, magnesium ions are expelled from the channel of NR1/2A receptors, one NMDA receptor subtype. Calcium ions then can flow through the open channel into the listening neuron at the synapse, causing the synapse to be strengthened and you to remember that "hot stove = pain."

Another type of NMDA receptor that is thought to help sculpt memories is called NR1/2D. Although NR1/2A receptors require strong excitation to let calcium ions flow across the membrane, NR1/2D receptors respond even to weak inputs.

In this paper, Johnson and Qian further elucidate how NR1/2D receptors do this. Johnson was most surprised to find that the magnesium ion, which strongly blocks the channels of NR1/2A receptors, flows much more easily in NR1/2D receptors. In those receptors, magnesium acts more like a "permeant" ion, which means it can flow through the channel without getting stuck in the middle.

In addition to computer modeling, the researchers used the technique of patch clamp recording, which takes a tiny piece of cell membrane and measures the charge that flows through one open channel. They were able to use the remarkable precision of the patch clamp to see exactly when the magnesium ion entered and exited the ion channel.

"Because of our currently limited understanding of NR1/2D receptors, drawing a direct link to human disease and memory is speculative, but I am confident that the links will become firmer as research progresses," Johnson said.

Source: University of Pittsburgh