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Neuroscientists show insulin receptor signaling regulates structure of brain circuits

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Impact of the signaling upon synapses and dendrites is shown for the first time in living creatures

A team of neuroscientists at Cold Spring Harbor Laboratory (CSHL) has demonstrated for the first time in living animals that insulin receptors in the brain can initiate signaling that regulates both the structure and function of neural circuits.

The finding suggests a significant role for this class of receptors and perhaps for insulin, not only in brain development, but also in cognition and in pathological processes in which cognition is impaired, as in Alzheimer's disease, for example.

Insulin receptors on the surface of cells throughout the body have long been understood to play a central role in controlling metabolism through the regulation of glucose. When a molecule of insulin, a hormone, "docks" with the receptor, a complex signaling cascade is set in motion inside a cell, culminating in the cell's uptake of insulin.

The Brain Is Not "Insulin-Insensitive" After All

Although insulin receptors are observed in certain parts of the mammalian brain, most scientists, until a few years ago, had assumed the organ was "insulin-insensitive," knowing that glucose could be taken up by brain cells without the involvement of either insulin or insulin receptors.

In recent years, however, it has been shown that the brain is indeed an insulin target, and in cell-culture experiments that insulin receptor signaling in neurons can have an impact on the formation and development of neural circuits. This had never been demonstrated in living organisms until it was shown in experiments performed in the laboratory of CSHL Professor Hollis Cline, Ph.D., and reported this week in the journal *Neuron*.

These experiments, in Xenopus tadpoles, show that insulin receptor signaling in neurons regulates the maintenance of synapses, contributes to the processing of sensory information and is also involved in adjusting the plasticity of brain circuits in response to experience. The latter function is particularly interesting, notes Dr. Cline, since "it is required for the incorporation of neurons into brain circuits."

Blocking the Receptor

To test the idea that insulin receptor signaling regulates the formation of brain circuits during development, the Cold Spring Harbor team used two different techniques to block the function of the receptor in neurons located in the visual pathway of tadpoles. One method "knocked down" expression of the receptors genetically, while the other left them in place but prevented them from initiating signaling cascades within the cell.

"Tadpoles are wonderful creatures for such experiments," Dr. Cline explained, "in part because they have translucent bodies, which makes it easy for us to visualize and record what happens to individual neurons as we manipulate the insulin receptors on their surface."

When insulin receptor function was blocked, neurons in the visual pathway connecting the tadpole's retina to a brain region called the tectum responded very poorly to light stimuli. The tectum is the area in which brain cells process incoming visual signals. "We showed that the

insulin receptor is critical for the proper operation of this circuit, and also that defects in receptor signaling cause a reduction in the animal's visual responses," Dr. Cline said.

Time-Lapse Images of Dendritic Branching

The team went on to perform other experiments that demonstrated two remarkable facts. One is that insulin receptor signaling correlates with the density of the synapses, or neuron-to-neuron connections, in brain circuits. In more technical terms, they found that insulin receptors maintain synaptic density and that synapse density decreases when insulin receptors are removed or dysfunctional.

The team also secured time-lapse images of dendritic formations, the ethereal, branch-like structures that receive chemical signals sent from one neuron to the next. Again, they found that when insulin receptors are engaged and sending signals inside the neuron, dendritic growth is enhanced, specifically in response to visual stimulation.

In this, as in the findings about synaptic density, the team found that insulin receptor signaling regulates the form and function of brain circuits in response to incoming visual information. Another way to put this is that the receptor regulates brain circuits in response to "experience."

Possible Links to Disease

This suggests that insulin receptors in the brain may play a key role not only in the brain's development early in life, but also in disease processes that usually occur late in life. People with advanced diabetes suffer memory loss and cognitive deficits, possibly because insulin receptor signaling in the brain is disrupted, synaptic connections are lost and brain

circuits don't work optimally.

In addition, other researchers have found a correlation between diminished insulin receptor signaling and Alzheimer's disease. Results of the Cold Spring Harbor team's research raise the question of whether deficits in learning and memory associated with Alzheimer's might be linked causally to decreased synaptic density as a consequence of lowered insulin receptor signaling. "We are a long way from knowing this for sure, but it's the direction in which our work now takes us," Dr. Cline said.

Source: Cold Spring Harbor Laboratory