Scientists unveil critical mechanism of memory formation

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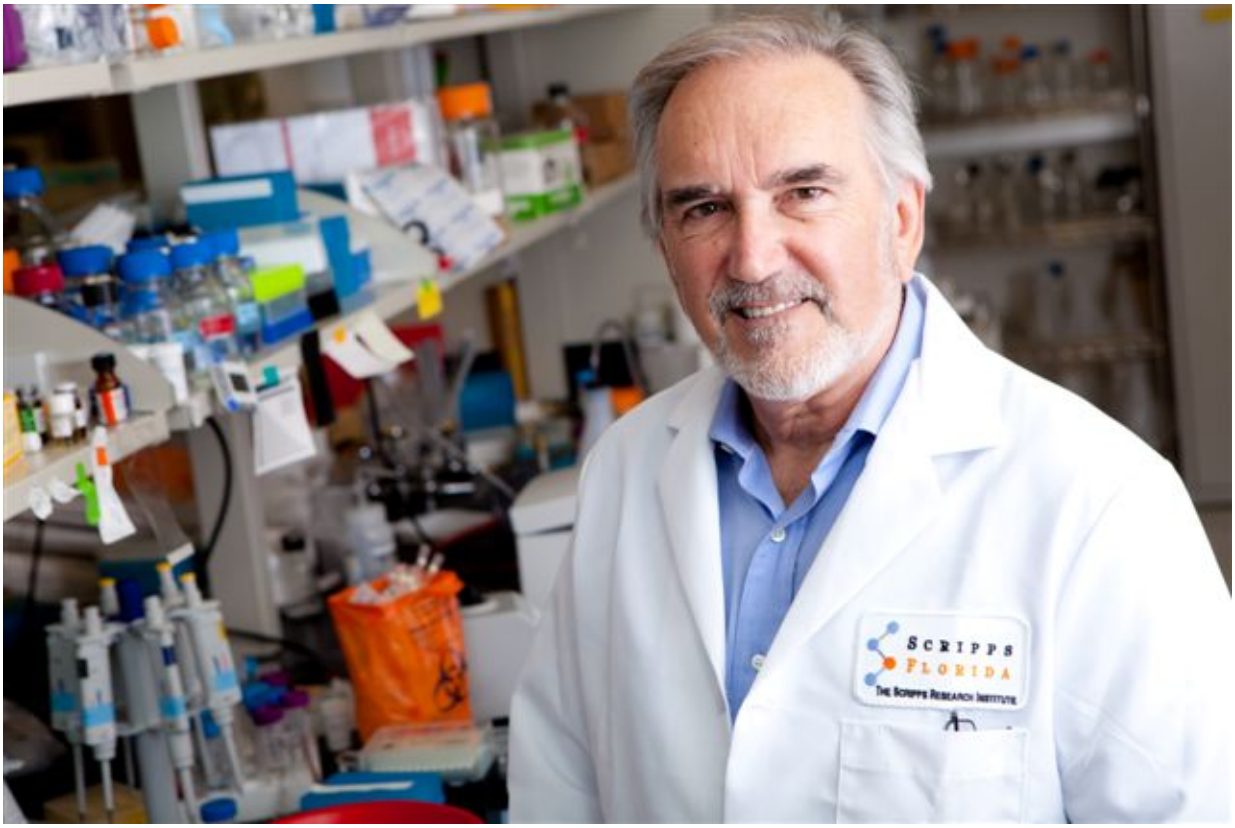

Roy Smith is chair of the Department of Metabolism and Aging at the Florida campus of The Scripps Research Institute. Credit: The Scripps Research Institute

In a new study that could have implications for future drug discovery efforts for a number of neurodegenerative diseases, scientists from the

Florida campus of The Scripps Research Institute (TSRI) have found that the interaction between a pair of brain proteins has a substantial and previously unrecognized effect on memory formation.

The study, which was published November 19, 2015 by the journal *Cell*, focuses on two receptors previously believed to be unrelated—one for the neurotransmitter dopamine, which is involved in learning and memory, reward-motivated behavior, motor control and other functions, and the other for the hormone ghrelin, which has been connected to appetite as well as the distribution and use of energy.

"Our immediate question was, what is the ghrelin receptor doing in the brain since the natural ligand—ghrelin—for it is missing? What is its functional role?" said Roy Smith, chair of TSRI's Department of Metabolism and Aging. "We found in animal models that when these two receptors interact, the ghrelin receptor changes the structure of the dopamine receptor and alters its signaling pathway. This is important because many drugs used currently in the clinic, for example for schizophrenia, have poor compliance because of adverse side effects. This discovery opens the door to using neuronal agents that indirectly modify dopamine signaling by pharmacologically targeting the ghrelin receptor—and potentially dramatically reducing side effects."

"This concept has potentially profound therapeutic implications," said Andras Kern, the first author of the study and a staff scientist in the Smith lab, "pointing to a possible strategy for selective fine-tuning of dopamine signaling in neurons related to memory. By using small molecules binding to the ghrelin receptor we can enhance or inhibit dopamine signaling."

Challenging the current theory, which involves canonical dopamine signaling in neurons, the new study shows that the biologically active ghrelin-dopamine receptor complex produces synaptic plasticity, the

ability of the brain's synapses (parts of nerve cells that communicate with other nerve cells) to grow and expand, the biological process underpinning long-term memory formation.

In addition, when the researchers blocked the ghrelin receptor, dopamine-dependent memory formation was inhibited in animal models, demonstrating the mechanism is essential to that process.

Combined with conclusions from earlier studies that showed a significant role for the ghrelin receptor in neurons that regulate food intake, insulin release and immune system deterioration due to aging, the new study further expands the ghrelin receptor's importance. In animal models, ghrelin inhibits neuronal loss associated with Parkinson's disease, and stroke, Smith noted, and the new study underlines its possible role in treating memory loss, age related or otherwise.

"All in all, it's a pretty amazing receptor," he said.

More information: "Hippocampal Dopamine/DRD1 Signaling Dependent on the Ghrelin Receptor," *Cell*, 2015.

Provided by The Scripps Research Institute

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