UT SOUTHWESTERN MEDICAL CENTER NEWS

Media Contact: Amanda Siegfried
214-648-3404
amanda.siegfried@utsouthwestern.edu

Brain's impaired ability to sense glucose might play role in type 2 diabetes

DALLAS – Aug. 29, 2007 – New findings from studies in mice suggest that defects in the brain's ability to respond to glucose play a role in the development of non-insulin dependent (type 2) diabetes, and that a high-fat diet may contribute to impairing brain cells' ability to regulate glucose throughout the body.

The new study, led by researchers at UT Southwestern Medical Center, Harvard Medical School and Oregon Health and Science University, is the first to demonstrate the mechanisms by which certain glucose-activated neurons respond to glucose, as well as the overall physiological role of glucose-sensing in these neurons, said Dr. Roberto Coppari, assistant professor of internal medicine at UT Southwestern and co-lead author of the study appearing online in the journal *Nature*.

In the 1960s, scientists discovered that certain neurons in the brain are activated by glucose. The physiological relevance of such neuronal glucose-sensing, and its underlying cellular mechanisms, have been elusive, however.

"By identifying glucose-sensing neurons in the brain as important players in regulating glucose, our findings may open a new avenue of research," Dr. Coppari said. "Because these neurons play a role in maintaining glucose homeostasis throughout the body, an impairment in their glucose-sensing ability could play a pathogenic role in type 2 diabetes, where homeostasis is altered."

The mechanism discovered by Dr. Coppari and his colleagues is related to how the body uses fuels circulating in the bloodstream. Glucose is among these fuels and is, in part, derived from foods consumed. It is used by the body to make a molecule called ATP, which provides energy to cells.

In the brain, ATP causes tiny pores in the membranes of glucose-sensing neurons to close. These pores, called ATP-sensitive potassium channels, allow potassium in and out of cells. When ATP is present to close the potassium channels, glucose-sensing neurons are active. When ATP levels are low, more channels are open, making these neurons less active.

The researchers genetically engineered mice to disrupt ATP's effects on these potassium channels in some of the glucose-sensing neurons thought to be involved in maintaining glucose balance. They found that the animals' whole-body response to glucose was impaired. This demonstrated the important role that glucose-sensing in the brain plays in overall physiological control of blood sugar, Dr. Coppari said.

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The researchers also determined that a protein called UCP2, present in energy-making parts of cells called mitochondria, disrupts the production of ATP. Dr. Coppari said this likely leads to more potassium channels remaining open in glucose-sensing brain cells, making them less active and less responsive to glucose.

They also found that UCP2 is more abundant in the brains of normal mice fed a high-fat diet, and that glucose-sensing was abolished in some of the glucose-activated neurons in these animals. This high-calorie-diet-induced loss of glucose-sensing in the brain may impair the body's ability to regulate glucose levels and may contribute to diabetes, Dr. Coppari said.

"An increase in UCP2 in the brain makes the glucose-excited neurons less sensitive to glucose," Dr. Coppari said. "Such impairment in glucose-sensing may be one of the links between a high-fat diet and obesity and the development of type 2 diabetes."

The researchers also were able to restore a normal glucose response in neurons of wild-type mice fed a high-fat diet by giving them a molecule called genipin, which antagonizes the actions of UCP2 and allows glucose-sensing neurons to function properly. The researchers further tested UCP2's role by studying genetically engineered mice that lacked the ability to make the UCP2 protein. The glucose-sensing neurons functioned normally in these animals, even when they were fed high-fat food.

Dr. Coppari performed some of the research while working with senior author Dr. Bradford Lowell at Harvard Medical School. Dr. Joel Elmquist, professor of internal medicine at UT Southwestern, played a key role in the research by validating the animal models, Dr. Coppari said. Other researchers contributing are from Beth Israel Deaconess Medical Center and Nanjing University in China.

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