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Scientists find new link between insulin and core body temperature

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A team led by scientists at The Scripps Research Institute have discovered a direct link between insulin—a hormone long associated with metabolism and metabolic disorders such as diabetes—and core body temperature. While much research has been conducted on insulin since its discovery in the 1920s, this is the first time the hormone has been connected to the fundamental process of temperature regulation.

The paper was published recently in an advance, online issue of the journal *Diabetes*, a journal of the American Diabetes Association, and will appear in the January print edition of the publication.

The scientists found that when insulin was injected directly into a specific area of the brain in rodents, core body temperature rose, metabolism increased, and brown adipose (fat) tissue was activated to release heat. The research team also found that these effects were dose-dependent—up to a point, the more insulin, the more these metabolic measures rose.

"Scientists have known for many years that insulin is involved in glucose regulation in tissues outside the brain," said Scripps Research neurobiologist Manuel Sanchez-Alavez, who was first author of the new paper with Bartfai lab colleagues Iustin V. Tabarean and Olivia Osborn (now at the University of California, San Diego). "The connection to temperature regulation in the brain is new."

In addition to suggesting a fresh perspective on diseases such as diabetes

that involve the disruption of insulin pathways, the study adds to our understanding of core body temperature—the temperature of those parts of the body containing vital organs, namely the trunk and the head. Normally, core body temperature stays within a narrow range so that key enzymatic reactions can occur. When core body temperature goes outside this range for prolonged periods—higher as in fever, or lower as in hypothermia—the result is harm to the body.

More modest variations in core body temperature are associated with our daily 24-hour sleep-wake cycle, the female monthly hormonal cycle, and, intriguingly, the effects of severe calorie restriction.

"Our paper highlights the possibility that differences in core temperature may play a role in obesity and may represent a therapeutic area in future drug design," added Osborn.

A Surprising Find

The laboratory of Tamas Bartfai, who is chair of the Department of Molecular and Integrative Neurosciences, director of the Harold Dorris Neurological Research Institute, and a member of The Skaggs Institute of Chemical Biology at Scripps Research, has been investigating the biology of temperature regulation for almost a decade. The idea for the new study came about from some recent experiments in his lab exploring the properties of cells called "warm-sensitive neurons." These cells exist only in the preoptic area of the brain, which is known to regulate core body temperature.

In work coordinated by Osborn to characterize these neurons and their transcriptome (all of the messenger RNA molecules in a cell, which reflect the genes being expressed), the team noticed something unexpected—a messenger RNA for an insulin receptor.

"We were surprised to find the insulin receptor," said Tabarean. "The insulin receptor is very well documented in the pancreas and in other peripheral tissues. But in the brain, it was not clear and we definitely did not know about its existence in warm-sensitive neurons."

Hypothesizing that insulin was acting in the regulation of core body temperature because of its presence in warm-sensitive neurons, the scientists set out to investigate. To do so, they used a rare combination of techniques including molecular biology at the single-cell level, electrophysiology, imaging techniques, and in vivo metabolic studies.

First, Tabarean led the single-cell work, examining the effect of insulin on individual warm-sensitive neurons, which fire more frequently when temperature rises. Results showed that insulin was potent in reducing the neurons' firing rate.

Next, members of the Bartfai lab designed several whole animal studies to confirm these findings and examine the pathways in the body that might be affected.

Lighting up Beautifully

The scientists suspected that insulin in the brain might work to warm the body through a specific pathway involving signals that traveled from the brain's preoptic area, down the spinal cord, to neurons that direct brown adipose tissue to expend energy to produce heat.

Brown adipose tissue, also known as brown fat, is distinct from white fat in that it burns calories rather than storing them. While in years past, brown fat was thought to exist in humans only when they are infants, recent studies have shown that brown fat deposits are also found in healthy adults, especially around their collarbones and necks. Interestingly, older people have less brown fat than younger people, and

obese individuals have less than lean individuals.

To see if brown fat was activated by insulin in the brain, the Bartfai group collaborated with members of Seimens Medical Solutions, who are experts in imaging techniques. Specifically, the scientists examined the effect of insulin injections in the preoptic area of rats on brown adipose tissue using Computerized tomography (CT) scans and positron emission tomography (PET) scans. Rodents possess brown adipose tissue in two large masses on their backs between the shoulder blades.

When the activity of the brown fat was captured visually, the data confirmed the scientists' projections.

"After insulin injection into the preoptic area, the brown adipose tissue lights up very beautifully," said Sanchez-Alavez.

Next, Sanchez-Alavez led studies examining the effects of insulin on metabolism, specifically by measuring the effect of insulin injections in the preoptic area of mice on oxygen consumption and carbon dioxide production. Again, results showed that metabolic rate increased with an increase in insulin.

"All the techniques—PET/CT scan, metabolic studies, telemetric work—support the hyperthermic effect of insulin in rodent models," Sanchez-Alavez summarized.

The authors note that while their new paper illuminates a key piece of the puzzle of the body's metabolic processes, it also raises many intriguing questions: How does insulin get to the brain's preoptic area—does it cross the blood-brain barrier or is it produced locally? Are diabetics, who are insensitive to insulin in peripheral tissues, still sensitive to insulin in the brain; if so, could this dichotomy be used in the development of a new therapy? Could scientists find a way to use these

new insights to increase energy expenditure for the purpose of weight loss?

"This is a very long project," said Sanchez-Alavez. "I hope we get funding to continue this research."

More information: diabetes.diabetesjournals.org/ …6/db09-1128.abstract

Source: The Scripps Research Institute (news : web)