(Kanazawa, 16 March 2016) Kanazawa University **researchers find similarities in the impeded signalling between central insulin activity and glucose production in the liver for both obese mice and mice that have had the vagus nerve removed. The results are published in** *Cell Reports*, March 2016.

The vital role of insulin in controlling glucose production is often disrupted in people suffering from obesity, a condition approaching global epidemic levels. Previous work has shown that central insulin action suppresses glucose production in the liver by increasing levels of the ligand interleukin 6 (IL-6) in the liver. The ligand activates the transcription factor STAT3, which in turn suppresses gene expression of glucose-producing enzymes. However, how the liver communicates with central nervous system and the vagus nerve, which controls unconscious processes like digestion, has so far not been understood. Now a collaboration of researchers in Japan led by Hiroshi Inoue at Kanazawa University's Institute for Frontier Science Initiative (InFiniti) has identified the molecular mechanism for this communication.

Acetylcholine is the main neurotransmitter in the vagus nerve. It also suppresses IL-6 via the α7-nicotinic acetylcholine receptor. The researchers administered insulin and monitored subsequent vagal nerve activity, as well as IL-6 levels in a type of white blood cell in the liver known as "Kupffer cells". They noticed a decrease in vagal nerve activity accompanied by increases in IL-6 in the Kupffer cells, resulting in decreased glucose production.

The researchers then investigated the effects of administering methyllycaconitine, which prevents α7-nicotinic acetylcholine receptor activity, as well as removal of the vagal nerve. They found that while STAT3 phosphorylation and IL-6 expression in the liver increased only slightly the IL-6/STAT3 signalling response to administered insulin was lost.

The researchers compared the response in lean and obese mice and found that the administered insulin "failed to elicit changes in vagus nerve activity of high-fat diet-induced obese mice." They conclude, "These findings suggest that the aberrant regulation of Kupffer

cells via the vagus nerve and α7-nAchR-mediated cholinergic action by central insulin action may have a significant role in the pathogenesis of chronic hepatic inflammation in obesity and of dysregulation of hepatic glucose production."

Background

Glucose metabolism

Insulin is a hormone responsible for maintaining glucose levels and regulating glucose production in the liver. It also interacts with the central nervous system to regulate glucose metabolism. These metabolic processes include glucose oxidation to release ATP - which powers cells – glucose storage as glycogen, and the production of fatty acids and other substances.

Obesity-related diseases

Excessive body weight and insufficient exercise has been linked to insulin resistance, which can develop into a lack of insulin and type 2 diabetes. The surge in global obesity levels has been reflected in the numbers of people suffering from type 2 diabetes, a disease that is reported to cause over a million deaths each year. In 2014 90% of the 387 million cases of diabetes registered were type 2 and this is expected to increase to 587 million by 2035.

Obesity is also closely linked to inflammation and cancer of the liver. Interleukin 6 is a cytokine that can cause inflammation. The researchers found that the ability of the vagus nerve to regulate IL-6 expression was impeded in high-fat diet-induced obese mice. As well as the detrimental effects on glucose homeostasis, the results of this research suggest a molecular mechanism that links obesity to liver inflammation. Administration of neostigmine – which has a cholinergic action – suppressed expression of inflammatory cytokines in the Kupffer cells of obese insulin-resistant mice.

Reference

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About Kanazawa University

As the leading comprehensive university on the Sea of Japan coast, Kanazawa University has contributed greatly to higher education and academic research in Japan since it was founded in 1949. The University has three colleges and 16 schools offering courses in subjects that include medicine, computer engineering, and humanities.

The University is located on the coast of the Sea of Japan in Kanazawa—a city rich in history and culture. The city of Kanazawa has cultivated a highly respected intellectual profile since the time of the Kaga fiefdom (1598–1867). Kanazawa University is divided into two main campuses: Kakuma and Takaramachi for its approximately 12,200 students including 500 from overseas.