MedicalXpress

Scientists identify culprit in obesity-associated high blood pressure

January 31 2013

Obesity and its related conditions such as type 2 diabetes, cardiovascular disease and stroke are among the most challenging of today's healthcare concerns.

Together, they constitute the biggest killer in western society. New findings, published in *Cell*, have identified a target that could hold the key to developing safe therapies to treat obesity and its associated conditions.

Although recent research has begun to unravel some of the pathways that control how information is processed by our nervous system regulating body weight and cardiovascular function, the exact mechanisms through which signals are sensed by the brain and translated into co-ordinated metabolic and cardiovascular responses remain unclear.

A University of Bristol team, with funding from the British Heart Foundation (BHF), has now identified that a target found to be critical in the brain's regulation of body weight, is also crucially involved in the development of obesity-associated conditions. Researchers describe the mechanism behind a key molecule, known as melanocortin-4-receptor (MC4R), whose mutation or loss in both human and animal models has shown to cause severe obesity with type 2 diabetes.

While previous studies have shown that small activators of the molecule, which increase MC4R activity, have the desirable effect of reducing food intake and insulin secretion from the pancreas (important to

suppress the development of type 2 diabetes), it is not clear how, at the same time, they trigger the undesirable effect of increasing blood pressure.

The team has now identified a mechanism for MC4R-mediated regulation of the activity of the autonomic nervous system to maintain appropriate blood pressure and insulin levels. The autonomic nervous system, which regulates internal organs and processes that are not under our control, is split into the parasympathetic and sympathetic nervous system, commonly exerting opposing influences on the structures they supply with nerves.

Researchers demonstrated that the activation of the MC4R inhibits parasympathetic neurons in the brain stem area of the central nervous system (CNS), while activating sympathetic neurons in the spinal cord. The team further demonstrates, in genetically-modified mouse models of human loss of MC4R function, that MC4Rs in these CNS areas are to blame for the development of obesity-induced increases in blood pressure.

They also report that MC4Rs in these CNS areas are pivotal in maintaining appropriate insulin levels to stave off type 2 diabetes. Thus, by carefully balancing positive and negative forces on the autonomic nervous system, the MC4R maintains equilibrium of appropriate blood pressure and insulin levels. This is independent of the MC4R's role in the regulation of food intake elsewhere in the CNS.

MC4R is a target of intense pharmaceutical interest and the data from this research helps in our understanding of the CNS mechanisms regulating homeostatic body weight, blood pressure and insulin levels through a distributed network of MC4Rs. These findings may facilitate the development of appropriate, safe therapies to treat obesity and its associated conditions.

Dr Nina Balthasar, one of the study's lead authors and a researcher in the University's School of Physiology and Pharmacology, said: "Obesity is a major risk factor for cardiovascular disease with recent statistics showing that obese adults are three to four times more likely to develop high blood pressure.

"In order to curb the escalating incidence of obesity and obesity-related diseases, a primary prevention goal must be to understand the physiological processes underlying our vulnerability to weight gain—knowledge that is central to the development of novel, effective therapies.

Our data illustrate the complexity of the CNS pathways governing the body's metabolic balance and highlight the challenges ahead for the development of safe therapies. "

Dr Shannon Amoils, Research Advisor at the BHF, which part-funded the study, added: "This research increases our understanding of how the nervous system affects our metabolism, and the development of high blood pressure due to obesity. With further knowledge of this complex area we hope scientists will be able to find safe and effective ways of treating obesity-related heart and circulatory disorders."

More information: Melanocortin-4-Receptors Reciprocally Regulate Sympathetic and Parasympathetic Preganglionic, *Cell*, 2013.

Provided by University of Bristol