Knocking out obesity

Drs Robert H Eckel and Hong Wang work closely together in the study of metabolic diseases. Here, they provide expert insight into the complex mechanisms involved in the development of obesity.

Could you introduce the focus of your research?

Obesity is a major health problem in the developed and developing world. Once obese, weight loss is difficult to achieve and even more difficult to maintain after weight reduction. This relates to the defence of body fat, a process coordinately regulated by the brain and other tissues in the body. The most influential enzyme involved in how fats are metabolised is lipoprotein lipase (LPL), which is the rate-limiting enzyme for the hydrolysis of the triglyceride (TG) core of TG-rich lipoproteins (chylomicrons and very low density lipoproteins – VLDL), which are increased with feeding. This enzyme is regulated in a tissue-specific manner and over the years my laboratory has focused on the divergent regulation of the enzyme in adipose tissue and muscle using human subjects, rodents including genetically-modified mice, and tissue culture. LPL is also made in the brain by neurons and glial cells, and in the spinal cord and peripheral nerves, but its function in the central nervous system (CNS) remains largely unknown. Thus, we chose to reduce expression of the enzyme in neurons using a knockout approach.

Does your research into preventive cardiology correlate with your studies on obesity?

Preventive cardiology is most closely linked to my clinical role directing the Lipid Clinic at the University of Colorado Hospital. Because obesity and diabetes are important to cardiovascular disease risk, my research merges nicely with steps in the clinic to reduce CVD risk in patients with obesity and/or diabetes. For the past 34 years, my research has largely been funded by the National Institutes of Health (NIH) with a theme of tissue-specific regulation of LPL focused on adipose tissue, skeletal muscle, the peripheral nervous system and, most recently, the brain. LPL is modified in patients with obesity, Type 2 diabetes and disorders of lipid and lipoprotein metabolism including hypertriglyceridermia and low levels of the good cholesterol, high-density lipoprotein (HDL).

The approach has been a balance of studies in human subjects (normal weight, obese, reduced-obese, Type 2 diabetics, hypertriglycerideremics); rats; and most often, mice with obesity, reduced-obesity, and/or diabetes; genetically-modified mice with skeletal muscle and over- and under-expression of the lipase enzyme, and now neuron-specific deficiency of LPL. In addition, a plethora of our studies have utilised cultured cell lines and primary cultures of adipocytes, myocytes and most recently neurons.

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What are the major differences between lipoproteins in the plasma and those found in the brain?

Because of the blood brain barrier (BBB), the exchange of lipoprotein particles between the systemic circulation and the CNS is minimal, with some smaller HDL-like particles able to traverse. Most of the lipoproteins inside the CNS originate from astrocytes, although some of the lipoprotein constituents can be synthesised and processed differently in neurons.

Lipoprotein particles are constantly synthesised, assembled, exchanged and modified between astrocytes and neurons. Astrocytes can secrete lipoprotein particles into the cerebrospinal fluid (CSF) or reabsorb the smaller particles for remodelling and reloading of lipids. Lipoprotein receptors and LPL located on the surface of astrocytes and neurons appear to play a regulatory role in lipoprotein metabolism in the CNS, effects that are brain region-specific.

Can you discuss some of the novel roles played by lipoproteins in the CNS?

Lipoprotein metabolism is important, tightly regulated, and involved in many functional processes in the brain. The coordinated synthesis, assembly, remodelling and transport of lipoprotein particles in the brain are all evident, but detailed mechanisms remain to be elucidated. When considering the essential role of LPL in peripheral lipoprotein metabolism, the functional roles of brain LPL protein in both energy balance (a proposed hypothalamic mechanism) and cognitive function (a proposed hippocampal mechanism), and the data from other lipoprotein receptors, it is tempting to suggest that lipoprotein-derived molecules provide signals to mediate essential pathways in different brain regions that contribute to neuronal plasticity underlying many important brain functions.

How do lipoproteins contribute to the regulation of neurobehavioral functions?

We have data under review demonstrating that 21 mo heterozygous NEXLPLA/- mice display substantial cognitive functional decline including poorer learning and memory and increased anxiety with no difference in general motor activities and exploratory behaviour. These neurobehavioral abnormalities are associated with a reduction in the 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoic acid (AMPA) glutamate receptor subunit (GluA1) and its phosphorylation, without any alterations in amyloid beta accumulation. Importantly, a marked deficit in omega-3 and omega-6 polyunsaturated fatty acids (PUFA) in the hippocampus precedes the development of the neurobehavioral phenotype of NEXLPLA/-. We interpret these findings to indicate that LPL regulates the availability of PUFA in the CNS and, in turn, impacts the strength of synaptic plasticity in the brain of ageing mice.

Could a more profound understanding of lipoproteins and their metabolism in the brain contribute to the development of effective therapeutics?

At present, there is insufficient knowledge about lipoproteins and their role in the brain. Long chain fatty acids are dependent on precursor fatty acids found in the diet, linoleic acid and linolenic acid (essential fatty acids). If either of these precursors or their long chain fatty acid products are delivered to the brain by plasma TG-rich lipoproteins, a better understanding of the regulation of LPL in the brain could result in targeted therapies to more effectively deliver these needed nutrients. Such a process could be contributory to favourable changes in energy balance, body weight regulation and age-related dementias.
The mind-body connection

Researchers at the University of Colorado Anschutz Medical Campus, USA, are striving to better understand the underlying causes of obesity through an examination of lipoprotein lipase deficiency in neurons. The end goal is the development of effective therapeutics for patients.

Due to economic growth, globalisation and modernisation, the rate of obesity worldwide has nearly quadrupled since 1980, and 1 billion adults are now diagnosed with the condition. Ranked as the most obese continent in the world, North America is struggling to contend with the consequences of growing patterns of unhealthy eating and infrequent exercise. Leading to the development of chronic diseases such as Type 2 diabetes, cardiovascular disease, hypertension and stroke, obesity can often drastically impact on quality of life.

Identified as a major contributor to obesity, the enzyme lipoprotein lipase (LPL) plays a significant role in lipoprotein metabolism, tissue-specific fuel delivery and utilisation, as well as energy balance, insulin action and body weight regulation. These functions have most commonly been attributed to LPL in peripheral tissues; however, researchers have now established that LPL could represent an important function in the brain and affect neurobehaviour. At the University of Colorado Anschutz Medical Campus, Dr Robert H Eckel’s research seeks to unravel the mechanisms of obesity in mice with neuron-specific LPL deficiency in order to develop effective therapeutics for use in human clinical settings.

Understanding lipoprotein signalling

Lipoproteins are found in both plasma and the brain, and transport lipids between tissues, with only high-density lipoproteins (HDLs) appearing to traverse the blood-brain barrier (BBB). Though the significance of discovering lipoproteins in the central nervous system (CNS) is still under investigation; scientists have thus far identified that some HDLs are not only transported into the brain but can also be formed here: “At this point, we do not know how LPL has access to the triglyceride (TG)-rich lipoproteins in the brain and whether its action depends on the ability to hydrolyse TGs or other functions of the protein,” Eckel elucidates. Moreover, most of the lipoproteins found within the CNS originate from astrocytes, which secrete lipoprotein particles into the cerebrospinal fluid (CSF) or, conversely, reabsorb the smaller particles for remodelling and reloading lipids. The lipoprotein receptors and LPL found on the surface of astrocytes and neurons have been identified as likely regulators of lipoprotein metabolism in the CNS, as brain region-specific functions. This suggests that lipoprotein-mediated processes help regulate neurobehavioural functions, contributing to the regulation of body weight and energy balance, and perhaps in part – via agouti-related peptide (AgRP), which is produced by neurons – stimulates food consumption and decreases energy usage.

Neuron-specific LPL knockout mice

Working in collaboration with Eckel is Dr Hong Wang, Assistant Professor of Medicine at the University of Colorado Anschutz Medical Campus. The research is focused on gaining insight into how the deficiency of LPL in neurons modifies the regulation of energy balance and leads to obesity. To examine this mechanism, Eckel’s team observed the consequences of work from other groups of injecting free fatty acids (FFAs), which function as appetite suppressors, into the hypothalamus of mice. Eckel and Wang developed a combinatorial approach to investigate whether LPL contributes to FFA-mediated signalling in the brain using neuron-specific LPL knockout mice, cultured neuronal cell lines and primary hypothalamic cells. In neuron-specific LPL knockout mice the group observed that when AgRP gene expression was increased in the brains of the knockout mice, there was a subsequent increase in food intake.
INTELLIGENCE

THE MECHANISMS OF OBESITY IN MICE WITH NEURON-SPECIFIC LIPOPROTEIN LIPOASE DEFICIENCY

OBJECTIVES

To explore the relationship between nutrition, insulin action, energy balance and body weight regulation with experiments carried out in both humans and mice.

KEY COLLABORATORS

Dr Ira J Goldberg, Columbia University, USA
Dr Daniele Piomelli, University of California, Irvine, USA
Dr Jacob E (Jed) Friedman, University of Colorado Anschutz Medical Campus, USA

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CONTACT

Robert H Eckel, MD
Professor of Medicine, Division of Endocrinology, Metabolism and Diabetes/
Division of Cardiology
Professor of Physiology and Biophysics
Charles A Boettcher II Chair in Atherosclerosis
Director, Clinical and Translational Research Centers Network
Division of Endocrinology, Metabolism and Diabetes
12801 East 17th Avenue, Box 8106
University of Colorado Anschutz Medical Campus Aurora
Colorado, USA, 80045
T +1 303 724 3921
E robert.eckel@ucdenver.edu

Dr Robert H Eckel is a graduate of the University of Cincinnati and Distinguished alumni of the University of Cincinnati School of Medicine. He did his internship and residency at the University of Wisconsin Hospitals and fellowship in Endocrinology and Metabolism at the University of Washington. Eckel is former president of both the American Heart Association and the North American Association for the Study of Obesity (now Obesity Society), and is a member of the Board of Directors for the Global Alliance for the Prevention of Obesity and Related Chronic Diseases.

Dr Hong Wang currently directs Eckel’s basic science research group and works closely with him on genetically modified mouse models to study the mechanism of metabolic diseases such as obesity, dyslipidemias, diabetes mellitus, and other metabolic associated disorders such as cardiovascular diseases and dementia.

The group observed that when AgRP gene expression was increased in the brains of the knockout mice, there was a subsequent increase in food intake and reduction in energy expenditure.