Disordered fat storage enhances development of type 2 diabetes

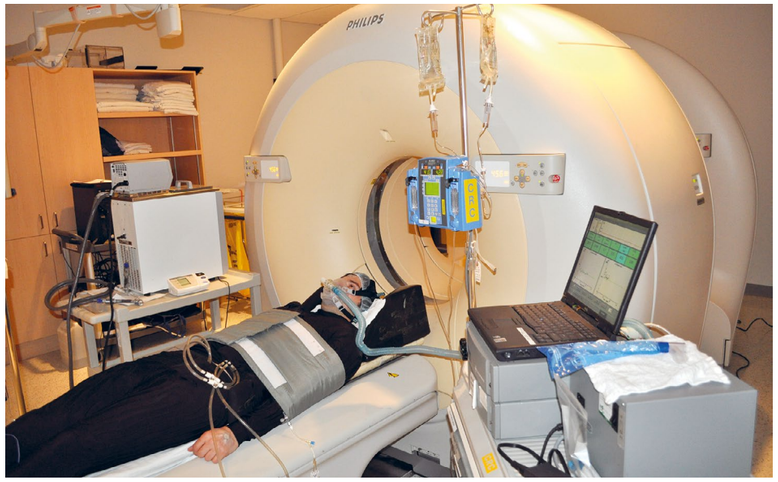
Diabetes is a devastating, life-changing condition. **Professor André Carpentier** and his colleagues from Université de Sherbrooke are exploring how obesity increases the risk of type 2 diabetes. After all, abnormal fat storage can lead to insulin resistance, which endangers organ function. Through his and his team's research, Dr Carpentier aims to develop therapeutic measures which reverse detrimental pre-diabetic effects.

In 2015, diabetes mellitus was the sixth leading cause of death worldwide. This chronic metabolic disorder results in insufficient glucose uptake from the blood, due to abnormal insulin activity. Pancreatic cells secrete the hormone insulin into the blood where it triggers skeletal muscle, liver and fat cells to absorb and store glucose. Irregular insulin activity can lead to hyperglycaemia (high blood glucose levels) which in the long-term can cause kidney disease, cardiovascular complications, foot ulcers and eye damage.

Insufficient insulin activity arises from either: i) an autoimmune response, leading to a loss of pancreatic cells and dangerously low insulin levels (type 1 diabetes), or ii) cells that become insulin resistant and are unable to respond to insulin signals with an inability of pancreatic cells to compensate by secreting enough insulin to counter this insulin resistance (type 2 diabetes [T2D]). Environmental factors such as obesity, smoking or a high, low-quality fat and carbohydrate diet all increase the risk of T2D development.

Although preventable, T2D is much more common, accounting for 90% of all diabetes cases worldwide – a statistic that is increasing rapidly. Globally, T2D cases have quadrupled since 1980 and currently 8% of the global population suffer from it. Increasing incidence rates are also costly, with direct medical costs for T2D exceeding $825 billion globally.

Clearly, there is an urgent need for therapeutic options to prevent T2D progression at the pre-diabetes stage, where blood glucose levels are high, but do not cross the 'diabetic' threshold. Professor Carpentier and his team are therefore researching how obesity-related abnormal fat storage/metabolism drives insulin resistance. Through this research, the team have been able to explore innovative measures to prevent T2D.



A healthy individual undergoing a study to measure brown adipose tissue (BAT) metabolic response to acute cold exposure using positron emission tomography coupled to computed tomography (PET/CT), indirect calorimetry and various metabolic tracers administered intravenously

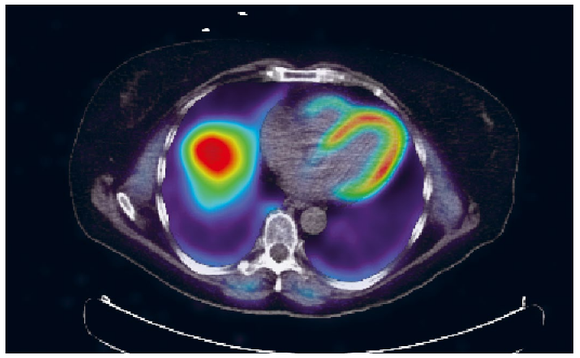
DIET-RELATED INSULIN RESISTANCE

Studies have shown that there is a strong link between a diet high in saturated fat and insulin resistance. Although the exact mechanisms are unknown, evidence suggests that the disordered storage of dietary fatty acids (DFA) in white adipose tissue (WAT) plays a key role. WAT is an extremely dynamic energy store and over-nutrition can result in adipose tissue remodelling. Adipocytes can then undergo drastic alterations in number, size and metabolic activity. Despite adipose tissue expansion, DFA storage efficiency per mass of adipose tissue is significantly lower in obese individuals, compared to healthy individuals. Consequently, lean tissues such as the heart, liver and skeletal muscles are overexposed to fatty acids, which leads to lipotoxicity, organ dysfunction and insulin resistance.

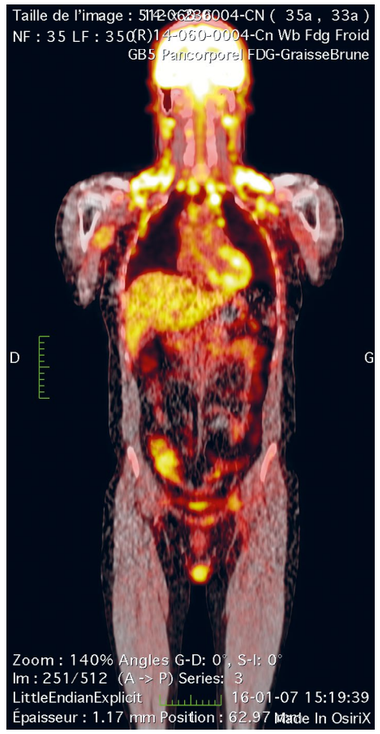
PET IMAGING

To investigate altered fat distribution, Professor Carpentier used an innovative molecular imaging tool to quantify organ-specific DFA partitioning. Previously, isotropic tracers have been used to assess organ-specific DFA uptake. Radioactively labelling DFA enables detectors to track movement and deposition location. However, isotropic tracers have several limitations: firstly, this method cannot be applied to all skeletal muscle/adipose tissues simultaneously, limiting the measurement of whole body DFA partitioning, and secondly, isotopic tracers are invasive, making it challenging to study internal organs such as the heart.

Inspired by their promising results, Professor Carpentier and his colleagues are now exploring other mechanisms to prevent development of type 2 diabetes



An axial view of the heart using PET/CT after intravenous injection of 11C-palmitate, a free fatty acid tracer. Incremental tracer uptake is depicted using a blue to red color scheme (low to high uptake)



Coronal view of PET/CT acquisition after intravenous injection of 18Fluorodeoxyglucose, a glucose tracer, during acute cold exposure. The bright yellow areas depict regions with high glucose uptake, including the brain, supraclavicular brown adipose tissues, the heart, and the liver

However, Professor Carpentier's method of using non-invasive PET (Positron Emission Tomography) imaging overcomes these limitations. PET is a sensitive imaging technique which can detect tiny (picomolar) tracer concentrations. Professor Carpentier performed a study in which healthy subjects were orally administered the radioactively labelled tracer FTHA (14-R,S-F-fluoro-6-thia-heptadecanoic acid), a long-chain fatty acid analogue. Sequential, whole-body PET acquisition was then performed over six hours. During this period, all tracer movements were recorded as a three-dimensional image to highlight whole-body tracer partitioning. Essentially, this allowed DFA fat storage in different tissues and organs to be measured. Results showed that in healthy men, DFA storage was high in the liver and heart. However, skeletal muscles and subcutaneous adipose tissue storage contained relatively low levels of DFA per volume of tissue.

Professor Carpentier also investigated DFA partitioning in brown adipose tissue (BAT). The function of BAT is thermoregulation via thermogenesis – heat generation by oxidation of fat stores to raise body temperature. Subjects were administered oral FTHA and exposed to low temperatures of 18°C. PET imaging results confirmed that BAT does uptake DFA during cold exposure. However, BAT DFA partitioning per volume of tissue was around 83% lower than the liver and 55% lower than in the heart, contributing to only 0.3% of total body DFA clearance.

DISORDERED FAT STORAGE

The team also explored organ-specific DFA partitioning per volume of tissue in pre-diabetic and obese (with normal glucose levels) subjects. Interestingly, results support the notion that a pre-diabetic state results in ineffective adipose DFA tissue storage, which is strongly related to obesity. In terms of lean organ partitioning, DFA storage did not differ between healthy, obese and pre-diabetic individuals for the liver or skeletal muscle. However, Professor Carpentier found that cardiac DFA uptake is significantly greater in pre-diabetic individuals. In both healthy and obese individuals, 2–3% of DFAs are stored in the heart. However, this rises to 4% in pre-diabetic individuals, which can lead to severe cardiac complications, such as left ventricular dysfunction, and potential heart failure. Although this finding is alarming, Professor Carpentier showed that by making lifestyle changes leading to a modest reduction of body fat, this can reverse DFA channelling to the heart. Inspired by this promising result, Professor Carpentier and his colleagues are now exploring other mechanisms to prevent T2D from developing.

BARIATRIC SURGERY TO TREAT T2D

Bariatric surgery is where the stomach is reduced in size by stapling and the small intestine bypassed, limiting food intake and intestinal fat absorption. The team investigated the benefits of bariatric surgery in terms of improved WAT activity and reduced overexposure of lean tissue to DFA in obese individuals with and without T2D. Twelve months following bariatric surgery, on average, an excess weight loss of 85% was achieved. Furthermore, all T2D subjects were in partial or complete remission after three months following surgery. This is due to improved insulin sensitivity in accordance with increased weight loss, better fatty acid handling by lean tissues, and significant reduction of WAT cell size.

FUTURE RESEARCH

Overall, Professor Carpentier and his team have greatly contributed to advancing our knowledge of how abnormal fat distribution enhances the risk of T2D development and how preventative mechanisms such as bariatric surgery can reverse these detrimental effects. However, several questions remain unanswered. For example, why is DFA channelling to the heart increased in pre-diabetic individuals and whether it could be targeted to reduce the risk of heart failure, and how exactly does lean tissue lipotoxicity result in insulin resistance?

Professor Carpentier and his team have greatly advanced our knowledge of how abnormal fat distribution enhances the risk of type 2 diabetes development

Q&A

How does excess fat cause insulin resistance?

Many mechanisms have been described including: 1) intracellular accumulation of reactive fat metabolites such as diacylglycerols and ceramides; 2) mitochondrial fatty acid overload with increased production of reactive oxygen species (ROS); 3) endoplasmic reticulum stress that also may lead to exaggerated ROS production; 4) changes in phosphorylation of the insulin signalling pathways by activation of cellular inflammation; and 5) activation of Toll-like receptors, triggering cellular inflammation pathways. In general, saturated fats have more profound effects on these pathways than unsaturated fats.

What cardiac complications could result from increased pre-diabetic channelling of fatty acids to the heart?

We and others have observed higher cardiac oxygen consumption, but reduced glucose utilisation when fat utilisation by the heart was increased. This may lead to enhanced susceptibility of the heart to lack oxygen when its blood flow is hampered. It may also lead to intracellular acidification, leading in turn to chronic heart damage. In our studies, whenever cardiac DFA uptake was enhanced, we found reduced cardiac pumping of the blood.

Why is PET imaging advantageous to observe abnormal fat metabolism?

PET is the most sensitive imaging modality to non-invasively detect labels administered into the body. With proper setup and expertise, one can design almost any labelled molecule that can then be detected by PET in any organ of the body. Because PET is so sensitive, you can safely administer very small amounts of these labels that are chemically altered to suit the needs of the investigations pursued. With PET, you also are not limited to one organ or tissue, but you can simultaneously study the uptake and metabolism of your preferred PET label in all tissues in the field of view of your scanner. That makes PET an ideal tool for multi-organ integrative metabolic studies.

Could diet-induced thermogenesis help to prevent type 2 diabetes?

This is an important question to which we still do not have a definitive answer. In animal experiments, there is a strong body of evidence that brown adipose tissues (BAT) may strongly increase energy expenditure and reduce the metabolic abnormalities leading to type 2 diabetes. In rodents, there is also strong evidence that BAT is an important effector of diet-induced thermogenesis. In humans, we now know that BAT can utilise DFA and, therefore, may somewhat contribute to energy expenditure occurring after meals. We however found that, at least during cold exposure, the relative contribution of BAT is small. There are many limitations to current work, however, including the fact that no one, including our group, is able to precisely quantify the total volume of BAT in the body. Therefore, the precise contribution of BAT thermogenesis may at the moment be severely underestimated, especially in individuals suffering from obesity and type 2 diabetes. This is the next outstanding question that needs to be addressed in the field of human BAT research.

What are your research goals over the next five years?

In addition to quantifying more accurately BAT thermogenesis in individuals with obesity and type 2 diabetes, our major goals will be to establish the mechanisms of enhanced cardiac DFA uptake in men and women with pre-diabetes and whether this functional biomarker can be used to successfully predict and monitor the benefits of nutritional, pharmacological and surgical interventions to treat type 2 diabetes.

The quantification of BAT thermogenesis and DFA organ-specific partitioning may serve as functional biomarkers leading to more individualised preventive and therapeutic approaches of people at risk of suffering from type 2 diabetes and its complications.

Detail

RESEARCH OBJECTIVES

Professor Carpentier's research interests include: 1) the role of postprandial fatty acid metabolism in the development of type 2 diabetes and cardiovascular diseases; 2) the investigation of brown adipose tissue metabolism in diabetes; and 3) the anti-diabetic mechanisms of bariatric surgery.

FUNDING

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BIO

Professor Carpentier is the recipient of the GSK Research Chair in Diabetes of Université de Sherbrooke and professor, endocrinologist-lipidologist and clinician scientist in the Departments of Medicine, Faculty of Medicine at the Université de Sherbrooke. He is also the director of the university's Centre de recherche sur le diabète, l'obésité et les complications cardiovasculaires.

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