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OVERVIEW

Inflammation, ectopic fat and lipid metabolism: view from the chair

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How meals containing large amounts of lipids induce insulin resistance in the short and long term remains a topic of intense research. Speakers of the afternoon session showed recent findings on the modulation of mitochondria-induced oxidative stress by energy substrates, both in chronic and acute (single high-fat intake) contexts, which have enabled a better understanding of insulin action at the molecular and cellular levels. These advances are highly amenable to being combined with innovative, elegant imaging techniques to look at the fate of these energy substrates at the *in vivo* level within optimally defined experimental protocols, both in human and nonhuman models.

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Whereas the clinical effects of high-fat feeding have been the subjects of research over a long time, the detailed mechanisms of its deleterious impact on health remain obscure partly because of a lack of very precisely controlled experiments. The afternoon session of the symposium was specifically focused on the dissemination of innovative developments regarding tools and data to decipher how changes in energy metabolism in response to a lipid load influence insulin sensitivity and oxidative stress. An impressive panel of outstanding scientists has highlighted how novel molecular, imaging and clinical tools have led to a largely redefined view of lipid metabolism.

Dr Darrell Neufer, Director of the East Carolina Diabetes and Obesity Institute (Greenville, NC, USA) started the session by offering a state-of-the-art presentation on how delicate shifts in respiration influence the oxidative status. By studying the bioenergetics of isolated mitochondria or permeabilized muscle fibers, Dr Neufer confronted two theories of why mitochondrial fat oxidation might be beneficial in one condition and bad in another. Indeed, it has long been recognized that increasing lipid oxidation (through physical exercise for example) is associated with improved mitochondrial oxidative phosphorylation and insulin sensitization. However, increased mitochondrial activity also stimulates the production of reactive oxygen species, especially hydrogen peroxide (H_2O_2), a powerful byproduct that has been shown to be a causal link in the etiology of inflammation and insulin resistance.[1] This paradox might be explained by novel insights[2] into the established concept[3] of incomplete fuel oxidation, which triggers a rise in the levels of partially oxidized acylcarnitines and lipid intermediates (for example, ceramides).[4,5] These incompletely oxidized molecules could be, in large part, responsible for the increase in H_2O_2. In light of these findings, it is not surprising that mechanisms to force complete fuel oxidation have become an important target of research for the development of agents that improve insulin sensitivity.

Dr André Carpentier, from the Université de Sherbrooke (QC, Canada), conducted clinical studies in which he took advantage of experimentally coupling ingested specific radiolabeled energy substrates to positron emission tomography (PET)/computed tomography (CT) imaging. Dr Carpentier elegantly illustrated that defects in the capacity of white adipose tissue (WAT) to properly handle dietary lipids leads to a diversion of fatty acids toward being partitioned into lean organs such as the heart.[6] As expected, insulin resistance (and diabetes), WAT localization (visceral versus subcutaneous) and the amount of fat in a meal greatly influence the extent to which WAT takes up and retains fatty acids. However, the nutrient composition of the previous meal also accounted for large differences in the response to a single high-fat load (see also below). By teaming up with Drs Denis Richard (Université Laval) and François Hamman (University of Ottawa), Carpentier took advantage of the technical advances of PET/CT to study fuel utilization in what was suspected to be brown adipose tissue (BAT). Without the quantification of molecular markers such as UCP1 expression, BAT is difficult to ascertain in human patients. The three researchers based their PET analysis on the assumption of increased BAT activity (and thus fuel uptake) upon cold exposure, which was achieved via a special suit to reduce the subject's body temperature while avoiding shivering. Under such conditions, cold exposure resulted in a net consumption of only 1% of circulating fatty acids but also in a clear-cut reduction in BAT triglyceride content,[7] suggesting that brown adipocytes can rapidly recruit from TG stores and synthesize most of their fatty acids for intracellular energy requirements. This appears to be unlike what occurs in rodents, in which BAT avidly takes up circulating lipids and robustly contributes to an acute reduction in triglyceridemia in such conditions.[8,9] Whether this apparent species specificity is due to fundamental metabolic or molecular disparities or the simple consequence of mass action (amount of BAT per unit body weight) remains to be determined.

In addition, using the PET/CT technology coupled to radiolabeled lipid substrates, Dr Elizabeth Parks, Associate Professor at the University of Texas Southwestern Medical Center, went on to show a complex interplay between dietary fat, enteral lipid metabolism and the development of fatty liver disease. Dr Parks thoroughly demonstrated that meal consistency (solid vs liquid), activation of taste receptors and lipid composition of the previous meal all had a robust impact on the enteral fate of ingested fat.[10]

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In total, approximately 15% of fat from the previous meal appears to reside within the enteral wall, and this pool is released upon intake of the next meal and is found in circulating chylomicrons. This release occurs with either a sham (no calorie) or a real meal, which strongly suggests an important neuroendocrine control system in the regulation of intestinal fat absorption in humans. The factors (metabolic, endocrine or nutritional) that modulate the capacity to retain lipids in the intestinal tract and to regulate subsequent fat absorption or excretion may be considered potential targets for drug development. This research also highlights the need for tightly controlled basal conditions when studying postprandial lipid metabolism in patients.

Finally, Dr Michael Jensen (Mayo Clinic, Rochester, MN, USA) concluded the afternoon session by reviewing the scientific evidence highlighting the effects of a high-fat diet on the development of insulin resistance. Whereas it is established that chronic intake of such a diet diminishes insulin sensitivity by approximately 10%, Dr Jensen illustrated that this effect is largely due to early events in the liver that are caused by an overload of lipids, which not only disturbs lipoprotein metabolism but also stimulates the production of inflammatory markers. Within an acute time frame, however, a single high-fat meal appears to have a very mild impact on insulin sensitivity *per se*, at least in healthy lean individuals. In susceptible (diet-induced or genetically programmed), insulin-resistant patients, the fate of ingested lipids is tissue specific and adipose depot specific.[11,12] These findings suggest that, contrary to a high-fat meal, chronic high-fat feeding reprograms highly metabolic tissues in the long term, which is likely due to profound changes in their transcriptional profile.

Overall, the findings presented during the afternoon session obviously raise several questions. First, the issue of ectopic fat accumulation needs to be placed quite early in the events that lead to the development of insulin resistance and tissue reprogramming. However, sustained research efforts are still required to understand the molecular and biochemical disturbances in adipocytes that trigger an incapacity of WAT to deal with lipid overload, which in turn leads to fatty acid overspill in lean tissues. This is important not only in the liver but also, significantly, in skeletal muscle as well, in which the accumulation of diacylglycerols has been put forward as a key mechanism for reduced insulin-stimulated glucose uptake.[13] Second, although not a specific topic of the symposium, how high-fat meals induce a dysfunctional unfolded protein response in the endoplasmic reticulum remains to be more fully understood. Resolving this issue might reconcile some divergent views on the acute and chronic responses to high-fat feeding. Third, the very elegant technical advances presented in this session could be used in many research areas discussed in the morning session. For example, the fate of lipids as measured by PET/CT imaging could be used in nonhuman primates and their fetuses/progeny[14] to better pinpoint the mechanisms related to epigenetics and transmission of metabolic information to the next generation. PET/CT could also be used to monitor how changes in membrane lipids, energy metabolism and mitochondrial fuel oxidation are linked with brain disorders such as autism.[15,16] From the chair's perspective, these ideas should be tackled by interdisciplinary teams, who could undoubtedly benefit from the vast and robust expertise of the speakers.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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