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The Tuesday Report: The obesity challenge

Obesity and its associated complications of diabetes and fatty liver disease represent key challenges globally. According to the World Health Organization, obesity has more than doubled since 1980, with about 2 billion adults overweight, and over 600 million obese.[1] Moreover, statistics for childhood obesity are even more frightening, with 42 million children under the age of 5 considered overweight or obese (2013 data).[1] Yet obesity is preventable, as discussed in the Joint International Chair on Cardiometabolic Risk (ICCR) and EAS session (*more later*).

Additionally, do novel insights from lipid biology offer therapeutic potential? This was the focus of presentations at Tuesday's plenary session. **Professor Rudolf Zechner (Institute of Molecular Biosciences, University of Graz, Austria)** discussed whether lipolysis, specifically adipose triglyceride lipase (ATGL), may represent a potential target for the management of metabolic disease. There are a number of lines of evidence to support this approach, including animal studies showing that ATGL knockout mice have significantly less body fat, are highly insulin sensitive on a high fat diet, and decreased lipogenesis in white adipose tissue (WAT). Additionally, in cancer patients, cachexia is associated with increased lipolysis. However, ATGL deficiency in humans has also been associated with severe cardiac steatosis and cardiomyopathy.[2] He described recent findings with the atglistatin, a competitive, reversible ATGL inhibitor, with effects specific for the mouse. Atglistatin-treated mice were resistant to high-fat diet induced obesity, due to a combination of effects including reduction in lipid synthesis, adipocyte size, and WAT inflammation, and improved insulin sensitivity. Moreover, atglistatin-treated mice were resistant to high-fat diet -induced fatty liver disease with no evidence of ectopic fat accumulation or cardiac steatosis. These findings therefore support the hypothesis that lipolysis has potential as a therapeutic target, although much remains to be done in bringing this approach to the clinic.

Another possibility may involve targeting browning of WAT, as discussed by **Professor Jörg Heeren (University Medical Center Hamburg Eppendorf)**. Brown (and beige) adipose tissue (BAT) is thermogenic, and this capacity is known to be stimulated by exposure to cold and beta-3 agonism.[3] However, increasing age and body fat are both inversely related to the thermogenic capacity of BAT. Studies in mice have shown that these thermogenic tissues can also control plasma glucose levels and triglyceride metabolism, as well as correct hyperlipidaemia in APOA5 deficient mice, suggesting potential benefit in the context of metabolic health. Initial studies using nanotechnology approaches have shown that activation of BAT is associated with increased uptake and internalization of triglyceride rich lipoproteins, increased uptake of cholesterol, stimulation of insulin release, promotion of bile acid synthesis and excretion via the alternative pathway, as well as potentially favourable effects on the gut microbiome. Improved understanding of the underlying mechanisms that contribute to the function of BAT in humans may offer new therapeutic potential for weight loss, insulin resistance and hyperlipidaemia and global improvement of metabolic health.

Fibroblast growth factor-21 (FGF21), an endocrine growth factor, may offer exciting therapeutic possibilities, according to **Professor David Mangelsdorf (University of Texas Southwestern Medical Center, Dallas, USA)**. Beyond an established role in regulation of energy homeostasis, emerging data suggest that FGF21 may mediate central effects that influence nutrient intake, as well as preference for sweet foods and alcohol. In a genome-wide meta-analysis of a population-based discovery cohort, the

locus for FGF21 was associated with carbohydrate and fat intake suggesting that FGF21 may affect nutrient preference.[4] Additionally, there is evidence from animal studies that FGF21 administration reduces sweet and alcohol preference, via a mechanism involving the FGF21 co-receptor β-Klotho in the central nervous system, and this was correlated with reduction in dopamine concentrations in the nucleus accumbens.[5] Given that FGF21 may play a role in reward behaviours in humans, targeting the liver-to-brain hormonal axis may suggest novel therapeutic possibilities for management of metabolic health.

Anitschkow Award Recipient Professor Peter Carmeliet also discussed *'Angiogenesis and endothelial cell dysfunction in atherosclerosis: a novel target for treatment.'* This will be the focus of a separate report.

Returning to lifestyle…

While the search for novel treatment targets clearly has a role, in the Joint ICCR-EAS session, **Professor Jean Pierre Després (Centre de recherche de l'Institut universitaire de cardiologie et de pneumologie de Québec, and Université Laval, Québec City, Québec, Canada)** made the case for refocusing on lifestyle. *'The approach to cardiovascular disease management is inefficient and costly. We need to refocus on lifestyle approaches.'* Notably, four common lifestyle risk factors – smoking, excessive alcohol intake, poor diet and lack of physical activity – are associated with four disease clusters, cardiovascular disease, cancer, chronic pulmonary diseases, and diabetes, that account for about 80% of deaths from non-communicable disease.[6] Indeed, a sedentary lifestyle causes more deaths than smoking.[7] Given this scenario, this should be the renewed focus for preventing obesity and cardiometabolic disease. *Professor Després provides an overview in an interview on the EAS website.*

A hot topic at the moment is nonalcoholic fatty liver disease (NAFLD), with prevalence escalating across the world, especially in the Middle East and Asia. **Professor Marja-Riitta Taskinen (Cardiovascular Research Group, Heart and Lung Centre, at Helsinki University Central Hospital, Finland)** gave a brief overview of the pathogenesis of NAFLD, for which increased de novo lipogenesis (DNL) is a key feature. Importantly, NAFLD associates with a myriad of related cardiovascular manifestations, including coronary heart disease, heart failure, aortic valve sclerosis, and atrial fibrillation. Cardiac steatosis is characterized by ectopic fat accumulation in the epicardial and pericardial spaces and in cardiomyocytes, and results in cardiac dysfunction and eventually, heart failure. '*Cardiovascular disease is a major killer in patients with NAFLD; put more simply, fatty liver leads to a broken heart,'* commented Professor Taskinen. A number of putative mechanisms link NAFLD and cardiovascular disease, including those mediated by insulin resistance and dysglycaemia, atherogenic dyslipidaemia, inflammation, oxidative stress and hypercoagulability. However, further work to dissect the exact mechanisms linking NAFLD, type 2 diabetes and cardiovascular disease is an urgent priority given the ongoing pandemic of cardiometabolic disease.

References

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