Pharmaceutical potential of inhibition of mitochondrial fat oxidation in skeletal muscle to treat obesity and diabetes

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Fatty acids are the primary fuel source for skeletal muscle function. On the different hand, impaired fatty acid oxidation is related with insulin resistance. To inspect the function of mitochondrial fatty acid oxidation in the development of obesity and obesity-related insulin resistance, we created a mouse model by deleting Carnitine palmitoyltransferase-1b particularly in skeletal muscle (Cpt1bm-/-). CPT1B is enzyme that transports long-chain fatty acid into mitochondria, consequently it is integral for β-oxidation in muscle. Since Cpt1b-deletion impaired fatty acid oxidation, we predicted Cpt1bm-/- mice to be overweight and diabetic. Surprisingly, Cpt1bm-/- mice take place extended glucose utilization and are resistant to diet-induced obesity. We determined that inhibition of mitochondrial fatty acid oxidation induces FGF21 expression specifically in skeletal muscle and FGF21 increases glucose uptake in muscle in a paracrine manner. Furthermore, secretion of FGF21 from muscle will increase circulating FGF21 level, as a result acts systemically redesigning metabolism in white adipose tissue. However, FGF21 seems partly responsible for the phenotype of resistant to obesity in Cpt1bm-/- mice. Also, we discovered that AMPK and Akt1 signaling pathways are concerned in the induction of FGF21 in Cpt1b-deficient skeletal muscle. Altogether, our findings advocate that pharmacologically targeted CPT1b inhibition particularly in skeletal muscle could trigger favorable adaptive responses, ensuing in extended glucose uptake and decreased fat mass.

Obesity is defined as atypical or excessive fats accumulation in the adipose tissue and other organs. The World Health Organization (WHO) defines obese as a body mass index (BMI; calculated as weight [kg] divided via height squared [m2]) equal to or higher than 25 kg/m² and chubby as a BMI equal to or higher than 30 kg/m². Current lifestyle traits and continuous nutrient excess are inflicting obesity to enlarge at alarming rates, specifically in younger people. There are greater than 500 million obese humans worldwide and, more importantly, overweight and weight problems are the fifth main risk for demise globally. Humanity is facing a new epidemic already dubbed “Prosperity's Plague”. Therefore, vast research is wanted in the race to find effective remedies and to minimize the huge charges of the related healthcare.

Weight acquire is influenced through numerous factors, such as genetics, maternal and perinatal environment, energy-dense diets, and sedentary lifestyle. Of high-quality subject are the concurrent and parallel will increase in the occurrence of pathological prerequisites associated with obesity, which consist of insulin resistance, type two diabetes, cardiovascular disease, non-alcoholic fatty liver, polycystic ovary syndrome, asthma, Alzheimer's disease, and some types of cancer. Elucidating the motives worried in the pathophysiology of obesity-related problems is one of the most fundamental endeavors in present day scientific research.

Several mechanisms have emerged in the previous two decades, for the duration of which obesity and mainly its connection to insulin resistance have emerge as a top-interest lookup subject matter being studied by using main agencies in the field. The pathophysiology of obesity-induced insulin resistance has also been correlated with an expand in circulation and tissue infection originating in the adipocyte injury and infiltration of immune cells. As fats accumulates in adipose tissue, adipocytes overcome their healthy size restrict and launch inflammatory cytokines and molecules regarded as adipokines. The immoderate accumulation of lipids in the adipose tissue leads to adipocyte hypoxia, endoplasmic reticulum (ER) stress, and mobile phone death, and motives FA spill over. Infiltrated immune cells additionally contribute to this chronic low-grade inflammatory milieu, whereby the amplify in inflammatory cytokines causes insulin resistance elsewhere in the body. Thus, anti-inflammatory strategies become central as feasible new redress of insulin resistance and different problems of obesity.

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