Decreased energy intake versus increased lipolysis in the prevention of type 2 diabetes

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A World Health Organization report says that taxing sugary drinks can lower consumption and reduce obesity and type 2 diabetes. Reduced consumption of sugary drinks means lower intake of calories overall and fewer people suffering from obesity and diabetes. It is well known that obesity results from increased energy intake and decreased energy expenditure. In the past decade, most of anti-obesity agents, however, have the inhibitory effect on energy intake rather than the stimulatory effect on energy expenditure. A high dose of liraglutide (3 mg), a human glucagon-like-peptide-1 (GLP-1) analog, which treats type 2 diabetes, was recently approved by the European Medicines Agency and United States Food and Drug Administration for weight reduction in human obesity [1]. The novel mechanisms by which liraglutide reduces obesity and hyperglycemia have been recently elucidated.

Systemic administration of liraglutide decreases food intake, body weight, and blood glucose levels independently of insulin and glucagon in obese and diabetic KKA’ mice with ectopic overexpression of agouti peptide, an endogenous melanocortin-4 receptor antagonist [2]. On the other hand, despite remarkably increased plasma active GLP-1 levels, the ingestion of alogliptin, a selective dipeptidyl peptidase-4 (DPP-4) inhibitor, has no effects on food intake, body weight, and blood glucose levels in KKA’ mice [2]. The anti-diabetic effect of liraglutide therefore results from the decreased energy intake rather than the insulinotropic action in KKA’ mice. Recent report by Nagakubo et al. also supported this evidence and demonstrated that the anti-diabetic effect of liraglutide results from the inhibitory action of food intake in diabetic WK/BKD rats with obesity and insulin deficiency [3]. Thus, liraglutide and the DPP-4 inhibitors can have different actions on diabetes and obesity.

Central GLP-1 receptors reportedly mediate body weight and anorectic effects of liraglutide [4] and central injection of liraglutide reduces body weight via decreased energy intake rather than increased energy expenditure in mice [5]. Although recent reports suggested that proopiomedullin (POMC) and cocaine and amphetamine-regulated transcript (CART) in the arcuate nucleus of the hypothalamus largely mediate chronic administration of liraglutide-induced feeding suppression in rats or mice [6,7], the anorectic effect of liraglutide actually occurs within 1 hour after the administration in mice [8]. The acute anorectic effect of liraglutide does not require functional leptin receptor, serotonin, and hypothalamic POMC and CART activities in mice [8].

In the white adipose tissue of obese mice, expression of β-Klotho, fibroblast growth factor receptor (FGFR)-1c and 2c, which bind FGF21, is decreased. Treatment with mouse monoclonal FGFR2-IIIc antibody suppresses body weight gain and epididymal white adipose tissue weight by increased lipolysis in KKA’ mice while having no effect on daily food intake, blood glucose levels, and the expression of uncoupling protein-1, uncoupling protein-2 or peroxisome proliferator-activated receptor-γ coactivator 1a in the epididymal white adipose tissue [9]. These findings suggest that the reduction of weight gain and adiposity induced by increased lipolysis without decreased energy intake might not lead to the prevention of type 2 diabetes. Reduced consumption of calories overall including sugary drinks will be beneficial for the prevention of type 2 diabetes.

References


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Received: December 04, 2016; Accepted: December 17, 2016; Published: December 20, 2016