Carbohydrate-induced weight gain models for diabetes research: Contribution of incretins and parasympathetic signal

Carbohydrate includes both fibers and sugars. There are many types of sugars: monosaccharides, such as glucose and fructose; disaccharides, such as sucrose; and polysaccharides, such as starch and dextrin. Excess intake of sugar causes obesity; since 2015, the World Health Organization has recommended reducing daily intake of free sugars, such as glucose, fructose, sucrose and table sugar to <10% of total energy. In contrast, the mode of administration of sugar has been shown to play an important role in bodyweight gain. When sucrose is provided to mice as liquid, they readily gain bodyweight, but when the equivalent amount of sucrose is taken in solid form, the mice show little or no bodyweight gain. Although energy intake from solid food was decreased in the mice with sucrose in their drinking water, the total energy intake was increased in the mice fed liquid sucrose compared with that in mice fed solid sucrose. Therefore, the mode of administration of the sucrose is considered to differentially affect sensitivity to sweet taste, postprandial glucose and fructose levels, and the satiety signal to the hypothalamus.

Although studies have shown that a low-carbohydrate diet is effective in reducing bodyweight, a high-carbohydrate diet is not often used for inducing obesity in experimental animals. Rather, a high-fat diet containing 60% fat of total energy that induces inflammation in the hypothalamus is generally used. This is partially because of the difficulty in drastically increasing starch-derived calories in mouse chow, as normal chow already contains 58% starch of total energy. However, a high-starch diet (ST) containing 74% starch, 13% protein and 13% soy oil of the total energy has recently been shown to effectively induce bodyweight gain in mice.

Pancreatic-intestinal hormones play important roles in bodyweight control. Insulin is an anabolic hormone that plays the central role in bodyweight gain. Glucagon, the counterregulatory hormone of insulin in terms of blood glucose homeostasis, is a catabolic hormone that promotes lipolysis, ureagenesis and energy expenditure. The incretins, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1, are also key players in bodyweight control. GIP contributes to obesity by promoting fat deposition in adipose tissue, and glucagon-like peptide-1 analogs have been shown to efficiently reduce bodyweight in patients with type 2 diabetes, mainly through reduction of appetite.

Recently, Maekawa et al. investigated the roles of GIP and insulin in bodyweight gain induced by a high-fat diet and high-carbohydrate (high-starch) diet. In wild-type (WT) mice, bodyweight gain was increased in both mice fed a ST- and moderate high-fat diet (mHFD; starch 58%, protein 13%, soy oil 29% of total energy), which contain considerably less fat than is typically used as a high-fat diet in animal experiments, in comparison with mice fed normal chow (NC; 58% starch, 29% protein, 13% soy oil). Bodyweight and epidydimal fat mass were significantly increased in both ST-fed mice and mHFD-fed mice, compared with those in NC-fed mice. Insulin tolerance test showed that insulin sensitivity was decreased in mHFD-fed mice compared with that in ST-fed mice and NC-fed mice. Bodyweight gain in GIP receptor-deficient (GIPrKO) mice fed mHFD was not significantly different from that in GiprKO mice fed NC, in accord with the pivotal importance of GIP in HFD-induced obesity. In contrast, GiprKO mice fed ST showed 30.1% weight gain compared with that in NC and mHFD-fed GiprKO mice, the ratio of bodyweight gain being almost the same as that in WT mice fed ST, which indicates that bodyweight gain by ST is independent of GIP action.

Glucose-induced insulin secretion in isolated islets was enhanced in WT mice fed ST, in comparison with those in WT mice fed NC or mHFD, whereas the GIP-dependent increase in insulin secretion was highest in mHFD-fed mice when compared with NC-fed and ST-fed mice. The expression levels of Gipr messenger ribonucleic acid in islets of mHFD-fed mice were significantly higher than those in islets of NC- and ST-fed mice. These results show that ST feeding enhances insulin secretion and weight gain independent of GIP signaling in these mice (Figure 1).

Furthermore, ST induces not only obesity, but also an increase in β-cell mass (BCM) and hyperinsulinemia in WT mice (Figure 1). Starch is digested to glucose, and glucose influx to β-cells stimulates insulin secretion. The β-cell adenosine triphosphate (ATP)-sensitive K+ (KATP) channel is composed of Kir6.2 and sulfonylurea receptors. In Kir6.2-deficient (Kir6.2KO) mice, glucose-induced insulin secretion and response to incretins are severely impaired, whereas insulin secretion induced through the vagal nerve is maintained. In addition, blood glucose levels and plasma insulin levels in Kir6.2KO mice are not significantly different from those in WT mice under the ad libitum-fed condition. Furthermore, ST-induced bodyweight gain and insulin secretion under the ad libitum-fed condition are enhanced in ST-fed Kir6.2KO. Thus, the
KATP channel in β-cells is not required for carbohydrate-induced bodyweight gain (Figure 2). Interestingly, voluntary feeding of carbohydrate, but not forced feeding (intragastric nutrient injection through gavage) of carbohydrate, induces insulin secretion in Kir6.2KO mice. These results suggest that insulin secretion during voluntary feeding is mediated by parasympathetic input to the β-cells. The parasympathetic activity is triggered by taste, mastication and swallowing, and induces cephalic phase-mediated insulin secretion through vagal nerve activity in a KATP channel-independent manner. Historically, the concept of cephalic phase insulin secretion was established in the 1970 and 1980s, and has been considered to be only a pre-absorptive phase, triggering a small response by, for example, sweet sensation mediated by the vagal nerve; it is now known that cephalic phase insulin secretion can persist after the post-absorptive

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**Figure 1** | The different mechanisms of bodyweight gain in a fat-rich diet and carbohydrate-rich diet. A chronic high-fat diet increases plasma glucose-dependent insulinoenotropic polypeptide (GIP) levels and potentiates insulin secretion through enhancement of the insulin secretory response to GIP. Thus, GIP plays an important role in high-fat diet-induced obesity. A chronic high-starch diet increases both GIP and insulin secretion, and the surplus insulin secretion due to excessive glucose, the final product of starch, is sufficient for weight gain independent of GIP.

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**Figure 2** | Hypothesis on high-starch diet-induced obesity. A high-starch diet increases insulin secretion by two pathways: one mediated by the parasympathetic nerve, that is, cephalic phase, adenosine triphosphate (ATP)-sensitive K⁺ (KATP) channel-independent insulin secretion; the other due to expansion of β-cell mass by supplemental glucose, the final product of starch, which is KATP channel-dependent.
phase. The excessive secretion of insulin observed in ST-fed Kir6.2KO mice; that is, cephalic phase-mediated insulin secretion, plays a more important role in ST-fed mice than it does in NC-fed mice. In contrast, ST feeding failed to significantly increase BCM and islet number in Kir6.2KO mice. Thus, the parasympathetic signal is insufficient to induce β-cell proliferation under ST feeding, and functional KATP channels might be required for feeding-induced β-cell proliferation (Figure 2).

Although ST feeding for 5 weeks is sufficient to significantly increase BCM and islet number in WT mice without inducing bodyweight change\(^5\), the condition is readily reversed by switching the diet back to NC for 2 weeks. As the mechanism by which carbohydrate intake modulates BCM is not known, the carbohydrate-induced changes in hormonal and autonomic signals\(^6\) should be analyzed in comparison with changes induced by a high-fat diet.

Regarding diabetes prevention and therapy, long-term observational studies focusing on carbohydrate intake and β-cell function are necessary. For most people in the world today, the staple food is rich in starch, and accounts for the major proportion of daily total energy intake. In addition, prediabetes and diabetes are occurring at epidemic levels. Future studies should therefore focus on both the quantity and the quality of carbohydrates in the diet. Although numerous studies in the field of nutritional science focusing on the quality and quantity of carbohydrates, protein, fat, and vitamins and minerals have been carried out, the impact of nutrition on diabetes and prediabetes has not been thoroughly explored to date. The impact of nutrition on islet hormones, incretins, parasympathetic signals and the microbiome requires considerably more detailed analysis.

**DISCLOSURE**

The authors declare no conflict of interest.