Glucose metabolism, diet composition, and the brain
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Chapter 1

General introduction - Part 2
Short-term diet-induced alterations in glucose metabolism
Insulin resistance and diabetes mellitus type 2

As described in part 1, glucose homeostasis is regulated, in part, by multiple brain nuclei to ensure that blood glucose concentrations are maintained within safe boundaries. Despite this central control through activation of neural and humoral pathways, many environmental factors have independent effects on glucose homeostasis. Excessive consumption (energy intake exceeding energy expenditure) of calorie dense dietary components has been shown to disturb glucose homeostasis by altering feedback signals resulting in insulin resistance (an inadequate response to insulin by insulin target tissues (Capurso & Capurso, 2012)) as well as impaired insulin secretion in response to glycemic challenges. Eventually, plasma insulin concentrations are insufficient to maintain glucose homeostasis, and this may eventually result in hyperglycemia, known as type 2 diabetes mellitus (T2DM), which is one of the metabolic disturbances associated with obesity. T2DM is becoming a global epidemic affecting 387 million people (8% of the total human population) and is expected to affect 593 million people around 2035 (www.idf.org). T2DM is proposed to develop in a two-step paradigm. In the first phase, individuals progress form normal glucose tolerance to impaired glucose tolerance, in which insulin resistance is the primary determinant. During the second phase, the impaired glucose tolerance progresses to T2DM, associated with progressive deterioration in β-cell function and further decline in insulin sensitivity (DeFronzo & Abdul-Ghani, 2011).

Almost thirty years ago, it was already proposed that excessive intake of the combination of dietary fat and sugar could be a potent determinant in the aetiology of both T2DM and obesity (Storlien et al., 1988). Recently, it was shown that not only many adults, but also many children exceed the daily recommended intake of saturated fat and sugar-sweetened beverages (Macdiarmid et al., 2009; Ogden et al., 2012). This stresses the importance to understand how the intake of sugar-sweetened beverages and saturated fat affect glucose metabolism, eventually contributing to a better understanding of T2DM development.
Short-term high-fat and/or high-sugar diet-induced dysregulation of glucose homeostasis

High-fat diets

The effects of increased dietary fat on glucose metabolism have been studied extensively in rodent models. For example, early studies showed that pelleted high-fat (HF) diets mainly affect hepatic insulin sensitivity and energy expenditure (Kraegen et al., 1985; Storlien et al., 1986), whereas exchanging a small portion of dietary fat from safflower oil to fish oil prevented insulin resistance development, independent of body weight changes (Storlien et al., 1987), stressing that the source of dietary fat is important in whole body insulin resistance development. A HF diet (safflower oil; 59% of total calories) induced hepatic insulin resistance after 3 days, whereas peripheral insulin resistance appeared after 3 weeks of HF diet feeding (Kraegen et al., 1991a). In these experiments, peripheral insulin resistance developed concomitant with an increase in muscle triglyceride (TG) content, suggesting that local lipid availability is related to insulin resistance (Storlien et al., 1991). In addition, it has been proposed that increased synthesis of diglycerides, also known as diacylglycerol (DAG), mediates the development of insulin resistance when there is increased lipid availability. More recent work showed that feeding rats a HF diet (40% fat of which 32.5% as lard and 7.5% as maize oil of total calories) for only 2 days already reduced insulin sensitivity (Cruciani-Guglielmaci et al., 2005), in absence of body weight changes (fat mass was not assessed). Three days of HF feeding (59% fat of total calories, mainly safflower oil) to rats induced hepatic steatosis, with increased gluconeogenesis, hepatic insulin resistance, increased hepatic DAG content and impaired insulin signalling, reflected by impaired insulin-induced activation of IRS-1 and IRS-2 tyrosine phosphorylation. Accumulation of DAG activates PKCε, which in turn induced hepatic insulin resistance (Samuel et al., 2010). Prevention of hepatic fat accumulation and PKCε activation protected rats on a HF diet from impaired insulin signalling and hepatic insulin resistance (Samuel et al., 2004) and knocking down hepatic PKCε expression prevented lipid induced hepatic insulin resistance despite increased hepatic lipid content. However, these mice also gained less body weight, which may indicate less adipose mass, which may contribute to the rescue of hepatic insulin resistance.

Insulin resistance results in hyperinsulinemia to compensate for the reduced insulin action. Indeed, feeding a pelleted HF diet (40% fat of which 32.5% as lard and 7.5% as maize oil of total calories) to rats for 2 days induces glucose-induced hypersecretion of insulin and insulin resistance (with unaffected basal concentrations of glucose and insulin) (Cruciani-Guglielmaci et al., 2005). Following 7 days of this diet, glucose intolerance developed and after 2 months insulin hypersecretion was lost, associated with a decreased sympathetic tone, and independent of concentrations of TGs or free fatty acids (FFA). This points to effects of the HF diet on the nervous system affecting insulin secretion, which are independent of concentrations of TG or FFA.
Within the pancreatic islets of Langerhans, insulin hypersecretion is associated with increased β-cell proliferation and increased β-cell mass. Stamateris *et al.* (2013) observed enhanced β-cell proliferation after 7 days of HF feeding (lard; 60% of total calories) in mice concomitant with impaired glucose tolerance. At this time point, HF diet mice were heavier than control mice. Even 3 days of HF diet feeding (60% calories from fat) resulted in increased β-cell proliferation in C57B1/6J mice, at this point also glucose tolerance and glucose-induced insulin secretion were impaired. B-cell mass increases were apparent after 3 weeks of HF diet feeding. These HF diet fed mice showed weight gain throughout the study in which the increase was largest from week 3-5 (Mosser *et al.*, 2015).

Together, these studies show that short-term feeding of a HF diet can affect insulin sensitivity, insulin secretion and β-cell proliferation in rodents, while a more prolonged period of HF feeding is necessary to increase β-cell mass. However, not all studies report on changes in body weight and changes in adiposity mass are even less reported. This makes it difficult to know whether diet-induced changes in adiposity mass may have independently affected metabolism.

**High-sucrose diets**

Short-term exposure to high sucrose diets and their effects on glucose metabolism have been studied less extensively than HF diets. Long-term (4 weeks) exposure to a pelleted high-sucrose (HS) diet primarily affected hepatic insulin resistance, in which insulin-induced inhibition of hepatic glycogen breakdown was lower in HS (69% carbohydrates of total calories) compared to starch-fed control rats. Moreover, in rats fed a HS diet, glycogenolysis rather than gluconeogenesis accounted for the increase in hepatic glucose production. These observations were independent of changes in body weight or adiposity mass (Storlien *et al.*, 1988). Later studies showed that prolonged (8 weeks) periods of non-liquid sucrose feeding (68% sucrose of total calories) impaired hepatic insulin sensitivity as well as muscle insulin sensitivity independent of a change in body weight or adiposity (Pagliassotti *et al.*, 1994). Moreover, both HS (68% of total calories) as well as low sucrose (18% of total calories) induced hepatic insulin resistance prior to peripheral insulin resistance dependent of the duration of the diet, but independent of a change in body weight or adiposity (Pagliassotti *et al.*, 1996). In addition, high sucrose diets have been shown to induce hyperinsulinemia, increase hepatic PEPCK activity, and increase *de novo* lipogenesis (Pagliassotti *et al.*, 1994), thereby increasing hepatic and muscle lipid overload, independent of changes in body weight (Storlien *et al.*, 1993) and adiposity mass (Thorburn *et al.*, 1989), as well as impairing insulin signalling in muscle tissue (Maegawa *et al.*, 1989). All these mechanism could contribute to sucrose-induced insulin resistance.

Seven days *ad libitum* HS feeding (35% water solution in addition to laboratory chow) caused glucose intolerance and basal hyperglycemia, and after 19 days of sucrose feeding glucose-induced insulin secretion was still not affected (Wilson & Hughes, 1996). This indicates that reduced insulin sensitivity probably contributed to the glucose intolerance and that a longer period (>19 days) of sucrose feeding is necessary to affect insulin
secretion. The latter is in line with longer sucrose feeding studies in which increased islet number, β-cell mass and replication rate were observed following a high-sucrose diet for 30 weeks. After 30 weeks of high-sucrose diet, also body weights were increased (Del Zotto et al., 2002).

Together these studies show that a HS diet, like a HF diet, induces insulin resistance. In contrast to a HF diet, however, a HS diet primarily affects hepatic insulin resistance. In most of the studies, effects on insulin resistance were observed in absence of changes in body weight or adiposity, indicating that intake of sucrose directly induced these effects. Of note, most of these HS studies used prolonged times of dietary exposure, making the comparison between HF and HS diet intervention studies difficult. In addition, there was a wide variance in the use of rodent species, strains and sources of fat and sugar.

**Combined high-fat, high-sucrose diets**

Western style diets that are held responsible for overconsumption, obesity, and insulin resistance/T2DM contain both fat and sucrose. Studying diets that are enriched in both dietary components will elucidate the synergistic underlying effects on glucose metabolism. Although often referred to as a high fat diet, many studies have actually been performed with a HF diet including a considerable amount of sucrose. For example, the most frequently used ‘research diet number D12451’, is a pelleted diet containing 17% sucrose in addition to the 45% fat content. It has been shown repeatedly that long term feeding of this diet results in obesity (Bruckbauer et al., 2012; Huang et al., 2008) and insulin resistance (Coomans et al., 2013; Ellenbroek et al., 2013; Kindel et al., 2011; Kusakabe et al., 2012; Vroegrijk et al., 2013). For example, 12 weeks of feeding diet D12451 results in overall reduced whole body glucose uptake under hyperinsulinaemic euglycaemic clamp conditions and severe liver steatosis (Yew et al., 2010). Short term (≤ 7 days) studies on the combination of dietary fat and sucrose and its effects on glucose metabolism are scarce. One study reports on the use of a cafeteria diet, which resulted in the rapid onset of obesity and hepatic insulin resistance followed by peripheral insulin resistance. Unfortunately caloric intake was not measured in this study making a direct comparison between caloric components and the development of the pathology difficult (Davidson & Garvey, 1993). Furthermore, the investigators did not distinguish between the role of obesity and the direct effects of the nutrients on glucose metabolism.

With respect to β-cell function, twelve weeks of D12451 diet feeding induced glucose intolerance with an increased, yet inadequate insulin response in C57BL/6J mice. Moreover, β-cell proliferation of islets from the splenic region of the pancreas was increased compared to islets from the duodenal and gastric region. In addition, isolated splenic islets showed a twofold enhanced glucose-induced insulin secretion compared to islets from the duodenal and gastric region. This indicated that β-cell adaptation in terms of insulin secretion is affected by a pelleted HFHS diet in a region specific manner (Ellenbroek et al., 2013).
Diet interventions in rodents mainly consist of diets with high energy dense pellets. However, this does not represent a Western-style diet, as outlined above. Furthermore, studies in which the effect of combined saturated fat and sucrose on glucose metabolism have been investigated, followed by dissection of the separate contribution of each palatable component to the metabolic change, are very limited. Therefore free-choice diets offered \textit{ad libitum} with two palatable components, in addition to regular chow and tap water (fcHFHS), better reflect human eating behaviour, and its metabolic consequences. Furthermore, obesity, resulting from this dietary habit, is characterized by persistent hyperphagia, which comprises an increase in meal frequency, meal size or both. Recently, it was shown that rats become hyperphagic when the sucrose component, as part of the fcHFHS diet, is provided in liquid form. In contrast, rats with a free choice to saturated fat and solid sucrose did not become hyperphagic (Apolzan & Harris, 2012). In addition, when the fcHFHS diet is offered as a non-choice, pelleted diet (with equal percentages of saturated fat and sucrose as a rat on a fcHFHS diet would consume), rats are initially hyperphagic, but compensate over time, \textit{i.e.}, they increase meal size, but decrease meal frequency. In this way their feeding behaviour is comparable to fcHF-fed rats, while fcHS rats increase meal frequency, but decrease meal size. Interestingly, fcHFHS-fed rats remain hyperphagic over an identical timespan, in which they increase meal frequency but do not compensate for meal size (la Fleur \textit{et al.}, 2014b). These studies indicate that choice, as well as the form by which the sucrose component is provided, are important in the development of persistent hyperphagia, which is relevant to the development of human obesity.

Using this free choice rodent model, we and others Apolzan & Harris (2012) showed that rats consuming a choice diet consisting of saturated fat, 30% sucrose water, standard pellet chow and tap water (a free-choice high fat, high sugar (fcHFHS) diet) become obese and glucose intolerant within a week (la Fleur \textit{et al.}, 2011). Interestingly, when rats are subjected to a dish of saturated fat only, in addition to chow and tap water (fcHF diet) they gain adiposity mass and increase circulating FFA similar to rats on a fcHFHS diet. However, they do not develop glucose intolerance (la Fleur \textit{et al.}, 2011). In addition, rats that are subjected to 30% sugar water only, in addition to chow and tap water (fcHS diet), consume more sugar water than rats on a fcHFHS diet, but they do not accumulate fat mass or increase circulating FFA, nor do they become glucose intolerant (la Fleur \textit{et al.}, 2011). These data show that dietary composition in a hypercaloric setting independently affects glucose metabolism. Considering the behavioural and metabolic similarities between these rodent models and obese, insulin resistant individuals, the fcHFHS diet is an appropriate animal diet intervention model to mimic diet-induced obesity and insulin resistance, and study diet composition independent effects on glucose metabolism.