Glucose metabolism, diet composition, and the brain

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Chapter 1

General introduction - Scope of the thesis
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When rats overconsume saturated fat and sugar water (fcHFHS) for one week, they rapidly become glucose intolerant. Interestingly, rats that are only overconsuming the fat component (fcHF) for one week, become equally obese but remain glucose tolerant (la Fleur et al., 2011), while rats over consuming the sugar water component (fcHS) do neither develop obesity nor glucose intolerance. The glucose intolerance after consumption of both saturated fat and sugar water is persistent for at least 4 weeks and accompanied by an impaired insulin response and basal hyperinsulinemia (la Fleur et al., 2011).

Taken together, it is clear that dietary composition in a hypercaloric setting independently affects glucose metabolism. In addition, although equally obese, rats on a fcHFHS diet do become glucose intolerant whereas rats on a fcHF diet do not, indicating that additional effects of the fcHFHS diet likely mediate disturbed glucose metabolism. These additional effects may well be located in the brain given the finding that consumption of the hypercaloric choice diets affected hypothalamic brain centers (involved in homeostatic feeding) of rats (la Fleur et al., 2007; van den Heuvel et al., 2014b). As described in part 1 of this General introduction, the hypothalamus is well known for its role in glucose metabolism. Moreover, overconsumption of saturated fat and sugar also affected the corticolimbic system (van de Giessen et al., 2012; van de Giessen et al., 2013; van den Heuvel et al., 2014a). Rats on a fcHFHS diet showed reduced D2/3 receptor availability and encephalin expression in the NAc and lower expression of tyroxine hydroxylase, which is the rate limiting enzyme for dopamine production, in the VTA, i.e., the area that contains the dopaminergic cells that project to the NAc (van den Heuvel et al., 2014a). As reviewed in part 1, the corticolimbic brain areas strongly project to the hypothalamus, and many of the limbic structures contain glucose sensing neurons. I therefore hypothesize that the corticolimbic system itself is also involved in the regulation of glucose metabolism.

The overall aim of this thesis was to investigate in more detail how glucose metabolism is peripherally (i.e., insulin sensitivity and insulin secretion) affected by dietary composition (i.e., hypercaloric choice diets composed of high palatable components), and how glucose metabolism is controlled by brain areas not yet acknowledged in glucose metabolism, but known to be affected by dietary composition.

Aim 1: To characterize free choice high fat and/or high sugar models for insulin sensitivity and insulin secretion.

Aim 2: To investigate whether brain areas in the corticolimbic system, that are affected by hypercaloric dietary components, are involved in regulation of glucose metabolism, independent of diet interventions.

Glucose intolerance occurs in case of reduced insulin sensitivity and/or reduced glucose-induced insulin secretion. The aim of the first part of this thesis was to investigate how insulin sensitivity and insulin secretion contribute to the previous observed glucose
(in)tolerance following saturated fat and/or sugar water consumption. In chapter 2, we assessed whether the previously observed glucose (in)tolerance (La Fleur et al., 2011) in either choice diet group (i.e., fcHF, fcHS, fcHFHS and chow as control) is associated with altered insulin sensitivity. As the measured metabolic response following experimental interventions might depend on the actual feeding condition of the animal, we first fed rats a fcHFHS or chow diet for one week and assessed insulin sensitivity after an overnight fast or in the fed state. The results of this study are described in chapter 3. In chapter 4 we focussed on the early phase glucose-induced insulin response and investigated whether an impaired glucose-induced early phase insulin response, following 4 weeks of fcHFHS diet, can be explained by enhanced insulin clearance. Furthermore, we determined the effects of the fcHFHS diet on insulin content and VIP innervation of the β-cell.

In the second part of this thesis, we focused on the role of the corticolimbic system in glucose metabolism, independent of diet interventions. In chapter 5, we investigated the role of the shell region of the nucleus accumbens (sNAc) -of which its projection to the lateral hypothalamic area is already well appreciated in food intake (Kelley & Swanson, 1997; Stratford & Kelley, 1999)- in glucose metabolism. We electrically stimulated the sNAc using deep brain stimulation (DBS) and showed that this increased systemic concentrations of glucose and glucagon, independent of corticosterone. To further elucidate the potential pathways through which the sNAc controls glucose metabolism, we locally increased either serotonin, described in chapter 6, or dopamine, described in chapter 7, by infusing a selective reuptake inhibitor in the sNAc, using reverse microdialysis. Because sNAc infusion of the selective dopamine reuptake inhibitor vanoxerine in the sNAc strongly reduced endogenous glucose production (EGP), independent of glucoregulatory hormones, we hypothesized that the dopamine sNAc-induced increased activity of the hepatic parasympathetic innervation decreased EGP. Therefore we extended this study by combining sNAc vanoxerine infusion with a selective hepatic parasympathetic denervation (Px) and assessed EGP.

An overview of this thesis is schematically represented in Figure 2.
**Figure 2.** Schematic representation of the outline of this thesis: “Glucose metabolism, diet composition, and the brain”.

Chapter 1, part 1

**Brain**
- Corticolimbic system
- Hypothalamic nuclei

Chapter 5, 6, 7
- DBS
- Serotonin
- Dopamine

Chapter 1, part 2

**Diet composition**
- Free choice diets

**Glucose metabolism**
- Insulin sensitivity
- Insulin secretion

Chapter 2, 3, 4