Autonomic nervous control of white adipose tissue: studies on the role of the brain in body fat distribution
Kreier, F.H.K.

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'The brain has a role in body fat distribution and its associated metabolic diseases' is the general hypothesis of this thesis.

The hypothalamus controls the body by means of pituitary hormones, and only recently we have started to appreciate the contribution of the autonomic nervous system (ANS). In chapters 2-5 we describe a part of the interaction between the hypothalamus and metabolic organs. In chapters 6-8 we discuss the implications of our findings and propose follow-up studies.

The present thesis consists of two main parts: findings and perspectives.

Finding #1
The brain uses two neuronal systems with an antagonistic effect on metabolic organs (chapters 2 and 4)

Finding #2
The brain distinguishes between organs from different body compartments and combines the organs of one body compartment (chapters 2 and 3).

Finding #3
Sex and stress hormones can access central neurons projecting to fat tissue (chapter 5).

Perspective #1
The metabolic syndrome might be a brain disease (chapter 6).

Perspective #2
HIV-associated body fat redistribution syndrome might be a brain disease (chapter 7).

FINDINGS
Chapter 2
Selective parasympathetic innervation of subcutaneous and intra-abdominal fat – functional implications
Fat tissue was reported earlier to be innervated by the sympathetic nervous system only, known for its catabolic effect. For the first time, we demonstrate parasympathetic input from the vagal motor nucleus to fat tissue, clearly modulating its insulin sensitivity and glucose and free fatty acid metabolism in an anabolic way. Moreover, we demonstrate that sympathetic motor neurons in the spinal cord and parasympathetic neurons in the DMV are specialized to project either to intra-abdominal or subcutaneous body compartment only.
Chapter 3
Neuronal tracing from metabolic organs: an autonomic (anatomical) basis for type 2 diabetes
In this chapter we extend the studies of chapter 2 on the specialization of autonomic motor neurons. We show that the same neurons control intra-abdominal organs (intra-abdominal fat, liver, and pancreas), whereas subcutaneous adipose tissue located outside the abdominal compartment receives input from another set of autonomic neurons. This differentiation persists up to pre-autonomic neurons in the hypothalamus, including the biological clock. Thus, pre-autonomic neurons have a distinct organization depending on the body compartment they command. Moreover, we demonstrate a neuronal feedback from adipose tissue that reaches the brainstem.

Chapter 4
Dual sympathetic and parasympathetic hypothalamic output to white adipose tissue
We describe a hypothalamic network behind the sympathetic and parasympathetic branches of the ANS projecting to fat tissue as described in chapter 2. Preautonomic neurons in the suprachiasmatic nucleus (SCN), the paraventricular nucleus of the hypothalamus (PVN) and the lateral hypothalamus (LH) are specialized to project either to sympathetic or to parasympathetic motor neurons. This dual hypothalamic pathway enables hypothalamic centers such as the biological clock, together with temperature and feeding centers, to coordinate adipose tissue physiology.

Chapter 5
Estrogen receptor alpha and glucocorticoid receptor expression in (pre-)parasympathetic neurons that project to fat tissue
Estrogen and glucocorticoids have strong effects on fat tissue metabolism and body fat distribution. So far, the differential effects of these hormones on the abdominal versus subcutaneous fat compartment have not been explained satisfactorily. We describe that a large proportion of neurons in the brainstem (DMV) and hypothalamus (PVN, LH and amygdala) projecting to abdominal fat express the glucocorticoid receptor (GR). In addition, some neurons were double stained for PRV and estrogen receptor (ER) alpha. These findings show, for the first time, that glucocorticoids and estrogens might affect adipose tissue metabolism and distribution indirectly via its autonomic innervation.


DISCUSSION AND PERSPECTIVES FOR FOLLOW-UP STUDIES

Chapter 6
Hypothesis: shifting the equilibrium from activity to food leads to autonomic unbalance and the metabolic syndrome
During the last century, life has changed dramatically in industrialized countries. Food has become abundant, snacking frequency increased and shifted toward the end of the day, and simultaneously, the necessity for physical effort became considerably reduced. Moreover, physical activity no longer needs to coincide with the light period anymore. As a result, the environment sensed by the brain has become metabolically flattened and arrhythmic. From the perspective of a longstanding evolutionary development, this has been an abrupt "environmental mutation." We hypothesize that in such conditions the susceptible brain loses its feeling for internal and external rhythm. Since the brain uses the autonomic nervous system to implement internal rhythmicity, we propose an unbalanced and arrhythmic autonomic nervous system as a major cause of the metabolic syndrome.

Chapter 7
Hypothesis: HIV-associated adipose redistribution syndrome as a selective autonomic neuropathy
Abnormal body-fat distribution in HIV-1-associated adipose redistribution syndrome (HARS) remains unexplained at present. White adipose tissue is controlled by humoral factors and by neural regulation. Sympathetic innervation stimulates lipolysis, whereas parasympathetic innervation has an anabolic influence on white adipose tissue. Results of neuroanatomical studies showed a clear somatotopy with respect to autonomic control of white adipose tissue by both the sympathetic and parasympathetic branch, with separate sets of autonomic neurons innervating either the subcutaneous or the visceral fat compartment. Thus, the CNS is likely to be a key player in the regulation of body-fat distribution. We propose that HARS is mediated by effects of antiretroviral treatment on the CNS and could indicate a change in autonomic balance resulting in redistribution of adipose tissue.

Chapter 8 contains suggestions for follow-up studies.