Neurobiological aspects of obesity: dopamine, serotonin, and imaging
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GENERAL INTRODUCTION
AND OUTLINE OF THESIS
GENERAL INTRODUCTION

Obesity

Obesity is a condition with an excess proportion of body fat. The most commonly used definition for obesity, as defined by the World Health Organization (WHO), is a body mass index (BMI) of \( > 30 \text{ kg/m}^2 \), whereas a BMI between 25-30 \( \text{kg/m}^2 \) is defined as overweight, a BMI between 18.5-25 \( \text{kg/m}^2 \) as normal-weight, and a BMI below 18.5 \( \text{kg/m}^2 \) as underweight. In addition, the category morbid obesity has been used for people with a BMI \( > 40 \text{ kg/m}^2 \).

The growing obesity epidemic is a well-recognized health problem. In the United States, over 30\% of the adult population is obese (1). In the Netherlands, this number has doubled from 5.3\% in 1981 to 11.4\% in 2011 (staline.cbs.nl). The obesity epidemic is not restricted to the Western world (2), but is also increasing in urban areas of some low- and middle-income countries (Fig. 1). Obesity leads to higher mortality and is a major risk factor for diabetes mellitus, cardiovascular diseases, cancers, musculoskeletal disorders, major depression and also Alzheimer's disease (3;4).

The cause of obesity is an energy imbalance, i.e. too much energy intake relative to energy expenditure, leading to accumulation of fat mass in the body. The rise of the availability of palatable food, usually high-caloric food rich in sugars and fat, goes hand in hand with the rise in obesity (5;6) and is considered one of the major causes. Still, the question remains why some people become obese and some do not in this high-caloric environment. This is a complex problem involving amongst others genetic factors and gene-environment interactions that influence metabolic and psychological mechanisms for regulation of food intake.

Neurobiology of obesity

Food intake is regulated by a homeostatic system involving peripheral metabolic signals and by a central system of cognitive, emotional, and reward-related signals in the brain. The homeostatic control system is well armed to control body weight when food is scarce, but in an environment with abundance of food the major control system for food intake is the brain (7). A key region involved in the homeostatic regulation of food intake is the hypothalamus, whereas the corticobulbar regions are important in learning and processing food-related reward and

Figure 1. World map with the prevalence of obesity per country (www.who.int/topics/obesity/en).
exerting cognitive control over food intake (8). It is hypothesized that in obesity the brain reward system is impaired, i.e. obese persons experience less reward from food leading to craving for food and a compensatory increase in food intake (9). Furthermore, it is assumed that obese persons have impaired inhibitory control, resulting in inability to withstand the urge to eat (9). These mechanisms have been compared to the pathophysiological mechanisms in addiction (10). It has even been proposed to include obesity in the DSM-V (fifth edition of the Diagnostic and Statistical Manual of Mental Disorders of the American Psychiatric Association), suggesting that obesity is a brain disorder (11).

A key region of the brain reward system is the mesolimbic pathway from the ventral tegmental area to the nucleus accumbens (part of the ventral striatum). The nucleus accumbens closely communicates with limbic regions involved in emotion and motivation, such as the amygdala and orbitofrontal cortex. Control regions in the brain are located in the prefrontal cortex and anterior cingulate cortex and also directly communicate with the striatum (12). All these regions are involved in the regulation of food intake and dysfunction could play a role in the pathophysiology of obesity. Neurotransmitters provide for the communication between these regions. The most important neurotransmitter in the brain reward system is dopamine, but other neurotransmitters such as serotonin, norepinephrine, opioids, and cannabinoids are also involved in the regulation of food intake.

Dopamine

In the mesolimbic pathway of the brain reward system, the ventral tegmental area is the region where dopamine is produced. From there, dopamine is transported through the axons of the dopaminergic neurons to the ventral part of the striatum, the nucleus accumbens, where it is stored in vesicles until its release into the synaptic cleft. The dopamine signal is then transmitted by dopamine receptors located on the postsynaptic neuron (Fig. 2). After the dopamine D1 receptor, the most abundant receptors in the striatum are the dopamine D2 and D3 receptors (DRD2/3). Synaptic dopamine levels are regulated by dopamine transporters (DATs), which are located on the presynaptic neuron and transport dopamine back into the presynaptic neuron.

![Figure 2. Dopaminergic synapse with dopamine receptors and dopamine transporters. For simplification, dopamine receptors are only drawn on postsynaptic neurons.](image-url)
Dopamine is released in the ventral striatum in response to rewarding stimuli and by cues for a potential reward (13). Food is a potent reinforcer and induces dopamine release after intake (14;15). The DRD\textsubscript{2/3} availability in the striatum is lower in obesity (16). This could mean that obese persons have an impaired reward experience from food due to the lower signal transmission capacity. Also the regulation of synaptic dopamine levels could be impaired in obesity, as the availability of DAT tends to be lower at higher BMI (17), although this is not a consistent finding (18). Knowledge about the striatal dopaminergic system in obesity is still limited, in particular in humans. Therefore, a major aim of this thesis is to increase our knowledge about the striatal dopaminergic system in obesity and test the hypothesis that striatal dopaminergic abnormalities are related to reward deficiency in obesity.

**Serotonin**

The primary brain region for the production of serotonin is located in the raphe nuclei in the brain stem, from where axons project to other brain regions. Similar to the mechanism described for dopamine, serotonin is released in the synapse, its signal is transmitted by serotonin receptors and serotonin is taken back into the presynaptic neuron by the serotonin transporter (SERT).

Serotonin is often associated with mood mainly due to the effectiveness of serotonin reuptake inhibitors as anti-depressants. However, it plays a role in a variety of behaviors and in cognition (19) and an increasing serotonin level inhibits food intake (20). The role of SERT in the regulation of food intake is suggested by the effect of the anti-obesity drug sibutramine, which is a SERT and norepinephrine transporter inhibitor (21). Animal research also demonstrates a role for SERT in hypophagia and obesity (22;23). There is one study suggesting that SERT availability might be related to BMI (24), but this finding is not consistent (18). In this thesis we further evaluate subcortical SERT availability in relation to cognition, behavior, and BMI.

**OUTLINE OF THE THESIS**

**Part I Introduction**

*Chapter 1* provides a brief introduction on obesity, its neurobiology and the role of the dopaminergic and serotonergic systems. This introduction is followed by a review on the current state of neuroimaging research in obesity (*Chapter 2*).

**Part II: Animal research on the dopaminergic system in obesity and the effects of anti-obesity medications**

The aim of the animal research in this part of the thesis is to collect information on obesity and the striatal dopamine system that cannot be obtained easily from humans. To enhance the translational value, we use a radioligand (\textsuperscript{123}I)IBZM) to study striatal dopamine D\textsubscript{2/3} receptor (DRD\textsubscript{2/3}) availability that is also used in our clinical studies described in part III.

The first two chapters of part II describe the effects of different diets on striatal DRD\textsubscript{2/3} availability in diet-induced obese rats. *Chapter 3* focuses on the aspect of choice in a high-fat diet. *Chapter 4* reports about a free-choice high-fat high-sugar diet, and describes the role of preference for fat or sugar and its relation to striatal DRD\textsubscript{2/3} availability.
The last two chapters of part II describe the effects of anti-obesity medications on striatal DRD$_{2/3}$ availability. **Chapter 5** describes the effects of the cannabinoid-1 receptor antagonist rimonabant in a study with dose-dependent design in adult rats. **Chapter 6** presents the effects of the triple monoamine inhibitor tesofensine on obesity parameters and striatal DRD$_{2/3}$ availability in diet-induced obese rats.

**Part III: Imaging the striatal dopaminergic system and its relation to obesity in humans**

The striatal dopamine system can be studied in humans using molecular imaging techniques like single photon emission computed tomography (SPECT). Both the presynaptic DAT and the mainly postsynaptically located DRD$_{2/3}$ can be measured, depending on the radioligand that is used. The first three studies assess striatal DAT availability in healthy adults. In **Chapter 7**, we present the effect of different polymorphisms in the dopamine transporter gene (SLC6A3) on expression of striatal DAT by measuring DAT availability with SPECT in young healthy adults. In **Chapter 8**, we describe the results of a follow-up of this study and evaluate whether polymorphisms linked to a newly identified splice variant in SLC6A3 affects DAT expression. Because the DAT is important in the regulation of synaptic dopamine and can thus influence food intake, we also examine the association between striatal DAT availability and BMI in a large sample of healthy adults, which is described in **Chapter 9**.

We also assess two other aspects of the striatal dopamine system in obesity, i.e. the striatal DRD$_{2/3}$ availability and striatal dopamine release. The first topic is covered in **Chapter 10**, describing a study that intends to independently replicate the previously mentioned finding that striatal DRD$_{2/3}$ availability is lower in obesity. Striatal dopamine release in obesity has not been assessed before and is possibly related to the reward experience from food. The results of this study can be found in **Chapter 11**.

**Part IV: Imaging the serotonergic system and its relation to obesity in humans**

Similar to imaging of the dopaminergic system, it is also possible to image the serotonergic system in humans using SPECT. This part focuses on imaging of the SERT. **Chapter 12** describes a methodological study on the selectivity of the radiotracer [$_{123}$I]ADAM for imaging the SERT in order to evaluate its quality for future studies.

As mentioned before, the serotonin system is involved in regulating different aspects of cognition, mood, and behavior, including eating behavior. In **Chapter 13**, we present data on subcortical SERT and DAT availability in relation to neuropsychological functioning, personality traits, and mood in a sample of 188 healthy subjects. In **Chapter 14**, we describe a study on the association between subcortical SERT and BMI in a sample of 127 healthy subjects, which includes a subgroup of obese subjects.

**Part V: Functional imaging of the brain in obese humans**

Another technique to assess brain function in obesity is the use of functional MRI (fMRI), using blood oxygenation level dependent (BOLD) signal changes to examine brain activation. This method has a high spatial and a relatively high temporal resolution, which allows assessing
changes in regional brain activation during subsequent manipulations. One practical issue when applying fMRI in obesity is the size of the bore of the MRI scanner. This means that persons with very high weight and large body dimensions, exceeding the size of the bore, do not fit in a conventional MRI scanner with a cylindrical bore. A solution to overcome this problem is using an open bore MRI scanner. As the use of fMRI on an open bore MRI scanner has not yet been tested, we assess fMRI on an open bore MRI with a relatively low field strength of 1.0 Tesla and compare this to fMRI results on a conventional 3.0 Tesla MRI with a cylindrical bore (Chapter 15).

Furthermore, we use fMRI data to study neural correlates of impulsivity in obesity since a lack of inhibitory control is thought to play a role in overeating behavior. Chapter 16 describes how we examined impulsive decision making and response inhibition in obesity and reports the differences between obese and normal-weight subjects, including gender differences and findings in an obese subgroup with eating binges.

Part VI: Summary, general discussion and conclusions
The most important findings of the studies described in this thesis are summarized and their implications are discussed in Part VI (Chapter 17). A Dutch summary of the main findings is provided in Chapter 18.

REFERENCE LIST


