UvA-DARE (Digital Academic Repository)

Brain, nutrition and metabolism
Versteeg, R.I.

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
1 General introduction
Obesity epidemic

Obesity has reached pandemic proportions and is declared by the World Health Organization as one of the major health problems of the 21st century. Recently, the American Medical Association classified obesity (body mass index (BMI) above 30 kg/m²) as a disease (1). In the USA, nearly 70 percent of adults is overweight (BMI>25 kg/m²) and 35 percent obese (BMI>30 kg/m²) (2) and the number of people who are obese or overweight has tripled in many European countries since 1980. Of special concern is the increasing prevalence of obesity in children, with one-third of children and adolescents being overweight or obese (3). Finally, the obesity epidemic is also emerging as a health problem in many developing countries (4).

The pathogenesis of obesity is complex and includes genetic, nutritional, metabolic, cultural, environmental and psychosocial factors (5). A key determinant of body weight is energy balance, i.e. caloric intake minus energy expenditure. Increased consumption of energy dense food and a reduction in physical activity both contribute to body weight gain and increase the risk for obesity (6-8). The obese state is associated with metabolic complications such as dyslipidemia, nonalcoholic fatty liver disease, type 2 diabetes (T2D) and the metabolic syndrome (9). Because of these metabolic complications and the high prevalence of obesity, the direct and indirect health costs related to obesity are very high and estimated to amount to 147 billion dollar per year in the USA (10).

Homeostatic control of energy balance

Energy balance is under tight control of the central nervous system (CNS) which regulates body weight by modulating food intake and energy expenditure. Within the CNS a network, involved in homeostatic control of body weight, orchestrates energy balance via a complex interplay between several feeding regulatory centers, peripheral signals and the autonomic nervous system (ANS) (11). The hypothalamus integrates most of the metabolic, neuronal and hormonal signals from the body, resulting in an appropriate response in feeding and energy expenditure (12). Within the hypothalamus, the arcuate nucleus (ARC) is considered a critical region as the neurons within the ARC are in close contact with the fenestrated capillaries of the blood-brain-barrier and thus in direct contact with circulating hormones and nutrients. Within the ARC, activation of orexigenic neuropeptide Y (NPY)/agouti-related peptide (AgRP) neurons increase food intake, whereas the activation of anorexigenic proopiomelanocortin (POMC) neurons decrease food intake (13). The ARC NPY and POMC neurons project to several nuclei within the hypothalamus such as the dorsomedial hypothalamus (DMH), ventromedial hypothalamus (VMH), paraventricular nucleus (PVN) and lateral hypothalamus (LH) to control energy homeostasis (14).

The neurotransmitter serotonin (5-hydroxytryptamine, 5-HT) is known to be involved in the regulation of food intake and body weight and inhibits food intake by acting as an anorexigenic signal (15). Extracellular serotonin levels are regulated by serotonin transporters (SERT), which facilitate the reuptake of serotonin from the synaptic cleft and by different types of serotonin receptors,
located on pre- and postsynaptic serotonin neurons (16). In rodents, central administration of serotonin and serotonin receptor activation reduce food intake, whereas neurochemical depletion of serotonin and serotonin receptor blockade induce hyperphagia and body weight gain (17-22). The serotonergic effects on feeding behavior are mainly ascribed to its role in the PVN and ARC as serotonin is produced in the dorsal and medial raphe nucleus and serotonergic efferents project to the PVN and ARC (23, 24). In addition, more than 90 percent of neurons in the ARC are serotonin sensitive, as the serotonin 1B receptor is expressed on NPY/AgRP neurons and the serotonin 2C receptor is expressed on POMC neurons (25). In line, chronic central administration of a selective serotonin reuptake inhibitor (SSRI) decreases hypothalamic NPY expression and infusion of a serotonin 2C receptor agonist increases POMC mRNA expression and reduces food intake and body weight (26, 27).

In humans, medication that increases serotonergic signaling affects food intake, indicating a similar role for serotonin in feeding behavior as found in rodents. For example, both lorcaserin, a selective serotonin 2C receptor agonist, and sibutramine, a centrally-acting serotonin-norepinephrine reuptake inhibitor, reduce food intake (28, 29). Interestingly, we recently showed that SERT protein was most markedly expressed in the infundibular nucleus (IFN) of the hypothalamus, the human equivalent of the ARC (30). That study suggests that, in line with studies in rodents, serotonin's effects on feeding behavior could be mediated through serotonin signaling within the ARC. Chapter 3 provides an overview of animal and human studies describing the serotonergic system and feeding behavior (16).
Figure 1. The central nervous system integrates nutrients and gut-derived satiety signals to regulate food intake and energy expenditure to maintain body weight. Positive energy balance, induced by overfeeding, inhibits the rewarding properties of food and enhances meal-induced satiety, while energy deprivation increases the rewarding properties of food and reduces the response to satiety signals. CCK, cholecystokinin; FFAs, free fatty acids; GLP1, glucagon-like peptide 1. Modified from G. Morton et al., Nature Reviews Neuroscience 2014. Reprinted with permission.

**Reward control of energy balance**

Besides the homeostatic control of food intake, non-homeostatic or hedonic aspects of food intake form an important component of feeding behavior. The brain does not solely respond to hunger and satiety signals, but also to the rewarding value of food (31). Several corticolimbic circuits including the nucleus accumbens (NAc), amygdala, hippocampus, dorsal striatum, insula, prefrontal cortex (PFC) and the orbitofrontal cortex (OFC), are implicated in the rewarding effects of food and are involved in the motivation to eat and reinforcement values. Dopamine is the key neurotransmitter modulating reward and is synthesized in the ventral tegmental area (VTA) and substantia nigra (SN). Dopamine signaling is regulated by dopamine transporters (DAT), pre-synaptic autoreceptors and postsynaptic dopamine receptors. Dopaminergic neurons project from the VTA to the NAc and frontal cortex via the mesocortical pathway and from the SN towards the caudate nucleus and putamen via the nigrostriatal pathway. Ingestion of high palatable food induces dopamine release in the NAc (32) and dorsal striatum which correlates with the degree of experienced pleasure (33).
Moreover, pharmacological manipulation of dopamine signaling with a dopamine D2 antagonist increases appetite and body weight in rodents and humans, while dopamine agonists induce anorexigenic effects (34). The hypothalamic and limbic feeding centers are highly interconnected to regulate feeding behavior. Thus, the hypothalamus transfers signals about energy status to mesocortical areas via direct and indirect connections including the LH and ventral striatum (35).

Figure 2. Dopamine and serotonin are released into the synapse, where it signals to post-synaptic neurons through dopamine- and serotonin receptors respectively. DAT and SERT facilitate the re-uptake into the presynaptic neuron for re-use. Amph., amphetamine; DA, dopamine; DAT, dopamine transporter; L-DOPA, L-3,4-dihydroxyphenylalanine; 5-HT, 5-hydroxytryptamine; SERT, 5-HT transporter; MPP+, 1-methyl-4-phenylpyridinium; MDMA, (+)-3,4-methylenedioxymethamphetamine. Modified from G. Torres, Nature Reviews Neuroscience, 2003. Reprinted with permission.

Rhythms in energy balance

Almost all pathways involved in feeding behavior and energy metabolism fluctuate over 24 hours to optimize the timing of metabolic processes according to the physiological needs during the light/dark cycle. These daily rhythms are generated by an endogenous circadian timing system located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus (36). Because the SCN oscillation period is not exactly 24 hours, external photic input is needed to entrain the circadian timing system to the external light/dark cycle. Specialized intrinsically photosensitive retinal ganglion cells (ipRGCs) transmit the light signal from the retina via the retinohypothalamic tract to the SCN (37, 38). The output of the SCN controls the daily rhythm in feeding/fasting behavior via a wide variety of projections to nuclei within the hypothalamus such as the ARC, PVN and LH (39). Within these nuclei, rhythms in several hormones and neuropeptides are responsible for the day/night rhythm in food intake. For example, in rats, the synthesis and release of NPY and orexin both exhibit a daily rhythm, characterized by a peak prior to the feeding period encoding...
information about arousal and energy balance (40-42). In addition, the SCN has several indirect projections from the SCN to cortico-limbic areas (43). Circadian oscillators have been found in the VTA and striatum and part of dopaminergic transmission is under direct circadian control (44). Interestingly, the fluctuation in DAT expression across the light/dark cycle is responsible for the diurnal variation in extracellular dopaminergic tone and dopamine release (45). These rhythms might explain the diurnal variation in sensitivity of the SCN to changes in motivational states related to palatable food intake in rodents (46-48). Serotonin secretion exhibits a clear rhythm in the raphe, SCN and striatum with a peak during the light/dark transition (49-51). SCN neurons receive direct serotonergic input from the raphe and are responding to behavioral arousal, locomotor activity and nutrient intake (52-54). Thus, serotonergic cell bodies provide direct non-photic projections from the raphe to the SCN. Whether rhythms in dopaminergic and serotonergic circuits affect time-of-day variation in food intake and reward related anticipation remains to be studied.

In addition to its role in feeding behavior, the SCN exerts direct control of glucose metabolism by affecting hepatic glucose production, glucose uptake and glucose tolerance (55). Glucose concentrations and insulin sensitivity fluctuate over the light/dark cycle with a peak in the morning, just before the active period (56, 57). These rhythms are generated by the ANS and glucoregulatory hormones. Projections from the SCN to preautonomic neurons in the PVN innervate autonomic motor neurons in the brainstem and spinal cord and subsequently affect hepatic glucose production via sympathetic and parasympathetic projections to the liver (58). Next to the central clock in the SCN, peripheral circadian oscillators are localized in almost all tissues involved in energy metabolism (59). The SCN dictates the entrainment of peripheral clocks via the ANS and the secretion of hormones (60-62).

**Metabolic effects of light exposure**

Since light is the dominant Zeitgeber for the SCN, exposure to light at an inappropriate time could lead to desynchronization of the internal clock and the 24h environmental cycle. Exposure to artificial light and irregular light schedules has increased over the past decades (63). Although artificial light provides many social and economic advances, changes in the light/dark schedule may have adverse consequences for energy metabolism. Several animal studies showed that chronic exposure to altered light/dark schedules negatively affects feeding behavior, body weight and glucose metabolism (64, 65). In humans, cross-sectional studies showed a positive correlation between artificial light intensity in home settings and the prevalence of obesity and incidence of T2D (66-68). Intervention studies about the effects of bright light on human metabolism are scare. Only two small studies investigated the effects of bright light therapy on body weight and fat mass and reported a small reduction in fat mass (69, 70). One study investigated the acute effects of bright light exposure on glucose metabolism in healthy subjects and showed increased postprandial insulin levels during blue-enriched light exposure compared to dim light (71). Thus, several
studies indicate that exposure to artificial light affects glucose metabolism, however the mechanisms behind this relationship are unclear. The effects could be mediated via glucoregulatory hormones and/or via the ANS, since in rodents, light stimulates the secretion of corticosterone directly via sympathetic innervation (72). Moreover, a light pulse increases the expression of liver PEPCK, the major gluconeogenic enzyme, through input from the ANS to the liver (73). To summarize, available data indicate that increased exposure to artificial light is associated with disturbances in feeding behavior and glucose metabolism. However, little is known about the effects of acute exposure to bright light on glucose and lipid metabolism and whether these effects are mediated through the ANS or hormonal changes.

Figure 3. Resetting signals of the central and peripheral clocks. Light is absorbed through the retina and is transmitted to the SCN via the RHT to dictate the entrainment of peripheral oscillators via humoral factors or the autonomic nervous system. Food and feeding regimens affect either peripheral clocks or the central clock in the SCN. Modified from O. Froy, Endocrine Reviews 2009. Reprinted with permission.

**Metabolic effects of meal timing**

Although light is the most important synchronizer for the SCN, the daily rhythm of food intake provides stimuli that entrain peripheral clocks. It has been shown that food restriction to a couple of hours per day induces robust anticipatory locomotor activity via entrainment of an oscillation system other than the SCN, suggesting a food-sensitive component of the circadian timing system (74). In our current lifestyle, food consumption patterns have changed markedly and have become more irregular. For example, meals are frequently skipped, or shifted towards the evening and night. These changes in the timing of food intake could lead to an uncoupling of peripheral clocks from the central clock. Moreover, unusual feeding times could result in chronodisruption, a desynchronisation between the internal circadian rhythms and the 24h environmental cycles. Indeed, unusual feeding times are associated with metabolic disturbances (75).
studies showed that shifting the availability of food to the inactive period results in obesity and perturbations in glucose and lipid metabolism (76). In humans, cross-sectional studies have identified that snacking in the evening after dinner is associated with a greater overall caloric intake and higher BMI (77). Moreover, obese subjects on a hypocaloric diet lose significantly more body weight when they consume an early lunch (before 3PM) compared to a later lunch despite similar caloric intake (78). In addition, being an evening type individual is associated with increased fast food and soda consumption, while morning type individuals show higher dietary restraint and are more successful at both weight loss and long-term weight maintenance (79, 80). In line with these association studies, consuming most daily calories at breakfast compared to at dinner results in more weight loss and improvement in insulin sensitivity after a 32 weeks hypocaloric diet in obese subjects (81). Interestingly, distribution of caloric intake across the day also influences the success of weight loss therapy, since obese patients who eat most of the calories in the morning compared to the evening during a 20 weeks hypocaloric diet, are more likely to remain weight stable and even show additional weight loss during the follow-up period (82). These studies imply that consuming food at inappropriate times of the day contributes to the development of obesity and metabolic disturbances and that diet interventions are more successful when the majority of calories are consumed earlier during the day. The underlying mechanism of these observations remains unclear. Since meal timing can entrain peripheral circadian clocks, misalignment in circadian control of feeding behavior and metabolism might contribute to these findings. Other studies suggested a role for circulating appetite-related hormones with less experienced satiety from a meal later in the day (82). This is supported by a circadian rhythm in hunger and satiety levels after meals (83). In addition, energy expenditure might be involved in meal timing effects on metabolism since diet induced thermogenesis is higher in the morning compared to the evening (84-86). Finally, eating at inappropriate times could have direct effects on glucose metabolism because insulin sensitivity exhibits a diurnal rhythm and skipping breakfast increases post prandial glucose responses and reduced insulin secretion to a test meal (87).

Taken together, eating at appropriate times during the day is important for the synchronization between the peripheral and the central clock. Several studies show independent meal timing effects on body weight regulation and glucose metabolism, but the underlying mechanisms have not been elucidated yet.

**Neuroimaging of brain areas involved in feeding behavior**

Most of the data on the central regulation of feeding behavior are obtained from animal studies because it is difficult to perform in vivo measures in the human brain. Over the last decades, however, the techniques to visualize the human brain have improved. The serotonergic and dopaminergic systems can be visualized using molecular imaging techniques like single photon emission computed tomography (SPECT). The radiotracer $^{123}$I-FP-CIT binds to DAT and SERT and provides an indirect measurement of major components of the central serotonin and dopamine system (88, 89). This functional neuroimaging study provides information on short-term physiological changes associated with local brain activity, but this technique is invasive, expensive and labor-intensive.
Functional magnetic resonance imaging (fMRI) is a less invasive technique and is widely used to study the regulation of food intake by the brain in humans and to a lesser extent in rodents. fMRI is based on differences in blood-oxygenation-level dependent (BOLD) contrast which occur during a change within the vascular system in response to a decrease or increase in neuronal activity (90). Thus, fMRI provides both structural and functional information and can be performed in the resting state or before and after tasks, like visual food cues or before and after food stimuli such as drinking a milkshake.

**Neuroendocrine control of feeding in obesity**

Alterations in serotonergic and dopaminergic systems were shown in obese rodents and humans (15, 91). We recently showed reduced SERT protein expression in the IFN in overweight/obese humans compared to lean controls (30). Furthermore, in obese women, reduced serotonin metabolites were found in the cerebrospinal fluid compared to lean controls (92) and a negative correlation between subcortical SERT binding, assessed using neuroimaging, and BMI have been reported (93). Moreover, manipulating these systems results in changes in body weight. In rodents, selective depletion of hypothalamic and whole body SERT resulted in obesity (19, 20) and these studies strongly suggest that obesity is characterized by reduced serotonin signaling. However, at present, it is unknown if reduced serotonin signaling is a cause or a consequence of obesity as nutrient intake itself affects the serotonergic system. In rodents, high fat diets reduce serotonin signaling in the hypothalamus (94, 95), and we showed that, in lean men, isocaloric eating pattern in itself affects central SERT, as a 6-weeks hypercaloric high-fat-high-sugar (HFHS) diet with six meals per day, but not with three meals per day, reduced diencephalic SERT binding (96). This reduction in SERT might reflect a decrease in extracellular serotonin levels and thereby reduced inhibition of food intake and predispose to an increase in body weight. However, whether reduced SERT reflects higher or lower extracellular serotonin remains a matter of debate.

In addition to changes in homeostatic components of food intake in obese subjects, several fMRI studies showed alterations in reward circuits. Obese versus lean subjects showed increased brain activation in response to high-calorie food pictures in the dorsal and ventral striatum, amygdala, OFC and insula (97, 98) and displayed reduced activation of the reward system in response to palatable intake in the caudate nucleus and putamen (99). Increased reward anticipation from high-calorie food cues might trigger increased motivation to eat and overconsumption. Some studies suggested that hyperreactivity of reward circuits to food cues is related to weight loss with one study reporting a negative association between reward activation to visual food cues and weight loss success (100).

In neuroscience, molecular imaging techniques such as (positron emission tomography) PET and SPECT are used to acquire functional and metabolic information on brain areas of interest. Using these techniques, neurotransmitter receptors and transporters can be visualized and quantified. We and others have shown reduced striatal dopamine D2/3 receptor availability in obese compared...
to lean individuals (101, 102). This reduction was partially reversible after massive bariatric surgery-induced weight loss suggesting that this reduction is a consequence rather than a cause of obesity (103). Furthermore, a blunted striatal dopamine release in obese compared to lean subjects was recently reported (102, 104). In contrast to dopamine D2/3 receptors, controversy exists about the role of DAT in food intake and obesity with some studies reporting no correlation, while others showed a negative correlation between striatal DAT availability and BMI in humans (105-107). In animals, several studies reported reduced striatal DAT binding in response to a HF diet (108, 109). In line with studies on SERT, it is unknown whether reduced DAT represents higher or lower extracellular dopamine levels. Long-term systemic dopamine depletion results in reduced striatal DAT binding, but a 90 percent reduction in striatal DAT led to increased striatal extracellular dopamine levels in mice (110-112). More detailed studies in humans are needed to dissect the interaction between DAT, extracellular dopamine levels and feeding behavior.

Weight loss management

Weight loss occurs when energy expenditure exceeds energy intake over time. Although this seems straightforward, the treatment of obesity is difficult and often unsuccessful because following diet-induced weight loss, weight regain is a recurrent problem (113, 114). Only 20 percent of overweight individuals is able to successfully lose weight, i.e., to lose at least 10 percent of their body weight and maintain that for more than one year (115). This low success rate is probably due to compensatory physiological changes in homeostatic processes, favoring weight regain to prevent starvation (116). First, diet-induced weight loss disproportionally reduces total energy expenditure, which even persists after one year of weight loss maintenance (117). Second, weight loss alters substrate oxidation rate with a shift towards carbohydrate oxidation and an impaired ability to increase fat oxidation, which is associated with weight regain over time (118-120). However others reported no relationship between weight regain and fat oxidation (121). Third, in response to caloric restriction, changes in appetite related hormones favor weight regain: weight loss results in long-term reduced levels of the satiety hormones leptin and insulin and increased levels of the hunger-promoting hormone ghrelin (122). And finally, humans are more motivated to eat palatable and energy rich food during caloric restriction and many diet intervention fail because of reinforcement of the omitted food and increased cravings for desired food (123). More insight in changes in food intake-regulating brain areas that occur during and after caloric restriction is, therefore, necessary to design effective methods in weight loss management.

Insulin resistance in obesity

Obesity is associated with ectopic fat accumulation and insulin resistance, although the underlying mechanisms of these metabolic alterations are complex and still not fully unraveled. Besides body weight and body fat distribution (124), meal composition and meal frequency affect insulin sensitivity and liver fat
accumulation. Rats snacking a free choice HFHS diet became glucose intolerant within a week, while rats on a free choice high-fat (HF) diet did not, despite similar adiposity (125). In humans, dietary fat and carbohydrate content are involved in the development of insulin resistance (126, 127). Moreover, hypercaloric diets with increased meal frequency, representing snacking behavior, increased intrahepatic triglycerides and abdominal fat, whereas similar diets with increased meal size and equal caloric content did not (128). In addition to meal frequency, several studies suggest that meal timing could be an important determinant of glucose metabolism (81, 82). Although these effects of the diet and meal patterns on insulin sensitivity and fat accumulation could be explained by effects on adipose tissue resulting in dysfunctional adipose tissue with subsequent insulin resistance, many studies point towards an additional role for the brain in the regulation of glucose metabolism. The brain can modulate glucose production and uptake via the sympathetic and parasympathetic nervous system and several nuclei within the hypothalamus are sensitive to glucose concentrations (129). Stimulating neuronal activity in the PVN results in hyperglycemia through activation of the sympathetic input to the liver (58). Moreover, direct activation of the central melanocortin system improves peripheral glucose homeostasis, whereas administration of NPY or melanocortin receptor antagonist causes insulin resistance independent of changes in food intake (130, 131). Finally, as previously stated, the SCN dictates the daily rhythm in glucose levels. Studies on the central regulation of glucose homeostasis in humans are challenging but with the ongoing development of molecular imaging techniques and innovative fMRI analysis, increasing information is available that shows the involvement of the brain in obesity-related insulin resistance. These studies are needed to fill the translational gap between rodent and human experiments and are likely to result in development of centrally acting agents to modulate glucose metabolism.

**Role of serotonin and dopamine in glucose metabolism**

Besides the effects on feeding behavior, the serotonergic and dopaminergic system both play a role in the maintenance of glucose homeostasis. Mice lacking the serotonin 2C receptor in POMC neurons show hyperglycemia, hyperinsulinemia, and insulin resistance despite normal body weight (132). Moreover, infusion of serotonin into the VMH induces basal hyperinsulinemia and elevated plasma insulin levels in response to a glucose challenge, whereas central insulin administration enhances hypothalamic extracellular serotonin levels (133). In addition, SERT deficient mice are hyperglycemic, hyperinsulinemic and have reduced insulin signaling in the liver prior to the onset if obesity (134). In humans, treatment with serotonin 2C receptor antagonist impairs insulin sensitivity, whereas SSRIs improve insulin sensitivity in healthy subjects and patients with T2D respectively (135-137).

The dopaminergic system is also associated with glucose metabolism. In rodents, deficiency of the dopamine D2 receptor leads to glucose intolerance in mice, while administration of bromocriptine, a dopamine D2 receptor agonist, improves insulin sensitivity (138, 139). In humans, the insulin sensitivity index is negatively
associated with striatal dopamine D2 receptor availability and acute dopamine depletion reduces insulin sensitivity (140). In addition, dopamine D2 receptor agonists improve glucose tolerance in obese subjects with T2D (141). Data on the relationship between DAT and glucose metabolism are scarce. Insulin modulates the expression and function of DAT (142, 143) and insulin administration into the VTA reduces dopamine concentrations via increased reuptake of dopamine through DAT (144).

In summary, several animal and human studies showed a link between the central serotonergic and dopaminergic system and glucose metabolism. However, it remains unclear whether central SERT and DAT are affected by the metabolic state or vice versa independently of body weight.

**Aims and outline of this thesis**

The overall aim of this thesis was to study the role of the brain in the regulation of feeding behavior and glucose metabolism under different metabolic and environmental conditions. We therefore investigated effects of meal timing during a hypocaloric diet on the brain and metabolism and studied bright light effects on glucose and lipid metabolism.

In the brain, serotonin and dopamine have been shown to be involved in the homeostatic and reward control of food intake and glucose metabolism. Whether central serotonergic and dopaminergic signaling is related to insulin sensitivity independently of body weight is, however, unknown. In chapter 2, we studied differences in diencephalic and hypothalamic SERT binding as well as striatal DAT binding between lean, obese insulin sensitive and obese insulin resistant subjects.

Food intake and glucose metabolism fluctuate over the day/night cycle and are controlled by the circadian timing system. Inappropriate feeding times disturb energy metabolism and eating most of the calories in the morning compared to the evening has beneficial effects on body weight regulation. However, the underlying mechanism linking meal timing and body weight is unclear. Chapter 3 provides an overview of animal and human studies addressing the relationship between the circadian timing system, feeding behavior, glucose metabolism and the serotonergic system under different metabolic conditions. We propose a hypothesis on how meal timing could affect serotonergic signaling and subsequently food intake, body weight and glucose metabolism. To study our hypothesis, we examined meal timing effects during a hypocaloric diet on SERT and DAT using SPECT in obese insulin resistant men before and after the diet (chapter 4). As SPECT studies provide mostly static information, we additionally performed functional neuroimaging studies to assess neuronal activity patterns using fMRI (chapter 5). We measured the effect of timing of food intake during weight loss on brain activity responses to visual food cues in reward areas before and after the diet. As glucose metabolism fluctuates over the day/night cycle and feeding behavior plays an important role in the regulation of glucose metabolism, we focused in chapter 6 on the metabolic effects of meal timing. We tested
whether meal timing during weight loss affects hepatic and peripheral insulin sensitivity, liver fat and resting energy expenditure independent of weight loss. Energy metabolism is not only responsive to meal timing, but also to light exposure, as light is the dominant entrainer of the SCN. Chapter 7 reviews the effects of exposure to light on food intake, body weight and glucose metabolism in animals and humans. Finally in chapter 8, we describe the acute effects of artificial light exposure on glucose and lipid metabolism in metabolically healthy and unhealthy subjects.
References


