Brain, nutrition and metabolism
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Summary and general discussion
Summary

In this thesis, we describe studies on the brain and glucose metabolism in different metabolic and environmental conditions in humans.

Part I
Numerous studies pointed towards a role for the central dopaminergic and serotonergic system in the regulation of feeding behavior and glucose metabolism. Serotonin transporters (SERT) and dopamine transporters (DAT) regulate synaptic serotonin and dopamine availability and are therefore important modulators of serotonin and dopamine signaling, respectively. To study the potential role of brain SERT and DAT in obesity, we assessed SERT and DAT binding in lean and obese subjects using \(^{123}\text{I}-\text{FP-CIT SPECT,}\) and show a trend towards lower hypothalamic SERT binding in obese compared to lean controls. Additionally, we found reduced SERT binding in the diencephalon in obese insulin resistant compared to obese insulin sensitive and lean subjects. These data suggest that metabolic alterations associated with obesity affect SERT binding in the diencephalon independently of body weight. In contrast, striatal DAT binding did not differ between lean and obese, either insulin sensitive or insulin resistant, subjects (chapter 2).

Part II
In this part we describe studies on the effects of meal timing on the brain and glucose metabolism. Several studies show associations between meal timing and body weight regulation and point to a beneficial effect of eating most of daily calories in the morning, however, an underlying mechanism has not yet been identified. We give an overview of current knowledge about the relationship between the circadian timing system, feeding behavior, glucose metabolism and the serotonergic system and provide a hypothesis on serotonin playing a major role in meal timing effects on body weight regulation via non-photic metabolic feedback to the raphe and suprachiasmatic nucleus (SCN) (chapter 3).

To study the effects of meal timing on the brain in humans, we performed a randomized diet intervention trial consisting of two hypocaloric (i.e. 50% of daily caloric need) diets with either consuming 50% of daily calories at breakfast or at dinner in obese insulin resistant men. We assessed striatal DAT and hypothalamic and thalamic SERT binding before and after the diet. We show that weight loss per se does not alter striatal DAT and (hypo)thalamic SERT binding.

However, consuming 50% of daily calories at breakfast increases striatal DAT and thalamic SERT binding, while consuming the majority of daily calories at dinner reduces striatal DAT and thalamic SERT binding. Importantly, these effects were independent of weight loss or macronutrient intake. Surprisingly, we did not find a difference in hypothalamic SERT binding between both diet groups (chapter 4). The increase in striatal DAT binding in the breakfast group might contribute to the earlier reported beneficial effects of consuming most of the calories in the morning during weight loss. However, the interpretation and functional consequences of the differences in DAT binding remain unclear since
the role of dopamine signaling in obesity is complex and not fully understood.
To further clarify the role of meal timing on neuronal circuits, we studied meal
timing effects on neuronal responses to visual food cues using fMRI. We show
increased neuronal responses to pictures of high calorie food in the pallidum and
putamen after weight loss in general. Moreover, we show a decrease in neuronal
response to high calorie food cues in the caudate nucleus in subjects who
consumed the majority of calories in the morning, whereas responses increased
in subjects who consumed most of the calories in the evening (chapter 5). Thus,
we found that meal timing during a hypocaloric diet in obese men affects striatal
DAT binding and neuronal responses to food cues in the caudate nucleus.
We then focused on the metabolic effects of meal timing and show that weight
loss improves basal endogenous glucose production (EGP) as well as hepatic
and peripheral insulin sensitivity and intrahepatic triglyceride content. However,
no differential metabolic effect of meal timing during weight loss was observed.
Additionally, we found that meal timing did not affect the weight loss-induced
decrease in resting energy expenditure (REE) (chapter 6). Thus, our data do not
support weight loss independent effects of meal timing on metabolic parameters.
Previous reported effects of meal timing on metabolism are probably biased by
differences in body weight loss.

Part III
A role for light exposure on metabolism has been shown repeatedly. In chapter
7, we provide an overview of animal and human studies showing effects of light
exposure on food intake, body weight and glucose metabolism and we discuss
potential underlying mechanisms. We conclude that increased exposure to
artificial light at unnatural times of the day may have adverse metabolic effects
on metabolism, feeding behavior, and body weight.
We then studied the acute effects of exposure to bright light on glucose and lipid
metabolism in metabolically healthy and unhealthy subjects. We show that, in
healthy individuals, bright light does not affect plasma glucose levels, while it
increases fasting and postprandial plasma triglyceride levels. In patients with
type 2 diabetes (T2D), bright light increases fasting and postprandial glucose
levels, postprandial triglyceride levels and appetite scores. We also observed
increased sympathetic nervous system activity in these subjects, suggesting a
potential role for the autonomic nervous system in the light induced effects on
glucose and lipid metabolism (chapter 8).
In summary, we show body weight independent effects of the metabolic state
and of meal timing on the brain in humans, providing evidence for a role of the
brain in glucose metabolism and in the modulating effects of meal timing on
body weight. Furthermore, we found that acute exposure to bright light affects
glucose metabolism in obese subjects with T2D and lipid metabolism in both,
patients with T2D and healthy controls. Further studies are needed to determine
optimal meal timing and light conditions in the regulation of body weight and
metabolism. This will eventually lead to novel evidence-based treatment
strategies to prevent and treat obesity and its related metabolic disorders.
General discussion

Feeding behavior, obesity and insulin resistance

The role of the serotonergic system in regulating feeding behavior has been extensively studied, and from animal data it is known that serotonin receptors within different areas of the brain play an important role in hunger and satiety and food-motivated behavior (1). Although several drugs targeting the serotonergic system have been linked to the induction of obesity and diabetes, only few studies (2, 3) focused on the mechanistic relation between the central serotonin system, obesity and insulin resistance and even less is known about human central serotonin in this regard. In chapter 2, we show that obese insulin resistant individuals have lower diencephalic SERT binding compared to equally obese insulin sensitive and lean individuals, pointing to a relation between central serotonin and glucose metabolism independent of body weight. Our data are difficult to compare to those in the literature as most human studies investigated effects of serotonin on glucose metabolism, while we studied the relationship between whole body SERT in the brain and insulin sensitivity (4, 5). In rodent models, a role for the hypothalamus in serotonin's effects on glucose metabolism has been shown (6), however, hypothalamic SERT binding did not differ between insulin sensitive and insulin resistant individuals in our study. This suggests that either another component than SERT of the serotonin signaling pathway is involved in the effects on insulin sensitivity or that a diencephalic region other than the hypothalamus is responsible for the observed difference. In that respect, the thalamus might be of interest being a glucose sensitive area and recently shown to be involved in motivated sugar-feeding behavior (7). Moreover, within the thalamus, a lower increase in glucose levels in response to plasma hyperglycemia was shown in type 1 diabetics compared to non-diabetic humans (8). SERT is highly expressed in many subregions of the thalamus (9), and thus involvement of thalamic serotonin signaling in glucose metabolism would be of interest to study in the future. We further show that hypothalamic SERT binding tended to be lower in obese subjects compared to lean controls. This is in line with our earlier findings of lower SERT immunostaining in the infundibular nucleus of the hypothalamus in post mortem brains of overweight and obese individuals (10). Given the role of the hypothalamus in feeding behavior, lower serotonergic tonus in the infundibular nucleus (IFN) might contribute to obesity or vice versa. Of note, our 4-week hypocaloric diet intervention and weight loss did not affect SERT binding in the hypothalamus or thalamus (chapter 4), whereas 6 weeks of overfeeding in healthy subjects did affect diencephalic SERT binding (11). This either suggests that presynaptic serotonin signaling does respond to short term overfeeding but does not adapt to weight loss or that in the obese state lower SERT binding in the hypothalamus is an irreversible phenomenon or a cause rather than a consequence of obesity. Our findings are in accordance with a previous study, showing no significant differences in subcortical (caudate, putamen, thalamus) SERT binding after weight loss following Roux-en-Y gastric bypass (RYGB) (12).
Although several studies showed that lower serotonin signaling enhances food intake, nutrients themselves also have direct effects on serotonergic signaling in the hypothalamus. Calorie dense nutrients decrease serotonin release, resulting in increased food intake (13-15). Furthermore, eating patterns affect the central serotonin system as we recently showed that in lean individuals, a hypercaloric high-fat high-sugar (HFHS) snacking diet reduces SERT binding in the diencephalon (11), suggesting a role for snacking both fat and sugar in predisposing subjects to obesity via reduced serotonin signaling with less inhibition of food intake. Given the effect of nutrients and eating patterns on the serotonergic system in the brain, it was unexpected that a hypocaloric diet intervention with a 3 meals a day schedule and a healthy diet macronutrient composition according to the current guidelines did not affect SERT binding (chapter 4). This could be explained by an existing pre-intervention healthy diet and eating pattern, since subjects had to be weight stable for 3 months to be eligible to participate, or by the earlier discussed limited reversibility of lower SERT in obesity upon weight loss.

In addition to the role of the serotonin system in feeding behavior and insulin sensitivity, the striatal dopamine system is a major regulator of food intake and has also been shown to be involved in glucose metabolism. We and others have demonstrated lower striatal dopamine receptor 2/3 (DR2/3) binding in obese compared to lean individuals and an increase in striatal DR2/3 binding 2-3 years after bariatric surgery induced weight loss (16). Also, striatal DR2/3 binding tended to correlate with insulin sensitivity in obese individuals (17). Surprisingly, our studies on striatal DAT between lean and obese subjects and before and after weight loss show no differences. This suggests that in obese conditions and after long-term weight loss, changes occur at the post-synaptic level of the striatal dopamine system and that lower DR2/3 binding in obesity is not compensated by a pre-synaptic increases in DAT expression. However, whether lower striatal DR2/3 binding in obesity is associated with a hyper- or hypodopaminergic state in humans remains a matter of debate.

**Obesity, caloric restriction and weight regain**

Weight loss due to food restriction led to expected changes in REE, appetite-related hormones and striatal neuronal responses to high calorie food cues (chapter 4-6) and these changes might account for the frequently observed post-dieting weight regain. Interestingly, changes in striatal responses to visual food cues were not accompanied by changes in striatal DAT binding. As a human imaging study has shown that exposure to visual food cues elicits an increase in extracellular striatal dopamine (18), these data suggest that weight loss affects postsynaptic rather than presynaptic neurons in the striatum. Meal timing during caloric restriction and weight loss on the other hand, had a distinct effect on both striatal DAT binding and striatal BOLD responses to visual food cues (chapter 4 & 5). Subjects who consumed most of the calories in the morning, increased striatal DAT binding and reduced neuronal activation in response to high calorie food pictures in the caudate nucleus, while consuming
most of the calories in the evening reduced striatal DAT binding and increased neuronal activation in response to high calorie food pictures in the caudate nucleus. These effects were independent of weight loss and macronutrient intake and thus suggest a direct effect of consuming nutrients at a certain time of the day on striatal neurons. Although it is not possible to differentiate between different neurotransmitters using fMRI, dopamine is the key neurotransmitter modulating reward in the striatum (19), and thus expected to be involved in the response to highly palatable food pictures. As dopamine release is correlated with the desire to eat food and is related to neuronal activation patterns with food-conditioned stimuli in the caudate nucleus following fMRI (18), it seems likely that the meal timing effects on neuronal responses in the caudate nucleus reflect changes in dopamine signalling in anticipation to food. It has been suggested that obesity is characterized by enhanced reward sensitivity when viewing high calorie food cues, but reduced dopamine signalling when actual food is consumed. This promotes overconsumption of palatable food to compensate for a mismatch between expected and delivered reward (20). Along the lines of this theory, our data might explain the earlier reported beneficial effects of eating most of the calories in the morning on weight loss maintenance. We hypothesized that the increase in striatal DAT binding in the breakfast group reflects an upregulation in response to increased extracellular dopamine level to reduce the reinforcement value of omitted food. Moreover, the reduced neuronal response to high calorie food pictures in the caudate nucleus in the breakfast group could reduce motivation for energy dense food as several studies showed that weight loss induces an increase in neuronal response to food cues positively associated with preference for high calorie food (21-23). Finally, increased striatal activation to high calorie food cues after diet-induced weight loss is negatively associated with weight loss maintenance during a follow-up period (24). When combining our SPECT and fMRI data, it is tempting to speculate that the beneficial effects of eating most of the calories in the morning is due to both, reduced neuronal-related reward anticipation (e.g. reduced BOLD response in the caudate nucleus) and increased striatal dopaminergic tone (e.g. increased dopamine signalling accompanied by an upregulation in striatal DAT binding). Decreased anticipatory responses when viewing food cues (e.g. decreased desire to eat) and increased dopamine signalling when consuming food, could decrease overall food intake via a reduction in the mismatch between expected reward and reward of actual consumption. However, this remains speculative at this point and future studies should be focussed on meal timing effects on dopamine release as well as neuronal responses when consuming food. Moreover, detailed studies are needed to unravel the relation between DAT and extracellular dopamine levels under normal and hypocaloric conditions.

**Ventral and dorsal striatum**

Interestingly, the increase in striatal DAT binding and the decrease in neuronal responses to food cues in the breakfast group occurred in the ventral part of the striatum, whereas the decrease in striatal DAT binding and the increase in neuronal responses to food cues in the dinner group were more pronounced
Several studies describe a functional difference between the ventral and dorsal striatum in relation to food reward. The ventral striatum mediates the liking/hedonic properties of food intake and motivation to eat, whereas the dorsal striatum is predominantly associated with eating habits and cognition (25, 26). However, extracellular dopamine levels increase in the dorsal, but not in the ventral striatum in response to the display and consumption of palatable food in humans (18, 27). Additionally, restoring dopamine in the dorsal striatum in dopamine-deficient mice restored normal consumption of regular chow, whereas restoring it in ventral striatum did not, suggesting that dopamine transmission in the dorsal striatum is crucial for normal feeding behavior (28).

The interpretation of these studies, however, is difficult, as some studies consider the entire caudate nucleus to be part of the dorsal striatum while others consider the ventral part of the caudate nucleus together with the nucleus accumbens (NAc) to be part of the ventral striatum.

We hypothesized that the earlier reported beneficial effects of meal timing on weight loss maintenance would occur via changes in metabolic feedback to the raphe and thereby to the serotonergic input to the hypothalamus (chapter 3). However, SERT binding in the hypothalamus did not change while SERT binding in the thalamus responded differently to eating most calories during breakfast compared to eating most calories during dinner (chapter 4). Only few studies investigated the role of the thalamus in relation to food intake. The thalamus is interconnected with several brain regions and relays information from neurons involved in homeostatic and reward functions (29). The paraventricular nucleus of the thalamus (PVT) receives projections from the brain stem and hypothalamus and projects to the striatum and cortical areas (30), and when the PVT is lesioned in rats (31) or when a GABA agonist is administered into the PVT, food intake is increased (32), pointing towards a role for the thalamus in controlling feeding behavior.

Several mechanisms might be involved in meal timing effects on striatal DAT and thalamic SERT binding. Meal timing affects food intake-related hormones (33) such as leptin and ghrelin, which signal in striatal dopamine neurons (34). Plasma leptin and ghrelin levels as well as hunger and appetite scores were however not different between the breakfast and dinner group. Alternatively, striatal dopamine and thalamic glutamate neurons are glucose-sensitive (7, 35) and changes in striatal DAT and thalamic SERT binding could be due to changes in circulating glucose. However, we did not observe changes in glucose metabolism between both diet groups (chapter 6) making it unlikely that this is mediated by peripheral changes in glucose metabolism. Although, we did not assess meal-induced changes in glucose metabolism and differences in glucose excursions or meal-induced hormones and gut peptides might be involved in the observed difference. Alternatively, circadian mechanisms could be involved. Dopaminergic transmission shows a diurnal variation and is under circadian control (36, 37) and striatal DAT binding differences between the breakfast and dinner group could be related to the amount of nutrient intake consumed at a specific time of the day. The diurnal rhythm in striatal DAT is responsible for
day/night fluctuations in extracellular dopamine levels and dopamine release (38). Previous studies show that the hedonic value of palatable food can entrain the circadian activity of the suprachiasmatic nucleus (SCN) (39, 40). Although we altered the distribution of calories over the active period rather than shifting meal timing, changes in meal size at a certain time point could mediate changes in metabolic feedback to the ventral tegmental area (VTA) and subsequently to dopaminergic input to the striatum. As dopaminergic projections from the VTA also reach the SCN indirectly via the medial preoptic nucleus and the thalamus (41, 42), feedback on feeding related signals according to the time-of-day to the SCN, could affect rhythms in DAT. This could result in a mismatch between non-photic metabolic feedback received from raphe and VTA and the photic information received from the retina by the SCN. This mismatch could lead to chronodisruption and may negatively affect body weight regulation.

Effects of meal timing on metabolism
Many studies, especially in rodents, show effects of meal timing on glucose metabolism leading to the general hypothesis that irregular eating patterns and shifting meals across the days are involved in the development of obesity and diabetes (43-45). It is well known that glucose metabolism is under circadian control (chapter 3), and peripheral oscillators are sensitive to food intake and could be synchronized to feeding schedules (46). Especially the liver could be entrained to feeding schedules as shifting the availability of food alters liver clock protein and mRNA rhythms as well as downstream lipid and glucose pathways (47, 48). It is thus proposed that inappropriate feeding times desynchronize central from peripheral clocks and subsequently alter intrahepatic liver fat accumulation and glucose metabolism. In contrast to this hypothesis, no effect of meal timing on glucose metabolism or liver fat content was observed (chapter 6). As expected, weight loss improved peripheral and hepatic insulin sensitivity, but did not differ between diet groups and thus our data do not fit the popular idea that eating earlier in the day benefits glucose metabolism and insulin action during weight loss. This does not exclude a favorable effect of meal timing on metabolism in a eucaloric state. The described beneficial effects of meal timing on metabolism can be biased by the differential effect on weight loss and weight maintenance. Furthermore, an earlier study reported positive effects of time restricted feeding on liver fat (49), although these data could be explained by differences in weight loss. Thus, although various studies point to beneficial metabolic effects of eating most of the calories in the morning, these effects might in part be attributed to the differences in weight loss rather than meal timing per se. One limitation of our study was that insulin sensitivity was measured at one time point, because a two-step clamp takes more than eight hours. We therefore cannot rule out that insulin sensitivity is different between the breakfast- and dinner group when the clamp would have been performed at another time point during the day.

Metabolic effects of light
Besides the effects of meal timing on feeding behavior and metabolism, light exposure has been shown to interfere with rhythms in energy metabolism as
well. Although several studies show a role for light exposure in food intake, body weight and glucose metabolism (chapter 7), data on the acute effects of light exposure in humans are scarce. Only one recent paper showed no effect of exposure to morning blue enriched room light on plasma glucose levels in lean individuals, which is in line with our data (50). We show in chapter 8 that acute exposure to bright light affects glucose and lipid metabolism and appetite scores in obese men with T2D. In lean subjects, bright light only affects triglyceride levels. These effects are likely mediated by the SCN which receives direct light input from the retina and transmits the signal via the autonomic nervous system to other nuclei within the hypothalamus, the liver and white adipose tissue (51-53). This theory is supported by increased heart rate and increased low frequency/high frequency (LF/HF) ratios in bright light compared to dim light that indicates increased sympathetic signaling (54). It is unclear why the effects on glucose metabolism are only apparent in the obese subjects with T2D. This could be explained by an increased sensitivity to enhanced sympathetic activity with subsequent increases in glucose or by the combined effect of higher sympathetic activity and insulin resistance resulting in higher glucose.

The central regulation of appetite is a complex interplay between many brain circuits and determined by several hormones and neuropeptides (55). As mentioned in chapter 7, orexin might be involved in the bright light effects on appetite, as light directly affects the activity of orexin neurons, while orexin stimulates sympathetic outflow and increases appetite (56). Additionally, it also affects glucose production which could be an alternative mechanism for the SCN to influence glucose metabolism (57). On the other hand, we hypothesized in chapter 3 that nutrients themselves provide metabolic feedback to the brain via serotonin projections from the raphe nuclei to the SCN. Thus feeding behavior could be affected via both, photic information, received from the retina projecting to the SCN, and non-photic information, received from the raphe providing input to the SCN. In turn, the SCN could affect other hypothalamic nuclei, including the lateral hypothalamus, to influence feeding and metabolism. Future studies in rodents and humans are needed to establish the pathways through which light exposure affects glucose and lipid metabolism and appetite. Moreover, studying the long-term modulating effects of bright light exposure on metabolism would be of interest.

Clinical implications
The most common behavioral approach to lose weight, i.e. dieting, is often unsuccessful and accompanied with post-dieting weight regain (58, 59). Changing caloric distribution across the day during a weight loss intervention could be a simple and effective strategy to improve weight loss maintenance as recent studies showed that eating most of the calories in the morning compared to in the evening has beneficial effects on weight loss maintenance (33, 60). We here report the first evidence in humans that these effects could be mediated via changes in striatal dopaminergic signaling and serotonergic signaling in the
thalamus. Thus, our study provides novel insights into possible mechanisms by which meal timing affects weight loss maintenance. The results also address the generalized concern that maladaptive neuroplasticity in the brain’s reward system might not be reversible. This may have important implications for obesity follow up and treatment, and provides evidence that neuronal mechanisms may affect weight loss success or predict proneness to relapse (61). Longitudinal studies are needed to study this further.

When lifestyle interventions do not induce sufficient weight loss, pharmacologic agents can be added to the treatment. We provide evidence in chapter 2 that SERT might be a potential target to treat obesity. Several studies have shown that short term treatment with serotonin reuptake inhibitors (e.g. d-fenfluramine and fluoxetine) and treatment with 5-HT$_{2C}$R agonists (e.g. lorcaserin) reduce body weight and food intake (62-64). Therefore, increasing synaptic serotonin or increasing serotonin signaling in brain areas involved in regulation of food intake (e.g. the hypothalamus and striatum) might be successful in long-term weight loss. However, many serotonergic agents are not approved or withdrawn due to serious cardiovascular and pulmonary side effects as serotonin receptors are widely expressed on valvular leaflets and pulmonary arteries (65, 66). Therefore, future studies should focus on drug target selectivity. In addition to its appetite suppressing effects, we describe in chapter 2 that targeting the serotonergic system might also be of potential interest in the treatment of insulin resistance and T2D. Indeed, short-term treatment with SSRIs has anti-hyperglycemic effects in rats and improves insulin sensitivity in humans with non-insulin-dependent T2D (4, 67). More studies are needed to study long-term effects on glucose metabolism and body weight.

We show in chapter 8 that exposure to morning bright light negatively affects fasting and postprandial glucose levels in obese patients with T2D. It would be of interest to study bright light effects on metabolism in the evening. Many people use bright light in the evening by turning on electric lights after sunset, watching TV late at night, and using smartphones and laptops prior to going to sleep. Earlier studies already showed that exposure to bright light during evening hours disturbs sleep (68). If the metabolic effects of morning light could be extrapolated to the night, it is possible that ambient light has a causal relation with the observed correlations between exposure to light at night and metabolic disorders (69, 70). Potentially, modulating light exposure in home settings and work places could contribute to the prevention of development of metabolic disturbances in lean and obese individuals. Especially avoidance of blue-rich light could be helpful, as intrinsically photosensitive retinal ganglion cells that project to the SCN are most sensitive to the blue light (71). Several tools are available to block blue light; for example, providing people who work in the evening with blue light-blocking glasses or blue light filtering apps on smartphones and computers could prevent nocturnal suppression of melatonin and subsequent enhance sleep quality. In shift workers, it has already been shown that preventing exposure to blue-enriched light in the morning could increase day time sleep.
episodes (72). Whether these adjustments affect glucose metabolism as well need to be investigated. Moreover, future studies are needed to investigate whether light therapy in home settings could be a potential strategy to affect the onset and progression of T2D. Additionally, as we show that exposure to bright light increases hunger and appetite scores, additional studies are needed to study appropriate lighting in restaurants or school cafeterias.

Taken together, this thesis supports the idea that both environmental cues, meal timing and light exposure, affect the brain and glucose metabolism. Our data help in understanding underlying mechanisms and thus in the development of strategies to optimize timing of feeding and light conditions to prevent the development of metabolic disorders. Further studies are needed to determine at what time of day and under which light conditions food can be best consumed to optimize feeding behavior, body weight regulation and glucose metabolism.
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