Light, the circadian timing system, and type 2 diabetes
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CHAPTER 1

General introduction and outline

Based on:
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GENERAL INTRODUCTION

Ever since the onset of evolution, life on earth has been subjected to the daily rhythm of light and dark. As a consequence, many organisms experience a daily rhythm in food availability. Most organisms, ranging from bacteria to humans, developed an endogenous circadian timing system to prepare for the alternating daily periods of activity and rest, and of foraging and fasting. There are some indications that disturbances of the circadian timing system may contribute to the pathophysiology of obesity and type 2 diabetes. In this thesis we report a number of studies on the relation between light, the circadian timing system and type 2 diabetes. As an introduction to these studies, in the present chapter we first describe the components of the circadian timing system, followed by the circadian aspects of energy metabolism and sleep. Next, we explore previous studies on the relation between the circadian timing system and type 2 diabetes. Finally, we describe the aim and outline of the thesis.

The circadian timing system

Central clock

In mammals, including humans, the central biological clock resides in the bilateral hypothalamic suprachiasmatic nucleus (SCN). The SCN generates an autonomic rhythm of electrical activity with a period of approximately 24 hours. This rhythm continues to oscillate even when SCN cells are removed from the brain and brought into culture (1-4). The SCN is located superior to the optic chiasm, and receives direct light information from the retina via the retinohypothalamic tract (RHT). Through this light input, the endogenously generated SCN rhythm of approximately 24-hours is synchronized with the environmental rhythm of exactly 24 hours (5; 6). The central clock in the SCN signals to several neighbouring hypothalamic regions including the subparaventricular zone (SPZ) and the paraventricular nucleus (PVN). The central clock is of utmost importance for the regulation of daily sleep-wake rhythms, daily rhythms in the secretion of hormones, and daily rhythms in feeding behaviour (reviewed in (7; 8)).

Approximately 20 years ago it was discovered that the endogenous SCN rhythm is based on a molecular clock mechanism. The core clock genes (Clock, Arntl, Per1, Per2, Per3, Cry1 and Cry2) are expressed in a transcriptional-translational feedback loop with a duration of approximately 24 hours (reviewed in (9)). In turn, the clock genes regulate the expression of a plethora of other genes in SCN neurons and thereby force SCN electrical activity into a 24-hour rhythm (10; 11).

Peripheral clocks

Soon after the discovery of the clock genes it became clear that virtually every mammalian cell contains a molecular clock (12; 13). Animal studies have shown
Peripheral clock gene oscillations in many tissues including digestive organs such as the liver (13-18), the pancreas (16; 19; 20), the stomach (21-23) and the intestine (18; 22; 23). In human adipose tissue, approximately 25% of the genes have been reported to show a circadian rhythm of expression (24). Elegant experiments targeting the molecular clock in specific tissues revealed several physiological functions of peripheral clocks. For instance, the molecular liver clock regulates the expression of important metabolic genes such as phosphoenolpyruvate carboxykinase (PEPCK) (25-29) and glucose-6-phosphatase (25-28), two key enzymes in gluconeogenesis. Furthermore, the liver clock controls the expression of major enzymes in oxidative phosphorylation and lipid metabolism (26; 27). In the pancreatic beta cell, clock genes play an important role in insulin secretion (20; 30; 31). The adipocyte clock also has a metabolic function: it regulates adipocyte differentiation and lipolysis (32).

Peripheral clocks also show an autonomic cycle of approximately (but not exactly) 24 hours (33; 34). Since most peripheral clocks do not receive light information, the SCN communicates its light/dark entrained rhythm to peripheral clocks to ensure synchronization with the external light-dark cycle. As indicated, the SCN signal is passed on via neural projections to several thalamic and hypothalamic brain areas. Subsequently the SCN signal is forwarded to peripheral clocks via hormonal signals and the autonomic nervous system (Fig. 1). For example, the SCN controls the circadian rhythm in the release of glucocorticoids by the adrenal gland (35; 36) as well as the circadian rhythm in the release of melatonin by the pineal gland (36). Glucocorticoids are potent synchronizers of peripheral clock rhythms (15; 37), and melatonin may have a role in synchronising peripheral clocks as well (38; 39). In addition to these hormonal pathways, the SCN has polysynaptic neuronal connections with a variety of tissues including liver (40-43), pancreas (42; 44) and adipose tissue (45), and the circadian signal is probably forwarded from the SCN to peripheral clocks via these autonomic projections as well (46-49).

In addition to the direct hormonal and neuronal signals described above, peripheral clocks are synchronized by several indirect signals. First, peripheral clocks are strongly influenced by energy metabolism. Animal studies show that clock rhythms in liver and pancreas can be inverted by feeding animals during the diurnal phase when they normally fast (16; 17). Presumably, this is due to the responsiveness of the molecular clock mechanism to metabolites such as NADH and AMP (50-52). Second, mammalian peripheral clocks are synchronized by the daily rhythm of body temperature (53; 54). Third, peripheral clocks are also influenced by hormones that are released upon feeding, such as insulin (55-57). Taken together, accumulating evidence indicates that a major function of peripheral clocks is to prepare the mammalian body for the alternating periods of food intake (day) and fasting (night) (9; 28; 50).
Diurnal and nocturnal animals

Most studies on the circadian timing system are performed in nocturnal (night-active) rodents. From a translational point of view, it is important to consider similarities and differences between diurnal (day-active) animals including humans on the one hand, and nocturnal animals including rodents on the other hand. For excellent reviews on this topic see (59; 60).

Both in nocturnal rodents and in diurnal humans, the circadian effects of light are mediated by ipRGCs. In both species, ipRGCs detect light with the photopigment melanopsin, and integrate this information with input from the classical photoreceptors in retinal rods and cones (61). Subsequently, ipRGCs transfer the integrated light information to hypothalamic areas including the SCN (61; 62). In the SCN, the light stimulus induces c-fos expression, indicating neuronal activity, both in diurnal (63; 64) and nocturnal rodents (65; 66). The resulting phase shift of the SCN can be expressed as a function of the timing of the light pulse (the so-called phase response curve), and also these phase response curves are similar between diurnal and nocturnal species (59).

Furthermore, the daily rhythm of clock gene expression is similar between nocturnal and diurnal species. The expression of Period genes is coupled to the light period, in diurnal ground squirrels (67), sheep (68), and grass rats (69) and in nocturnal mice (70), and rats (71). To our knowledge, there are no studies investigating clock gene expression rhythms in human (post-mortem) SCN, but the daily rhythm of the neuropeptide arginine vasopressin (AVP), which is tightly coupled to the daily rhythm in clock gene expression (72) has been investigated. In human post mortem brains it was shown that AVP shows a daily rhythm in the SCN with high expression during the light period (73; 74), which is very similar to data in nocturnal rats that also show high AVP levels during the light period (75; 76). Of note, nocturnal mice show high AVP mRNA expression during the light period (72), but protein levels show a peak shortly after lights off (77). In line with data on clock gene and AVP expression, electrophysiological recordings showed increased firing activity of SCN neurons during the light phase in nocturnal rats (78-80) and mice (81), as well as in diurnal chipmunks (82).

Despite these rhythmic similarities in the SCN, nocturnal animals by definition have an opposite phase of the behavioural output (i.e., the sleep-wake rhythms) when compared to diurnal animals. The daily rhythm of glucocorticoid secretion is coupled to the active phase, with high cortisol (the major glucocorticoid in humans) levels at the beginning of the light phase in diurnal humans and high corticosterone (the major glucocorticoid in rodents) levels at the beginning of the dark phase in nocturnal rodents (reviewed in (83)).

Thus, the difference between nocturnal and diurnal animals in circadian output must originate distal from the SCN. An example of such a ‘circadian switch’ is the control by the SCN of the release of corticosterone by the adrenal gland. In nocturnal rats, vasopressin derived from SCN neurons during the light phase inhibits CRH secretion from the PVN, and thus suppresses plasma corticosterone levels (84; 85). In contrast, in diurnal grass rats, vasopressin from SCN neurons during the light phase stimulates CRH secretion from the PVN (86). Thus, in this case the circadian switch is represented by an opposite reaction by the PVN to vasopressin, the underlying mechanism probably involving GABA- and glutamate-containing interneurons surrounding the SCN (86).

For peripheral clock rhythms, there probably is a similar circadian switch. For example the diurnal rhythm in adipose tissue clock gene expression is characterised by peak Period gene expression at the onset of the active phase, i.e. the light phase for humans (24; 87) and the dark phase for rodents (88-90).

Circadian aspects of digestion and metabolism

Food intake

During the day, most people grow hungry at regular intervals. At night however, most people sleep without the arousing effect of appetite despite the much longer period of fasting. In humans, the endogenous circadian timing system controls appetite, with a circadian trough in appetite in the morning and a peak in the evening (91). Animal research suggests that the circadian control of appetite is governed by the SCN, via its connections to the hypothalamic arcuate nucleus (92-94), CRF-producing neurons in the PVN (95), and orexin producing neurons in the lateral hypothalamus (96).

The arcuate nucleus contains two sets of neurons that have a major role in the control of food intake. One subset of neurons produces Agouti-related peptide (AgRP) (97; 98) and Neuropeptide-Y (NPY) (99; 100) that serve as orexigenic signals. Another subset of neurons in the arcuate nucleus produces α-melanocyte-stimulating hormone (αMSH) (101) that serves as an anorexigenic signal. With their output signals, both subsets of neurons regulate the activity of so-called second order neurons in 1) the PVN that release neuropeptides including corticotrophin releasing hormone (CRH) (102) and thyrotropin releasing hormone (TRH) (103-105) which modulate food intake, and 2) the lateral hypothalamus, that release orexin (106-108) and increase food intake (for an extensive review on the hypothalamic control of food intake see (109)).

The involvement of the SCN in the timing of food intake was demonstrated using a number of approaches. Lesioning the SCN or isolating it from its surrounding tissue results in a loss of diurnal rhythms in food intake (110; 111), and changes of the light-dark regimen strongly affect the timing of food intake in rodents (112; 113). Furthermore, several genetic knockout models show that whole-body disruptions of the molecular clock also abolish diurnal rhythms of food intake (e.g. (114; 115)).
Gastrointestinal system
Since most people eat during the day, increased day-time activity of the digestive system would be convenient. Indeed, clear daily rhythms exist in gastrointestinal motility, exocrine secretion and the activity of digestive enzymes. First, human stomach emptying after identical meals occurs faster in the morning than in the evening (116). Furthermore, small bowel propagation velocity of the migrating motor complex (MMC) (117; 118) and colonic motor activity (119; 120) are higher during day-time than during night-time. Here, we limit ourselves to data concerning the motor activity of the human gastro-intestinal system. An extensive review covering animal experiments on circadian gastrointestinal motor activity can be found elsewhere (121).

Second, the exocrine secretion of several digestive fluids is influenced by the time of day. For example, the production of saliva increases over the day in humans (122). During fasting, human gastric acid secretion shows a daily rhythm with increased production in the evening. Presumably, this rhythm in gastric acid secretion is regulated by the parasympathetic branch of the autonomic nervous system as vagotomy (performed as a treatment for gastric ulceration) abolishes this rhythm (123). Furthermore, animal research shows that the exocrine production of pancreatic juice is increased during the period of habitual food intake (124; 125). Third, diurnal rhythms exist in the activity of digestive enzymes in the brush border of the small intestine. Oligosaccharidases including sucrase show a circadian rhythm of increased activity during the period of food intake, and this rhythm proceeds during several days of fasting (126; 127). Furthermore, transporters that absorb glucose and protein from the intestinal lumen are more active during the period of food intake in rats fed ad libitum, but this rhythm does not seem to persist under constant conditions (128; 129).

Bile acids
Classically, bile acids are considered to serve as a solvent to facilitate absorption of consumed lipids. However, it recently became clear that plasma bile acids also bind to nuclear and membrane bound receptors outside the entero-hepatic cycle. Via this mechanism, absorbed bile acids entering the systemic circulation may affect glucose and lipid metabolism (130). In humans, the hepatic synthesis of bile acids shows a diurnal rhythm with increased daytime synthesis (131; 132). Thus, it seems likely that this diurnal rhythm in bile acid synthesis represents an adaptation to the daily feeding/fasting schedule, but studies on diurnal patterns of postprandial plasma bile acid excursions are scarce.

Carbohydrates
Considering the daily rhythms in many gastrointestinal processes, it makes sense that metabolic meal responses show daily rhythms as well. Indeed, in healthy humans plasma glucose excursions after identical meals are higher in the evening than in the morning (133; 134). However, intestinal processes are not the only determinant of plasma glucose values. Plasma glucose levels depend on glucose influx from intestinal absorption and (especially during fasting) hepatic glucose production and glucose efflux to muscle, brain, adipose tissue and (after feeding) the liver.

Daily rhythms in human glucose metabolism have been clearly demonstrated by studies in which glucose is administered intravenously. A single intravenous glucose bolus results in lower plasma glucose levels in the morning than in the evening ([135; 136], for an excellent review on human circadian glucose metabolism see (137)). This phenomenon is probably caused by daily rhythms in the separate glucose fluxes. Human fasting studies suggest the presence of a day-night rhythm in hepatic glucose production (138). Animal studies from our department have shown a daily rhythm in hepatic glucose production as well, with increased glucose production at the onset of the active period, which is the dark period in nocturnal animals. The SCN determines this rhythm in hepatic glucose production (139), via a diurnal rhythm of GABA-ergic inhibitory output to pre-autonomic neurons in the PVN (43; 140). From the PVN, the SCN signal is transferred to the brainstem and spinal cord, and subsequently via parasympathetic and sympathetic nerves to the liver (43; 141). Interestingly, one of our studies not only showed that hepatic clock gene expression is independent from these autonomic signals to the liver, but moreover that rhythmic hepatic clock gene expression is sufficient to maintain the circadian rhythm in hepatic glucose production after complete hepatic denervation (142). This observation is in contrast with the proposed role of the liver clock in the regulation of gluconeogenesis (25-29), and most likely for an optimal glucose homeostasis both components are necessary.

In addition to glucose production, glucose uptake by various tissues shows daily rhythmicity as well. At rest, human skeletal muscle consumes more glucose in the morning than in the evening (136). This rhythm is probably the net result of rhythms in insulin production, insulin sensitivity and insulin-independent glucose uptake.

In healthy humans, a daily rhythm in pancreatic insulin production is observed in response to the administration of tolbutamide, with increased insulin production in the morning compared to the evening (143-145). The same rhythm has been described both in response to intravenous glucose (145-147) and intravenous glucagon (147). Cultured rat pancreatic islets show an autonomous circadian rhythm of insulin production with enhanced night-time insulin production, that persists for seven days in culture (148). In line, in vivo rats show increased night-
time insulin responses when consuming 6 evenly distributed equal meals over the 24-hour L:D cycle (149). In contrast, after intravenous glucose administration, rats show a tendency towards increased day-time insulin production (139). This paradox may be explained by the observation that in vivo, insulin-independent mechanisms also determine the circadian rhythm in glucose tolerance (see above and below), and insulin production is in itself dependent on plasma glucose levels. Furthermore, mammals show a daily rhythm in insulin sensitivity. After an intravenous insulin bolus, blood glucose levels show a more rapid decline at the onset of the activity period (light period in humans, dark period in rats), both in humans (150) and in rats (139; 151). Finally, some studies indicate a circadian rhythm in insulin-independent glucose uptake: after an intravenous glucose tolerance test, the calculated evening insulin-independent glucose uptake is lower than the calculated morning insulin-independent uptake (146), and cultured adipocytes show a rhythm in glucose uptake in the absence of insulin (152). Taken together, it is obvious that the circadian timing system strongly influences virtually all aspects of glucose metabolism. A likely physiological explanation for the daily rhythms in glucose metabolism is that an organism needs to be prepared for the active period, i.e. the period of foraging (with increased metabolic needs) and food intake (137; 153).

Lipids
In addition to carbohydrate metabolism, lipid metabolism seems adjusted to the daily rhythm of fasting and feeding as well. In humans who eat during the day, plasma free fatty acids (FFA) show a strong increase at night due to increased lipolysis during the night-time fast (154). Evidence for an underlying circadian regulation of lipolysis is provided by studies that compare morning and evening responses to identical stimuli. Thus, in the morning fasting FFA levels are lower than in the evening (145; 155; 156). Moreover, plasma FFA show a smaller decrease in the morning than in the evening, not only after an oral glucose tolerance test (156) but also after identical meals (157; 158) and after an intravenous insulin bolus (145; 155; 159). Finally, plasma levels of triglycerides and free fatty acids show a slight increase during the night in humans under conditions of continuous 3-hourly sucrose ingestion (160). The night-time increase of lipolysis is possibly regulated by the nightly surge of growth hormone (GH) secretion, since patients with GH deficiency do not show the nightly increase of FFA levels, and GH replacement (albeit in a supra-physiological dosage) restores this normal nocturnal increase of lipolysis (161). However, the autonomic nervous system may have an additional role in regulating the circadian rhythm of lipid metabolism, considering the strong effects of the autonomic nervous system on the metabolic activity of adipose tissue (162).

Furthermore, hepatic cholesterol production shows a clear day-night rhythm. In humans, cholesterol synthesis shows a strong increase during the night (163). Interestingly, in rats, hepatic cholesterol synthesis also shows an increase during the night, due to increased night-time synthesis of the rate limiting enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase (164). Thus, unlike many other physiological processes, the day-night pattern of cholesterol synthesis is not inverted in nocturnal animals.

The circadian rhythm in hepatic cholesterol synthesis has clinical implications. Clinical trials show that the cholesterol-lowering effect of simvastatin is increased when patients take the statin in the evening compared to the morning (165-167). Therefore, it is now common practice to instruct patients to take simvastatin in the evening.

Hypothesis: The circadian timing system and type 2 diabetes
The human circadian timing system evolved in the setting of a clear diurnal rhythm of light and darkness, feeding and fasting, activity and sleep. However, the development of artificial light, fridges, and the present 24-hr society, enabled many people to be active and consume food whenever they desire. As a consequence, components of the circadian timing system can be desynchronized from the behavioural rhythms of feeding/fasting and activity/sleep, or the external rhythm of light/darkness (9; 168).

Figure 2. In humans, wakefulness, food intake and anabolic metabolic processes usually coincide with the light period. Sleep, fasting and catabolic metabolic processes are coupled to the dark period. Desynchrony between components of the circadian timing system and the behavioural rhythms of feeding/fasting and activity/sleep, or the external rhythm of light/darkness may contribute to the pathophysiology of obesity and type 2 diabetes.
The first line of evidence for the desynchronization hypothesis is provided by shift workers, who by definition disturb their regular behavioural diurnal rhythms. Shift workers are at increased risk to develop obesity (172; 173) and type 2 diabetes (174). In addition, human experimental protocols that induce misalignment between the circadian timing system and external rhythms, cause reduced glucose tolerance at misalignment (175). Several rodent shift work models show negative metabolic effects of forced desynchronization (176).

Second, people with night eating syndrome (NES), characterised by excessive food intake late at night, difficulties falling asleep and frequent nightly awakenings, often show obesity and an inability to lose weight (177). In addition to desynchronization, this may be due to disturbed sleep, since we know that short sleepers are at increased risk of obesity and diabetes (reviewed in (171)). One single night of sleep disruption already strongly reduces glucose tolerance (178), while two nights of short sleep causes an increase of appetite and an increased intake of high calorie food (179).

Third, there is a seasonal variation in the incidence of type 2 diabetes (180) and in plasma glucose levels, with higher fasting plasma glucose levels in the winter in healthy subjects (181; 182) and higher plasma HbA1c levels in the winter in patients with type 2 diabetes (183-185).

Fourth, molecular studies showed reduced diurnal amplitudes of clock gene expression in rodent models of obesity and type 2 diabetes (88; 186). One human observational study in patients with type 2 diabetes showed reduced clock gene rhythms in peripheral blood leukocytes compared to healthy controls (187). Furthermore, animal studies show that germline modifications of the molecular clock can induce obesity (115; 188) and insulin resistance (115; 189). In addition, tissue specific ablation of the clock gene *Arntl* in the pancreatic beta cell (31; 190) or the liver (191) causes hyperglycemia, and adipose tissue specific *Arntl* deletion causes obesity (192). Vice versa, a recent study showed that the natural citrus peel compound nobiletin, which enhances the amplitude of clock gene expression, is effective as a treatment of obesity in several different rodent obesity models (193).

Finally, the observation of an altered daily rhythm in glucose tolerance in patients with type 2 diabetes provided the first link between disturbed circadian rhythms and the metabolic syndrome (194). Whereas healthy individuals show a decrease of insulin sensitivity towards the night (135; 195), insulin sensitivity (as measured with a 72-hour hyperglycemic clamp) increases towards the night in patients with type 2 diabetes (196). Also, when patients with type 2 diabetes are fed three identical meals, morning glucose excursions are higher than evening glucose excursions (197).

In conclusion, human and animal studies suggest that desynchrony between components of the circadian timing system and the behavioural rhythms of feeding/fasting and activity/sleep, or the external rhythm of light/darkness may contribute to the pathophysiology of obesity and type 2 diabetes.

AIM AND OUTLINE

For this thesis, our overall aim was to study the relation between light, the circadian timing system and type 2 diabetes.

In chapter 2 we describe a new rat model investigating the effects of dim light at night on the circadian control of sleep-wake behaviour and energy metabolism. In chapter 3 we describe a randomised trial investigating the direct effect of bright morning light compared to dim morning light on fasting and postprandial glucose levels, in healthy subjects and obese patients with type 2 diabetes. Rodent studies linked disturbed clock gene rhythms to the development of obesity and type 2 diabetes, but data on molecular clock rhythms in human patients are scarce. Therefore, in chapter 4, we describe a case-control study investigating the diurnal rhythm of adipose tissue gene expression (using RNA sequencing) in obese patients with type 2 diabetes compared to healthy lean control subjects. Furthermore, we investigated the diurnal rhythm in postprandial glucose excursions. In chapter 5 we describe the diurnal rhythms in postprandial bile acid excursions. Chapter 6 is a commentary on a research paper investigating the diurnal rhythm in insulin sensitivity in patients with type 1 diabetes and its consequences for the development of the artificial pancreas. In chapter 7 we describe a randomised clinical trial based on the reduced morning glucose tolerance in patients with type 2 diabetes, investigating an isoenergetic low glycaemic response breakfast as a possible treatment for patients with type 2 diabetes.
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Chapter 1

General introduction and outline
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