Light, the circadian timing system, and type 2 diabetes
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CHAPTER 8
Summary and general discussion
SUMMARY

In the present thesis, we describe several studies on the relation between light, the circadian timing system and type 2 diabetes. In chapter 1 we first introduce the circadian timing system, and describe the circadian aspects of energy metabolism. Next we discuss previous studies on the relation between the circadian timing system and type 2 diabetes.

Light is the main signal that synchronizes the circadian timing system with the external 24 hr rhythm. Therefore we first performed two studies on the circadian and metabolic effects of light. In chapter 2, we describe a new rat model for the chronic effects of light at night on the circadian control of energy metabolism and sleep. We subjected Wistar rats to either a regular 12:12 light (200 lux):dark cycle or to a 12:12 light (200 lux):dim light (5 lux) cycle. Light at night caused a strong reduction of the amplitude of the daily rhythms in food intake, sleep-wake behavior and suprachiasmatic nucleus (SCN) clock gene expression. In a subsequent circadian experiment, light at night caused a free running rhythm with a period of approximately 25 hours, in addition to the light/dark cycle entrained 24-hour rhythm. Light at night did not affect body weight or glucose tolerance. In chapter 3 we describe a randomized cross-over trial investigating the acute effects of bright morning light on plasma glucose and lipid levels in healthy men and obese men with type 2 diabetes. In healthy men, bright ambient light (4000 lux, comparable to outside light intensity on a cloudy day) did not affect plasma glucose levels, but increased fasting and postprandial plasma triglyceride levels compared to dim light (10 lux). In obese men with type 2 diabetes, bright light increased fasting and postprandial glucose levels, postprandial triglyceride levels and appetite scores compared to dim light.

Previous human studies suggested that patients with type 2 diabetes may show an altered daily rhythm in glucose metabolism, and animal models suggested that molecular clock rhythms may be altered in obesity and type 2 diabetes. Therefore, in chapter 4 we describe a case control study, in which we provided obese male patients with type 2 diabetes and age-matched healthy control males with three identical mixed meals at fixed time points, for three days. We measured postprandial glucose excursions, and adipose tissue gene expression rhythms with RNA sequencing. The healthy controls showed a diurnal rhythm of postprandial glucose excursions with the lowest glucose excursions after breakfast compared to lunch and dinner. The patients showed a partial reversal of this rhythm in glucose excursions, with highest postprandial glucose excursions after breakfast compared to lunch and dinner. Furthermore, the patients showed reduced amplitude oscillations of core clock genes compared with the healthy controls in subcutaneous adipose tissue. The patients also showed a reduction in the total number of genes with a significant diurnal expression rhythm: in patients, 1.8% (303 genes) of expressed genes showed a diurnal rhythm, versus 8.4% (1421 genes) in healthy controls. Enrichment analysis revealed that patients showed a loss of rhythm of the canonical pathways AMPK signaling, PPARα/RXRα activation and cAMP mediated signaling. In chapter 5 we describe bile acid measurements in the samples from the study described in chapter 4, to investigate if the altered diurnal rhythm in glucose excursions in patients with type 2 diabetes may be associated with an altered diurnal rhythm in postprandial bile acid excursions. We did not find a diurnal rhythm in postprandial excursions of total bile acids or individual bile acid subtypes, neither in patients with type 2 diabetes nor in lean control subjects. However, patients with type 2 diabetes did show earlier postprandial bile acid peaks compared to the control subjects.

In the next two chapters, we explored potential clinical implications of the relation between the circadian timing system and metabolism. In chapter 6 we comment on a research paper investigating the diurnal rhythm in postprandial glucose excursions with a labeled tracer technique in patients with type 1 diabetes, with the aim to improve the control algorithms of the artificial pancreas. In chapter 7 we describe a randomized controlled trial investigating a dietary intervention in patients with type 2 diabetes, based on the altered rhythm of postprandial glucose excursions in patients with type 2 diabetes as shown in chapter 4. In a randomized cross-over design, 20 patients with type 2 diabetes replaced their breakfast with an isoenergetic low glycemic response liquid formula for three months, compared to their regular breakfast for three months. As expected, the low glycemic response breakfast reduced post-breakfast glucose excursions compared to the regular breakfast, both at home and in the clinical setting. However, the reduced postprandial glucose excursions did not affect fasting plasma glucose, HbA1c or lipid levels.

Finally, in chapter 8 (the present chapter) we summarize our findings, discuss them in context of the current knowledge and provide future perspectives.
Chapter 8 Summary and general discussion

GENERAL DISCUSSION

Most mammalian species are subjected to the daily alternation of light and darkness as governed by the rotation of the earth around its axis. Conveniently, mammals possess an adaptive circadian timing system consisting of a central brain clock in the hypothalamic suprachiasmatic nuclei (SCN) and peripheral clocks in many tissues including muscle, liver and adipose tissue (1). The pivotal molecular clock mechanism is the transcriptional-translational feedback loop of the core clock genes that oscillate with a period of approximately 24 hours (2). However, in view of their imprecision, the many autonomous clocks in the mammalian body have to be synchronized to the environmental 24-hour light-dark cycle. Therefore, ambient light intensity is detected by intrinsically photosensitive retinal ganglion cells and directly transmitted to hypothalamic areas including the SCN (3). The SCN regulates the daily sleep-wake and fasting-feeding cycle through its output to other hypothalamic areas including the subparaventricular zone and the arcuate nucleus (4-6). The SCN also forwards the entrained circadian signal to peripheral clocks in metabolic tissues via the regulation of hormonal signals, autonomic nervous system activity, food intake behavior and body temperature (7).

The circadian timing system and energy metabolism are strongly intertwined. This makes sense from an evolutionary point of view, since for many organisms, food availability, the presence of other advantageous opportunities, and the presence of dangers, are linked to either the dark phase or the light phase of the diurnal cycle. At the molecular level, the transcriptional-translational feedback loop has a reciprocal relation with the cellular energy balance (i.e., NAD+, ATP and redox state) (2). At the cellular level, cultured adipocytes show autonomic circadian rhythms in glucose uptake (8), insulin sensitivity (9) and lipolysis (10). At the tissue level, isolated pancreatic islets show a circadian rhythm in insulin secretion (11) and need a functional clock to enable insulin secretion (12). At the organ level, healthy human beings show diurnal rhythms in pancreatic insulin secretion (13; 14) and whole body insulin sensitivity (15). Animal studies showed that the circadian rhythm in insulin sensitivity is dependent on a functional SCN (16), as well as a functional molecular clock (17).

Obviously, also the regulation of the sleep-wake cycle is strongly tied to the circadian timing system. The regulation of sleep drive is classically considered to be a combination of homoeostatic sleep drive (sleep debt) and circadian sleep drive (18). The SCN forwards its signal to the subparaventricular area and orexin neurons in the perifornical area, which both have a pivotal role in sleep-wake regulation (6; 19). In constant conditions, humans show persisting circadian sleep-wake rhythms (with individual-specific period duration) (20). Interestingly, sleep quality directly affects glucose metabolism, since one night of disturbed sleep already causes reduced insulin sensitivity in healthy humans (21).

Technological advances such as artificial light and fridges enable people in modern society to perform activities and consume food at any time around the 24-hour cycle. These advances coincide with the current pandemic of obesity and type 2 diabetes (22; 23), two correlated disorders that frequently cluster in the metabolic syndrome (24). Classically, obesity and type 2 diabetes are thought to result from excess energy intake in combination with reduced physical activity (25). However, in addition to this quantitative disbalance, desynchronization between daily rhythms in behaviour and food intake and the various clocks in the body, may also contribute to the pathophysiology of the metabolic syndrome. For the present thesis, we hypothesized that desynchrony between the circadian timing system and behavioral rhythms of feeding/fasting and activity/sleep, or the external rhythm of light/darkness, contribute to the pathophysiology of type 2 diabetes. This hypothesis is supported by the observation that shift workers are at increased risk to develop obesity and type 2 diabetes (26). Also evening chronotypes (owls) are at increased risk to develop obesity and type 2 diabetes compared to early chronotypes (larks) (27; 28). Experimental protocols that induce misalignment between the internal circadian timing system and the external world, induce reduced glucose tolerance in humans (29) and obesity in mice (30). In addition, with transgenic animal models, it was shown that tissue specific ablation of the clock gene Arntl in pancreatic beta cells (12; 31) or liver (32) causes hyperglycemia and that adipose tissue specific Arntl ablation causes obesity (33).

Ambient light is the main synchronizing input of the circadian timing system. As a consequence of the ubiquitous availability of artificial light, many people are exposed to light during the habitual dark phase, either in the form of light pollution (sky glow) or by voluntarily turning on the lights at home. The exposure to light at night is correlated to obesity (34; 35) and diabetes (36) in humans. In Swiss Webster mice, exposure to light at night induces obesity and diabetes by increasing food intake during the daytime (the habitual fasting period for nocturnal mice) without affecting total food intake (37; 38). In chapter 2, we aimed to develop a rat model for the effects of light at night on the circadian control of energy metabolism and sleep. We subjected Wistar rats to either a regular 12:12 light (200 lux):dark cycle or a 12:12 light (200 lux):dim light (5lux) cycle. Similar to the mouse model, light at night caused a shift of food intake to the light (inactive) phase with no effects on total food intake. In addition, light at night caused a major redistribution of the vigilance states, with a gradual reduction of sleep during the light (inactive) phase and a gradual increase of sleep during the dark (active) phase. The combination of a reduced rhythm in the circadian 16-19Hz frequency domain of NREM sleep, and an increased effect of dim light at night on sleep over time, suggested an altered circadian control of sleep-wake behavior. Indeed, the diurnal expression rhythm of the clock genes Per1 and Arntl showed a reduced amplitude in the SCN.
In chapter 3, we studied the effects of light on the circadian timing system and energy metabolism, it is important to take into account the immediate effects of light. In rats, a single light pulse affects the hepatic expression of the gluconeogenic enzyme PEPCK (45) and recent observations from our lab indicate that light has a time-dependent immediate effect on intravenous glucose tolerance (unpublished observations). In chapter 3, we studied the effects of bright ambient light on fasting and postprandial plasma glucose and lipid levels in healthy human subjects and patients with type 2 diabetes. In healthy men, bright ambient light (4000 lux, comparable to outside light intensity on a cloudy day) did not affect plasma glucose levels, but increased fasting and postprandial plasma triglyceride levels compared to dim light (10 lux). In obese men with type 2 diabetes, bright light increased fasting and postprandial glucose levels, postprandial triglyceride levels and appetite scores compared to dim light. The effects of light on plasma glucose and triglyceride levels may be mediated through increased sympathetic output to the liver and the pancreas, as suggested by the finding of increased heart rate and LF/HF ratio in heart rate variability in bright light. In line, animal studies also showed increased sympathetic nerve activity upon retinal light exposure (46) and increased sympathetic signaling towards the pancreas has been shown to decrease insulin secretion (47). Indeed, our C-peptide minimal model analysis suggests reduced beta cell sensitivity due to bright light (compared to dim light) in obese men with type 2 diabetes. Sympathetic signaling is also known to increase hepatic VLDL secretion (48). The physiological function of increased plasma glucose and triglyceride levels due to bright light exposure in the morning may be to mobilize energy in order to prepare the body for the diurnal activity phase. In conclusion, in chapter 6 we showed for the first time that ambient light intensity has an immediate effect on fasting and postprandial glucose levels in patients with type 2 diabetes. Our findings are important for the interpretation of long term circadian studies investigating the effects of light on metabolic health, as well as for the interpretation of plasma samples obtained for the diagnosis and follow up of type 2 diabetes and dyslipidemia.

The circadian rhythm in glucose metabolism has been an area of investigation since 40 years. In the 70’s it was discovered that healthy human subjects show a diurnal rhythm in glucose tolerance with lower glucose excursions in the morning versus the evening, both after identical meals (49; 50) and after intravenous glucose tolerance tests (51; 52). Furthermore, increased pancreatic insulin production in the morning versus the evening was demonstrated with timed tolbutamide administration (53; 54). Increased morning versus evening insulin sensitivity was demonstrated with intravenous insulin tolerance tests (15). In a recent study using labeled tracers it was demonstrated that in healthy subjects, reduced morning versus evening postprandial glucose excursions are caused by a combination of increased beta-cell sensitivity, increased inulin sensitivity and reduced hepatic insulin extraction (55). Animal studies from our department showed that the diurnal rhythm in glucose tolerance is governed by the SCN (16), via a GABA-ergic inhibitory output to pre-autonomic neurons in the PVN. From the PVN, the signal is forwarded to the liver via projections to the brainstem and spinal cord and parasympathetic and sympathetic nerves innervating the liver (56; 57). In fact, the observation that the daily rhythm in glucose tolerance may be altered in patients with type 2 diabetes was one of the first clues linking circadian rhythms to the metabolic syndrome (58). However, until now, the diurnal rhythm in postprandial glucose excursions of patients with type 2 diabetes has never been compared to healthy subjects in a single prospective design. Therefore, in chapter 4 we provided obese patients with type 2 diabetes and age-matched healthy control subjects with three identical mixed meals at fixed time points, for three days. With continuous glucose measurements as well as plasma samples, we confirmed that the normal diurnal rhythm in postprandial glucose excursions (lower glucose excursions in the morning) was lost in patients with type 2 diabetes. In fact, patients with type 2 diabetes showed higher postprandial glucose excursions after breakfast compared to lunch and dinner. Possibly, this loss of rhythmicity may be related to the observed alterations in peripheral molecular clock functioning in patients with type 2 diabetes, as described in the following paragraph.

Also in chapter 4, we analyzed the diurnal rhythm of adipose tissue gene expression. The accumulation of adipose tissue is a key process in the pathophysiology of the metabolic syndrome. Like all other metabolic tissues, adipose tissue contains an autonomous molecular clock. Adipocytes show circadian rhythms in glucose uptake (8) and lipolysis (10). The adipocyte clock regulates adipogenesis (59), and adipose tissue specific ablation of the clock gene Arntl causes obesity in mice (33). In mouse models of the metabolic syndrome, the adipocyte clock shows reduced amplitude...
diurnal oscillations (60; 61). However, data on the diurnal rhythm of adipose tissue gene expression in humans with type 2 diabetes are limited. Using RNA sequencing, we detected reduced amplitude oscillations of core clock genes in obese patients with type 2 diabetes compared to age-matched healthy subjects. Furthermore, patients showed a reduction in the total number of genes with significant diurnal expression rhythms: In patients, 1.8% (303 genes) of expressed genes showed a diurnal rhythm, versus 8.4% (1421 genes) in healthy control subjects. Enrichment analysis revealed that patients showed a loss of rhythm of the canonical pathways AMPK signaling, PPARα/ RXRα activation and cAMP mediated signaling which are involved in the regulation of cellular energy balance and lipolysis. The reduced amplitude of intracellular metabolic signaling pathways may contribute to increased FFA levels, and altered adipocyte differentiation in patients with type 2 diabetes.

To generate insight in the pathophysiological mechanisms in the development of obesity and type 2 diabetes, other authors used a single time point adipose tissue transcriptomics approach (62; 63). We showed in an additional analysis that the selection of sampling time affects the identified genes, canonical pathways and upstream regulators. Furthermore, investigating only the 1392 genes with either upregulation or downregulation at all time points yielded increased power to detect between-group differential expression. We identified the upregulated canonical pathway LPS/IL-1 mediated inhibition of RXR function, which may be involved in altered lipid biosynthesis in patients with type 2 diabetes. Potential upstream regulators with increased activity include TNF and TGFβ1, in line with previous literature on the role of these inflammatory mediators in insulin resistance (64-66). Potential upstream regulators with decreased activity include FOXA1, which may be related to the development of obesity (67), and AMPK which has a central role in cellular energy metabolism (68). Novel adipocyte treatment targets may be represented by additional identified upstream regulators, such as the ubiquitin ligase SYVN1 which affects body weight in mice (69), the ubiquitin ligase MDM2, and the transcription factor EHF. In conclusion, in chapter 4 we showed the first evidence of reduced diurnal expression rhythms of circadian and metabolic genes in obese patients with type 2 diabetes compared to lean control subjects.

In chapter 5 we investigated if the altered diurnal rhythm in glucose tolerance in obese male patients with type 2 diabetes may be due to an altered diurnal rhythm in postprandial bile acid excursions. The hypothesis for chapter 5 was based on the observations that 1) bile acid synthesis has a clear diurnal rhythm in humans (70; 71), and 2) reabsorbed bile acids may affect hepatic glucose production as well as muscle insulin sensitivity (72). We measured postprandial bile acid concentrations in plasma from the study described in chapter 4. We did not find a diurnal rhythm in postprandial excursions of total bile acids or individual bile acid subtypes, neither in patients nor in healthy controls. Therefore the hypothesis that the altered diurnal rhythm in glucose tolerance in patients was the result of an altered rhythm in postprandial bile acid excursions was rejected. We did however detect earlier postprandial bile acid peaks in patients, which may be explained by increased intestinal uptake or decreased liver sinusoidal uptake of bile acids (73). Specifically, increased intestinal absorption can be facilitated by hypertrophic changes of the gut mucosa in patients with type 2 diabetes (74; 75). In addition, the expression of hepatic BA transporters shows a negative correlation with BMI (76), and reduced hepatic BA uptake may contribute to the earlier peak levels in patients with type 2 diabetes. The difference in peak time did not extend to differences in BA peak concentrations or AUCs, which are mostly determined by meal size and composition (77).

A potential clinical implication of the diurnal rhythm in insulin sensitivity is related to the development of the artificial pancreas. The artificial pancreas consists of a glucose sensor, an insulin pump and an automated control algorithm. In theory, knowledge of diurnal patterns in insulin sensitivity may improve control algorithm functioning. In chapter 6 we comment on a research paper investigating the diurnal rhythm in postprandial glucose excursions with a labeled tracer technique in patients with type 1 diabetes, aimed at improving artificial pancreas control algorithms (78). Chapter 6 is the only chapter of this thesis concerning patients with type 1 diabetes. Whereas type 2 diabetes results from reduced insulin sensitivity and eventually beta-cell exhaustion, type 1 diabetes results from auto-immune destruction of pancreatic beta cells, and therefore mainly reduced insulin secretion. Consequently, the development of the artificial pancreas was primarily aimed at the treatment of patients with type 1 diabetes (79), although recent studies have applied the artificial pancreas also in patients with type 2 diabetes (eg.(80; 81)). The research paper did not find a diurnal rhythm in any of the investigated parameters of glucose metabolism in patients with type 1 diabetes (78), which may be due to large intersubject variability. Individual diurnal patterns were not described, and thus it may be possible that individual subjects do show diurnal rhythms. Therefore, the question whether the artificial pancreas control algorithm may benefit from knowledge of diurnal patterns in glucose metabolism remains to be answered.

Dietary interventions may represent another practical implication of the diurnal patterns in glucose tolerance. In chapter 7 we aimed to use the pattern of increased glucose excursions after breakfast compared to lunch and dinner (as described in chapter 2) for a dietary treatment of patients with type 2 diabetes. In a randomized clinical trial with a cross-over design, we provided 20 patients with type 2 diabetes with a low glycemic response liquid formula as an isoeenergetic replacement of their regular breakfast for three months, compared to their regular breakfast for three months. As expected, the low glycemic response breakfast
reduced post-breakfast glucose excursions compared to the regular breakfast, both at home and in the clinical setting. However, the reduced postprandial glucose excursions did not affect fasting plasma glucose, HbA1c or lipid levels. Possibly, replacing only the breakfast meal may be insufficient to affect long term glycemic control, and it may be necessary to replace multiple meals per day. Alternatively, the absence of a clinically relevant effect may be due to low baseline HbA1c levels of included patients, which makes it difficult to further improve their glycemic regulation. Thus, the question whether the daily rhythm in glucose tolerance provides opportunities for dietary interventions in poorly regulated patients with type 2 diabetes, remains open for investigation.

CONCLUSIONS

In conclusion, in this thesis we investigated if disturbances of the circadian timing system may be involved in the pathophysiology of type 2 diabetes. We showed in a rodent study that the low intensity of 5 lux light at night decreases the amplitude of the daily sleep-wake and feeding-fasting rhythms, by introducing a behavioral free running rhythm of approximately 25-hour in addition to the entrained 24-hour rhythm. These rhythm disturbances however did not affect body weight or glucose tolerance. In a human intervention study, we showed that ambient light intensity directly affects glucose metabolism in patients with type 2 diabetes. Furthermore, in a case control study we demonstrated that obese patients with type 2 diabetes show a strong reduction of the diurnal rhythm of 1) postprandial glucose excursions, and 2) adipose tissue circadian and metabolic gene expression compared to healthy subjects. Thus, the major effects of a small amount of light on circadian synchrony, the immediate metabolic effects of light on humans, and the alterations of circadian metabolism in patients with type 2 diabetes, together support our hypothesis that disturbances in the circadian timing system may contribute to the pathophysiology of type 2 diabetes.

Also in this thesis, we explored potential clinical implications of circadian disturbances in patients with type 2 diabetes. As described in a commentary, the question whether the artificial pancreas may benefit from the knowledge of circadian time remains open for investigation. Furthermore, we performed a randomized clinical trial investigating a dietary intervention specifically aimed at reducing post-breakfast glycemia. This intervention was based on the observation of reduced morning glucose tolerance in patients with type 2 diabetes. Despite clear effects on postprandial glycemia, fasting plasma glucose and HbA1c levels were not affected, which may be due to the low baseline HbA1c levels of included patients.
**FUTURE DIRECTIONS**

Our findings provide leads for future studies, on the level of basic science and in terms of clinical applications.

In **chapter 2** we observed in a rodent model that dim light at night can induce behavioral desynchronization by introducing an approximately 25-hour rhythm in addition to the entrained 24-hour rhythm. Yet, we did not identify the neuronal origin of this free running rhythm. Others have shown that desynchronization between SCN subdivisions can represent behavioral desynchronization (42), but never in a normal 12:12 L:D schedule. Our *in situ* hybridization results showed a clear disturbance of SCN rhythmicity but no desynchrony between SCN subdivisions, which may be due to reduced sensitivity of our two time point approach. Future studies with clock-gene luciferase transgenic animals (82) or *ex vivo* electrophysiological recordings may elucidate the origin of the 25-hr free running rhythm. In addition, future studies will explore methods to prevent rhythmic desynchronization in this model, for example via timed food restriction, thereby using the reciprocal connections between the SCN and the arcuate nucleus (4; 5; 83).

In **chapter 3** we observed a direct effect of light on plasma glucose and triglyceride levels in humans. Our results suggest that optimization of ambient light exposure is a potential strategy to prevent or treat hyperglycemia and dyslipidemia. Therefore, the metabolic effects of bright light at other times across the 24-hr cycle, the metabolic effects of other light intensities and wavelengths, and the long term effects of modified ambient light exposure on the prevention and treatment of hyperglycemia and dyslipidemia need to be evaluated in future clinical trials.

In **chapter 4** we observed reduced diurnal rhythms of adipose tissue gene expression *in vivo* in patients with type 2 diabetes compared to healthy subjects. The major question to be resolved is whether these reductions are cause, consequence, or a combination of cause and consequence, of the reduced insulin sensitivity in patients with type 2 diabetes. Cell culture models including immortalized mouse pre-adipocytes lines or human *ex vivo* pre-adipocytes may elucidate the causal relation. In a pilot experiment we showed that the induction of insulin resistance in differentiating 3T3-L1 pre-adipocytes causes reduced clock rhythms (unpublished observations), suggesting that reduced clock rhythms are at least in part the result of reduced insulin resistance. Future experiments may investigate if improving clock rhythms in pre-adipocytes actually improves insulin resistance.

In **chapter 7** we showed that an isoenergetic low glycemic response breakfast replacement can strongly reduce postprandial glycemia in the home setting in patients with type 2 diabetes. However, after three months there was no effect on plasma HbA1c levels, which may be due to the low baseline HbA1c levels of included patients. Future trials should determine if a similar strategy is effective in patients with high baseline HbA1c levels.

Finally, our observations of reduced metabolic rhythms in patients with type 2 diabetes in **chapter 4**, in combination with animal (30; 37; 84) and human (26; 29) data showing adverse effects of circadian desynchronization, provides ground for a combined lifestyle intervention aimed to improve circadian functioning in patients with type 2 diabetes. For example the combination of morning light and exercise, and a regularly timed diet may affect the molecular clock and improve metabolic health in patients with type 2 diabetes. Furthermore, genetic screens identified several circadian molecules that improve molecular clock rhythms (85). In a recent study, it was demonstrated that the natural compound nobiletin was able to reduce obesity and improve glucose tolerance in different rodent obesity models, by enhancing *clock* rhythm amplitude (86). It seems likely that within several years, the first circadian molecules will be assessed in human clinical trials.
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