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Review

Should we listen to our clock to prevent type 2 diabetes mellitus?

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ABSTRACT

The circadian clock drives a number of metabolic processes including energy intake, storage and utilization coupled with the sleep/wake cycles. Globally, the increasing prevalence of type 2 diabetes (T2DM) has become a significant international public health concern. In view of the heavy societal burden caused by diabetes, and further, to reduce its growing incidence, it is clearly essential to understand the causes of this disease and to devise more effective strategies for its treatment. Although many factors cause T2DM, this article centers on the role of circadian regulation of metabolism. The correlation between the increased occurrence of T2DM and the ubiquity of modern social pressures such as 24/7 lifestyles as well as nocturnal lighting conditions point strongly to the hypothesis that malfunctioning of circadian controls may be involved in the etiology of the illness. Nocturnal light exposure, unusual timing of food, irregular sleep/wake schedules and traveling between different time zones are some of the factors responsible for improper entrainment of the clock. Recent reports have proposed that strengthening of circadian clock functioning and proper timing of food intake could stabilize glucose homeostasis. This strategy thus represents a chronotherapeutic option for non-pharmaceutical intervention in treating T2DM patients.

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1. Introduction

Globally the prevalence of diabetes has progressed at an alarming rate and has become a significant international public health concern. According to the International Diabetes Federation, 382 million people (8.3%) worldwide currently have diabetes. Further, this number is expected to increase to 592 million, implying that there will be around a 50% increase in diabetes by 2035 [1]. In 2012, the worldwide mortality rate associated with diabetes was 4.8 million people, while the associated level of expenditures to treat diabetes and its related complications amounted to 471 billion US dollars [2]. In view of the heavy societal burden caused by diabetes, and further, to reduce its growing international prevalence, it is essential to understand the causes of this disease and to devise more effective strategies for its prevention and treatment.

This article focuses mainly on type 2 diabetes mellitus (T2DM) since it constitutes up to 90% of the diabetes population. A number of factors play an unequivocal role for increasing the risk of developing T2DM. These factors include pancreatic β cell dysfunction, abnormal adipogenesis and absence of adequate insulin responsiveness [3], genetic susceptibility [4], excessive food consumption and/or high calorie food intake [5] and a sedentary life style [6–8]. In addition to these predisposing factors there is now an increasing amount of evidence that disruption of circadian timing mechanisms contributes to the development of T2DM [9–13]. Various types of circadian disturbances have been correlated with the onset of T2DM including disruption of the timing of bodily functions that are normally synchronized [9,12,13], improper timing of food intake [14], dampened clock gene expression and polymorphisms [15–17], sleep loss/disturbance [6,18–20] and impairments to the melatonin signaling pathway [21,22].

2. Clock genes are involved in maintaining circadian rhythms in cells

Circadian rhythms in organisms are driven by three components including input factors (zeitgebers), the molecular clock network, and the generation of rhythmic output. Zeitgebers (time cues) set the clock for about a 24 h period and the quality of the entrainment depends on its strength. At the cellular level, clock genes are involved in the regulation of circadian rhythm. Mutational studies of clock genes have aided in the understanding of their function in the maintenance of circadian rhythm and other physiological processes, including metabolism. Their expression is controlled by environmental zeitgebers (such as light/dark cycles/food/social cues). The circadian clock system consists of transcription–translation loops comprising clock gene products and occurs once in a day or about 24 h. Advances and delays in the circadian period are regulated by the modification of mRNA and protein concentration of clock genes [23]. So far, many clock genes involved in the feedback loop have been identified in humans. These include *Clock* (Circadian locomotor output cycles protein kaput), *Npas2* (Neuronal PAS domain protein2), *Bmal1* (Brain and muscle ARNT-like protein), *Per1* (Period), *Per2*, *Per3*, *Cry1* (Cryptochrome), *Cry2*, *Rev-Erbs* (Reverse erythroblastosis virus α/β), *Rors* (Retinoid-related orphan receptors $\alpha/\beta/\gamma$) and *CkI* (Casein kinase). CLOCK and BMAL1 form a heterodimer and then bind to E-box sequence and promote the transcription of three *Per* genes (*Per1*, *Per2* and *Per3*), two cryptochrome genes, (*Cry1* and *Cry2*) *Ror*α and *Rev-Erb*α [24]. PER and CRY bind together to form a complex and this dimer blocks the transcription process of CLOCK and BMAL1, thus completing the negative limb of the loop. PER and CRY proteins are phosphorylated by *CkI*ε and *CkI*δ. This phosphorylation process and degradation of PERs can be considered as rate limiting steps in the regulation of circadian periodicity [25]. Moreover, REV-ERBα is a nuclear-receptor protein which suppresses *Bmal1* transcription. The function of *Clock* has been replaced by *Npas2* in the suprachiasmatic nucleus (SCN) but peripheral clocks require CLOCK for their normal time keeping function [26]. Although many of the functions of clock genes have been elucidated, their molecular mechanism remains complex and requires further exploration.

3. Circadian disruption results in impaired glucose metabolism

Among the numerous physiological functions which are governed by the circadian apparatus is glucose metabolism

Table 1 – Clock gene mutations showing aberrant phenotypes similar to diabetes.

Clock gene	Metabolic abnormalities	References
Clock	Hyperleptinemia, hyperlipidemia, hyperglycemia, hypoinsulinemia, attenuated feeding rhythm, decreased level of polypeptides associated with energy balance, impaired gluconeogenesis, dampened glucose tolerance, reduced pancreatic cell size, delayed growth and development, low expression of genes involved in insulin signaling and glucose response	[32,33,35]
Bmal1	Impaired glucose metabolism, impaired gluconeogenesis, hypoglycemic during resting phase, glucose intolerance, altered expression in glucose metabolic genes, adipocytes differentiation, adipogenesis, hypoinsulinemia, reduced pancreatic cell size, delayed growth and development, loss in insulin rhythm, increased levels of triglycerides, fatty acids, cholesterol	[10,11,33,35,36,40]
Per2	Absence of glucocorticoid rhythm, obesity, lack of rhythmic feeding, altered expression of neuropeptides responsible for appetite regulation, high level of corticosterone	[34]
Cry1/Cry2	Glucose intolerance, high level of corticosterone	[41]
Rev-erbα/Rev-erbβ	Hepatic steatosis, hyperlipidemia, altered lipid metabolism	[38,39]
Per3	Adipogenesis, altered body mass and composition	[37,42]

[10,27]. It is now known that the distribution of glucose to all parts of the body is organized by the molecular clock present in liver [11]. Half of the nuclear receptors identified in liver and adipocytes exhibit a 24 h periodicity [5,28]. Circadian regulatory mechanisms utilize both neural and humoral communication to exert close control over insulin, leptin and plasma glucose levels [29]. Rats in which the SCN, where the central circadian pacemaker resides, has been lesioned show abnormalities in glucose metabolism and insulin function [30,31]. Direct evidence of the association between circadian clock disruptions and T2DM has been provided by studies in mice in which linkages between clock gene mutations and diabetes states have been examined [10,11,32–39] (Table 1). It has been demonstrated that factors associated with glucose optimization and appetite control are impaired in circadian clock mutant mice [32,33,35].

Deletion of *Rev-erbα/β* in mice has been shown to result in hepatic steatosis, abnormal lipid metabolism, and high circulating glucose and triglyceride levels [38,39]. High circulating levels of triglycerides, free fatty acids and cholesterol have also been reported in mice devoid of *Bmal1* [36]. *Per2* mutant mice have been shown to exhibit several abnormal profiles including absence of rhythmicity in plasma glucocorticoid levels, obesity and low levels of neuropeptides involved in appetite regulation [34]. Hence, the core clock gene, *Per2*, is essential for the maintenance of the glucocorticoid pathway and its expression significantly alters glucose metabolism [43]. It has also been shown that the presence of clock gene mutations promotes delays in pancreatic gene expression, which in turn affects the regulation of the growth, development and survival of insulin cells and thus of the glucose signaling pathway [35]. In one study *Clock* mutant mice showed lack of rhythmicity in the action of insulin, a state which was reversible once the clock protein was re-introduced [10]. Additional confirmatory evidence of circadian control over metabolic activity was provided by a study of mice in which the *Bmal1* gene was knocked specifically in the pancreas. This produced an animal model which replicated T2DM in that blood glucose levels were found to be elevated throughout the 24-h cycle [35].

In mice, lipid storage and synthesis occurs during the feeding/wakefulness cycle whereas during the fasting/rest cycle, the metabolic mode converts to producing glucose. Similarly, insulin responsiveness and glucose levels undergo predictable variations which closely follow the rest/fasting and feeding/wakefulness cycles [10]. Abnormal sleep times and poor sleep quality are associated with low levels of glucose tolerance in humans, further suggesting that sleep disturbance could be a major contributing factor to the development of diabetes [5,19,44]. The maintenance of glucose levels, which is critical for survival, depends on the close synchronization of key functions in the glucose cycle. Taken together, the accumulated experimental evidence supports the hypothesis that in the absence of circadian regulation, the ensuing desynchrony could induce a metabolic disorder which, if sustained, could ultimately cause T2DM [45].

4. Experimental circadian disruption causes a prediabetes state

Stimulation of circadian disruption in diabetes-prone human islet amyloid polypeptide transgenic rats has been shown to produce a rapid manifestation of T2DM. In one study diabetes prone genetically engineered rats were maintained in LL and jet lag like conditions (6 h phase advance). This treatment led to circadian disruption, which was confirmed by aberrations in the animals' locomotor behavior and melatonin secretion. This experimental treatment produced metabolic impairments in glucose-triggered insulin synthesis, increased beta cell apoptosis, and a consequent decrease in beta cell population resembling diabetes [13]. Similar findings were obtained in a study of 10 humans subjected to a forced desynchronization protocol for a period of 28 h. The treatment produced circadian misalignment in all subjects, with three individuals exhibiting a disturbed glucose metabolism which resembled diabetes [12]. Also, all subjects showed a decreased concentration of leptin, a reversal of cortisol rhythm and high amounts of glucose (postprandial) even in the presence of increased insulin. Reduced levels of leptin could potentially produce an abnormal appetite and energy utilization resulting in diabetes and obesity. Additionally, it has been suggested that increased levels of cortisol late in the day, i.e., during the end of wakefulness, are a possible potentiating factor for

insulin resistance and hyperglycemia [10]. These findings thus suggest that misalignment of clock functions may accelerate the development of T2DM.

5. Importance of timing of food in T2DM

Important metabolic processes are dictated by the timing of food intake. Indeed, a peripheral oscillator activity, a mechanism by which circadian cycles are regulated in peripheral tissues, closely controls temporal processes in liver and pancreas [46]. Hormones involved in food metabolism showed rhythmic fluctuations and their secretion altered according to the availability of food [47]. Disruptions of the timing of food intake have been shown to promote obesity and impaired glucose metabolism in mice, thus supporting suggestions that clock mechanisms and T2DM are related [14,32,48]. Experimental restriction of feeding cycles has been found to alter clock gene expression in streptozotocin-induced diabetic rats more effectively than in controls [48]. Blood glucose level is directly related to the food intake in streptozotocin-induced diabetes, thus indicating that the circadian clock system is weakly coordinated in diabetes. Conversely, restrictions in the feeding cycle can improve glucose metabolism and motor regulation in mice in which a metabolic syndrome had been induced [49]. In one study mice fed during the daytime accumulated more body mass than the mice fed during the night time, additionally underscoring the importance of timing factors in food intake in maintaining normal glucose and motor functioning [14]. In *Clock* mutant mice, the time of feeding occurred both during light and dark phase whereas food intake is more concentrated towards dark phase in wild-type mice [32]. Lack of rhythmic feeding has been reported in *Per2* mutant mice [34].

Night light exposure, even at low levels, has been reported to alter food timing and body mass accumulation in mice, thus suggesting that artificial lighting may be an important contributing factor to the increased prevalence of metabolic disorders [27,50]. It was speculated that peripheral clocks could be entrained by manipulating the timing of food administration, and that this could be accomplished without the participation of the SCN [46]. Taken together, all of the cited evidence suggests that the administration of food at inappropriate times may disrupt the metabolic profile, thus creating a desynchronized physiological state which is causally linked to the development of T2DM.

6. Perturbed circadian rhythm contributes to obesity

Many studies have demonstrated that a link exists between perturbation of circadian rhythms and obesity. Body mass and composition in SCN-lesioned mice are altered, with more fat tissue accumulated than in the sham operated mice [31]. High-calorie food intake in mice [51] and rats [52] has been shown to disrupt circadian organization, further indicating that clock activity and metabolic processes are closely linked. Also, mice that are fed high fat diets have been shown to develop obesity and dampened glucose tolerance, when these markers are measured in altered lighting conditions [51]. Moreover, the circadian period of fat tissue is different from the circadian period of sleep/wake cycle of animal. These findings thus indicate that an internal desynchronization of the time keeping organization between master pacemaker (SCN) and peripheral oscillator (adipocytes) may play a central role in reduced glucose tolerance [10,50]. The feeding of *Clock* mutant mice with a high calorie diet was found to produce an accumulation of body mass and energy to a level about twice that of controls [32]. Mice which totally lack *Per3* have an altered body mass and body composition [37]. Additionally, compared to normal wild mice controls, mice which lack the *Per3* accumulate more adipose tissue [42]. The constant expression of *Per3* has been found to inhibit adipogenesis in mesenchymal stem cells whereas *Per3* removal enhanced the process, thus supporting the inference that adipogenesis is regulated by circadian clock activity [37]. It is well-established that obese individuals are more susceptible to T2DM [53,54].

7. Genetic variant association studies

The possible association between clock gene polymorphisms and T2DM has been explored in several investigations in humans. In one study a polymorphic allele was identified in *CRY2* which correlated with T2DM [55]. Two *BMAL1* variants have been found to be associated with diabetes and hypertension in a British population [56]. Circadian clock variants have been linked to metabolic syndrome and obesity affected individuals [57,58]. For example, in a recent study which sought to examine the existence of *Per3* variants in patients with T2DM we reported that, compared to the group without diabetes, the frequency of occurrence of the five repeat allele of *Per3* among affected patients was greater, and that of the four repeat allele less [17]. Circadian clock variants have also been found to correlate with body mass index (BMI) [59], and with weight loss, sleep duration and total plasma cholesterol in obese Caucasian individuals [60]. Although the number of genetic association studies remains limited their findings are suggestive that clock gene variations are involved in the onset of T2DM.

8. Impaired clock gene expression in T2DM

Several studies demonstrate associations between genetic markers of circadian regulation and metabolic disruption. High fat diet intake in rats alters the 24 h rhythmic expression of clock genes, thus implicating the existence of an association between glucose and time keeping mechanisms [52]. In an animal model of diabetes, restricted food cycles were found to alter clock gene expression under cycling environmental light/dark (LD) conditions [61]. Reversing the LD conditions resulted in significant changes in behavioral activity in control rats whereas no shift was observed in rats with diabetes [62]. LD reversal produced larger variations in blood glucose levels of rats with diabetes than in controls. Both observations suggest that the changes in behavior and insulin levels are due to misalignment of clock functioning as a result of LD changes [62].

In T2DM patients, clock gene expression has been found to be directly associated with fasting glucose levels as well as with insulin mRNA and protein concentration [63]. Additionally, markedly reduced levels of clock transcripts have been reported in T2DM patients [15,16,63]. Further, in an in vitro model mimicking pathogenetic conditions, the PER3 mRNA level was reduced in human islets exposed to a high glucose concentration [64]. The current evidence thus suggests that these processes have a reciprocal relationship since an abnormal functioning of metabolism promotes low expression of clock genes while an impaired clock functioning can disrupt metabolic activity. The findings thus underscore the importance of circadian regulation for normal metabolic functioning, and further, that clock gene expression appears to be disturbed in T2DM.

9. The relationship of insulin with melatonin

Melatonin plays a vital role in the regulation of many body functions including circadian rhythm, aging, tumor growth, mood behavior, immunity, reproduction and sleep [65]. Information in the form of light signaling is transduced by the retinal cells and is further transmitted to the pineal gland via the SCN. Melatonin peaks during the night time hours but is undetectable during the light phase. Melatonin synthesis, which is influenced by the presence of light, thus exhibits a circadian pattern. Dusk promotes the onset of melatonin whereas dawn suppresses the secretion. The secretion of melatonin is regulated by circadian clock whereas circadian clock is entrained by environmental zeitgebers [66]. When individuals were exposed to artificial light before sleep time, their melatonin secretion levels were suppressed [67]. Proper light intensity entrains the clock whereas inadequate light or exposure to light at unusual times of the night can inhibit the secretion of melatonin [68].

Several lines of evidence point to the conclusion that the reported variations in insulin sensitivity in T2DM patients are the result of circadian influences and are independent of glucose concentration, insulin metabolism, rest/activity cycles or food intake [10,69,70]. The possibility that a relationship might exist between melatonin and T2DM is supported by findings that insulin secretion is inversely proportional to plasma melatonin concentration [22]. It is known that melatonin can alter insulin function [71] and that, compared to normal healthy individuals, T2DM patients have lower circulating levels of melatonin [72]. In vitro co-incubation of pancreatic cells with melatonin has been shown to inhibit the glucose-mediated release of insulin, additionally supporting the conclusion that melatonin activity plays a role in the function of insulin [22]. Further, circadian disruption has been shown to alter melatonin secretion and to cause dysfunctions in pancreatic β cells. Genetic association studies which have shown that mutations in the melatonin receptor gene are correlated with an increased susceptibility to T2DM [21,73,74]. Circadian disruption may lead to abnormal phasing and synthesis of melatonin, a finding which has been reported in night shift workers [75,76]. It could be postulated that alteration of phase, amplitude and synthesis of melatonin could lead to impaired glucose metabolism in circadian disrupted individuals [21]. Suppression of melatonin secretion by nocturnal light exposure could be a crucial factor for T2DM development [27]. Taken together, multiple sources of evidence support the conclusion that melatonin can alter the activity of pancreatic cells, activity which is essential for preventing the development of a diabetes state.

10. Consideration of clock function in the treatment of T2DM

An increasing number of studies have shown that manipulation of circadian mechanisms may be helpful for treating a number of metabolic disorders including T2DM. In one study administration of metformin in mice accelerated the degradation of the *Per2* gene, thus inducing a phase advance in the circadian clock in peripheral tissues in wild-type mice but not in AMPK α2 mutant mice [77]. Also, metformin has been found to reduce the period length of rat-1 fibroblasts by 1 h. It seems that metformin has an unknown function related to circadian rhythms.

Peroxisome proliferator-activated receptor γ (PPARγ), which belongs to a group of nuclear receptors, is a key component in the integration of both circadian and metabolic processes, and additionally has a role in the regulation of adipogenesis [78]. Insulin function has been improved by a new group of anti-diabetes drugs including thiazolidinediones [78] that are targeted to the PPARγ. It has been suggested that the development of drugs which coordinate processes of the circadian clock system as a means to regulate glucose metabolism represents a new frontier for the management of T2DM [5].

11. A chronobiological approach to T2DM treatment

A number of studies have now shown that environmental factors have pronounced effects on metabolism. Shift work, insufficient sunlight exposure, sleep disturbances, late night eating and nocturnal light exposure are all known to produce circadian clock disruption [12,79,80]. Various surveys have documented the increased prevalence of T2DM in night/shift workers. This category of employees, whose work involves irregular schedules and forced exposure to nocturnal lighting, show significant disruptions in sleep architecture and other markers of circadian synchronization [81].

Artificial light exposure has been found to enhance fat tissue accumulation in mice, thus indicating that the system does not adjust to the environmental change [10]. This metabolic non-responsiveness in turn creates a corresponding lack of responsiveness by cells to insulin. The consequence of these effects is that food intake and/or increased levels of glucose may not be assimilated into cells. In one case study, nocturnal light exposure was found to change the expression of enzymatic genes associated with glucose metabolism [82]. These findings point to the possibility that nocturnal lighting, shift work, jet travel, and other stressors in contemporary "24/7" societies may be contributors to clock dysfunction, and this in turn may account for the increasing worldwide prevalence

of T2DM. The findings also support the suggestion that the goal of maintaining metabolic health would be aided if individuals were to develop a greater awareness of the importance of the timing of food intake, of daytime activity, and of exposure to sunlight.

In this respect, the successful management of T2DM may require an ideal drug that besides antagonizing the triggers of T2DM also corrects the disturbed circadian rhythm. Melatonin is an interesting chronotherapeutic option which can reset the phase and amplitude of circadian rhythms [83–85]. As has been shown in animal models of diabetes and obesity, melatonin also possesses cytoprotective properties which may prevent a number of unwanted effects [86,87]. Several controlled trials have implied that melatonin can be given for treating metabolic and cardiovascular comorbidities in T2DM [88–93]. At an early stage of T2DM treatment nonpharmacological approaches such as lifestyle modification, low fat diet and exercise are recommended. Patients who are refractory to these are treated with medications that can have significant undesired effects. Compared to many pharmaceutical agents melatonin has a strong safety profile and limited toxicity effects [94]. Furthermore, it is generally very well tolerated, e.g., very high melatonin doses (300 mg/day) have been given for up to 2 years for patients with amyotrophic lateral sclerosis and have been found to be safe [95].

Therefore the suggested regimen of exogenous melatonin administration in combination with the strategically timed application of bright light appears to be justified for normalizing melatonin amplitude and synchronizing endogenous circadian rhythms in the metabolic syndrome [52]. Considering the respective phase response curves of melatonin and light therapy, their time of administration is critical. Administration of both bright light in the morning time and melatonin before bed time could be an ideal treatment for the restoration of circadian rhythm in T2DM patients.

12. Conclusions

A growing body of experimental and clinical evidence supports the conclusion that impairment of clock functions can affect metabolic activities and cause T2DM, and, by extension, the survival of an organism (Fig. 1). This can be seen in the high mortality rate associated with T2DM in the human population [2]. From a public health perspective, it is essential that measures to reduce this risk should be advocated. The proper timing of food intake, establishing a regular schedule of sleep/wake activities, and avoiding nocturnal light exposure and activity are practical steps that can be performed by individuals for lowering the risk of developing metabolic disorders such as T2DM. In addition, melatonin can be a useful add-on approach in the chronobiological treatment of T2DM.

There is a need to support scientific efforts aimed at elucidating the mechanisms by which clock functions create the conditions associated with the development of T2DM. It is evident that the mechanism by which the human biological clock adapts and evolves under artificial lighting condition needs to be elucidated [51]. Additional evidence regarding these interactions could further aid in the development of therapies for disrupted timing mechanisms and their sequelae. In addition effort should be directed to educate world populations in dealing with the stressors of modern industrialized societies. Exactly how the challenge of this task can be met remains an enormous unresolved public health issue [2]. The circadian time keeping system is a critical interface between cellular processes and the external world. Enabling this system to operate normally and reduce metabolic disorders, including T2DM, is a relevant public health objective. "Listening to our clock" offers the potential to normalize glucose metabolism and may reduce the prevalence of T2DM worldwide.

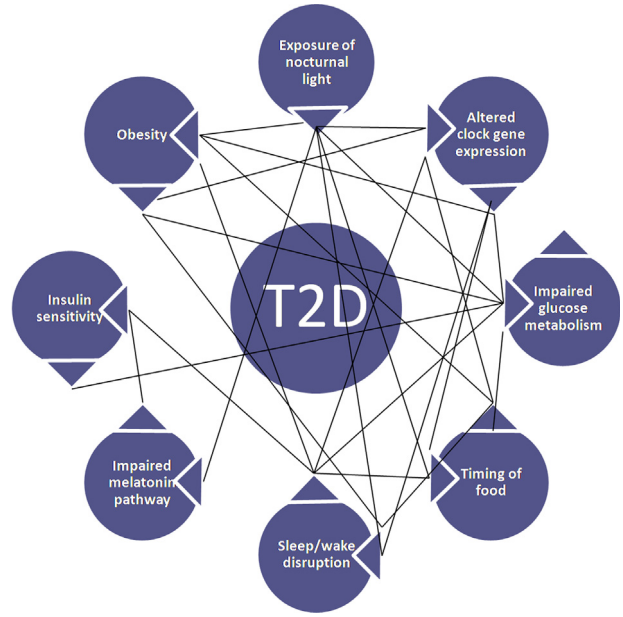

Fig. 1 – Proposed model of circadian and metabolic factors responsible for T2DM.

Conflict of interest

All authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript.

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