Conference on ‘Roles of sleep and circadian rhythms in the origin and nutritional management of obesity and metabolic disease’
Symposium 1: Relevance of circadian rhythms and sleep to obesity and metabolic disease

Sleep, circadian rhythm and body weight: parallel developments

Margriet S. Westerterp-Plantenga*
Department of Human Biology, Nutrim, Maastricht University, MUMC+, P.O. Box 616, 6200 MD, Maastricht, The Netherlands

Circadian alignment is crucial for body-weight management, and for metabolic health. In this context, circadian alignment consists of alignment of sleep, meal patterns and physical activity. During puberty a significant reduction in sleep duration occurs, and pubertal status is inversely associated with sleep duration. A consistent inverse association between habitual sleep duration and body-weight development occurs, independent of possible confounders. Research on misalignment reveals that circadian misalignment affects sleep-architecture and subsequently disturbs glucose–insulin metabolism, substrate oxidation, leptin- and ghrelin concentrations, appetite, food reward, hypothalamic–pituitary–adrenal-axis activity and gut-peptide concentrations enhancing positive energy balance and metabolic disturbance. Not only aligning meals and sleep in a circadian way is crucial, also regular physical activity during the day strongly promotes the stability and amplitude of circadian rhythm, and thus may serve as an instrument to restore poor circadian rhythms. Endogenicity may play a role in interaction of these environmental variables with a genetic predisposition. In conclusion, notwithstanding the separate favourable effects of sufficient daily physical activity, regular meal patterns, sufficient sleep duration and quality sleep on energy balance, the overall effect of the amplitude and stability of the circadian rhythm, perhaps including genetic predisposition, may integrate the separate effects in an additive way.

Sleep disruption: Circadian misalignment: Overweight: Insulin sensitivity: Metabolic disorders

Energy- and food-reward homeostasis are the essential components for maintaining body weight and body composition. Disruption of such homeostasis may lead to metabolic disorders, including obesity, diabetes and cancer(1–3). The organism’s ability to coordinate daily patterns of activity, feeding, energy utilisation and energy storage, supported by a synchronised pattern of release of the relevant endocrine components across the daily 24-h cycle, is crucial for energy homeostasis(4–6). Circadian alignment implies synchronisation of behavioural and physiological rhythms by the master circadian clock, i.e. the suprachiasmatic nucleus (SCN) of the hypothalamus. The master clock is connected to peripheral tissues of the body that contain the molecular clock machinery required for local circadian oscillation and rhythmic gene expression(7,8). However, metabolic processes are decoupled from the primarily light-driven SCN when food intake is desynchronised from normal diurnal patterns of activity(4,5,9), and a dissociation of feeding patterns from SCN-based timing occurs, resulting in changes in energy availability, substrate oxidation, storage and metabolic status(1,2,7,10–13). If feeding becomes

Abbreviations: GLP-1, glucagon-like peptide-1; HOMA-IR, homeostasis model assessment of insulin resistance; HPA axis, hypothalamic–pituitary–adrenal axis IR, insulin resistance; QS, quality sleep; REM, rapid eye movement; SCN, suprachiasmatic nucleus; SWS, slow wave sleep; WT, wrist temperature.

*Corresponding author: Professor M. S. Westerterp-Plantenga, email m.westerterp@maastrichtuniversity.nl
the dominant entraining stimulus, adaptation to the changed food-intake patterns occurs, facilitated by an autonomous food-entrainable oscillator that governs behavioural rhythms (2,5,7,8,11,12). Moreover, core circadian clock genes involved in reciprocal transcriptional feedback with genetic regulators of metabolism, and directly responsive to cellular energy supply, are involved (7,8). In addition, the reward and motivational value of food is a potent synchroniser for the SCN clock (14). This suggests that energy metabolism and motivational properties of food can influence the clock mechanism of the SCN. Food-related cues may entrain clock genes of the SCN directly or indirectly, and play an integral role as a food-entrainable oscillator, responsible for anticipation of meal-time (8). This close interaction is likely to be critical for normal circadian regulation of metabolism, and may underlie the disruption of proper metabolic rhythms observed in metabolic disorders, such as obesity and type-II diabetes (4,10,15–19).

This review deals with effects of disruption of sleep and quality sleep (QS), and with effects of circadian misalignment on energy- and food-reward homeostasis, endocrinological factors, body weight and body composition. Before considering these topics in adults, the development of sleeping hours and body weight during puberty, and the consequences, will be addressed.

Development of sleep duration and body weight during puberty

During puberty, sex differences in anthropometric and endocrine variables are observed in the transition from Tanner stages 1–5 (20–23). Puberty is initiated through pulsatile gonadotropin-releasing hormone release from the hypothalamus and activation of the gonadal axis (1,24,25). The subsequent development of secondary sex characteristics originates from shared neuronal systems, with the hypothalamus as integration point (1). The hypothalamus regulates the sleep–wake and feeding circuits (1,26). Circuits are connected through the hypocretin-1 hormone that regulates feeding and locomotor activity via the nucleus accumbens, as well as signal transduction on the light–dark cycle to the SCN. Changes in hypothalamic functioning, such as disturbed hypocretin-1 signalling, are associated with disturbance of the circadian cycle and feeding behaviour, affecting energy balance and body composition (1–26).

Furthermore, during puberty a significant reduction in sleep duration occurs (20–23), and pubertal status appears to be inversely associated with sleep duration (20–23). Moreover, studies report a consistent inverse association between habitual sleep duration and body-weight development (20–23), independent of BMI at the start of puberty, fat mass and obesity-associated allele genotype (rs9939609), parent BMI, as well as changes in physical activity and hours of television viewing. Therefore, the changes in hypothalamic functioning during puberty may explain the relationships between the changes in BMI and in sleep duration during puberty. Since these developments occur in parallel, cause and effect cannot be distinguished.

Sleep and metabolic disorders in children and adolescents

Sleep, and sleep architecture are important factors for normal growth and development during childhood (27–32). Especially total sleeping time and QS ((slow wave sleep (SWS) + rapid eye movement sleep (REM))/total sleeping time) are crucial sleep factors associated with outcomes on physical, cognitive, emotional and social development in children (30). Sleep deprivation and poor QS have been identified as an independent risk factor for the development of insulin resistance (IR) (27–30). Studies on sleep in relation to IR in adolescents (33–35) show for instance that acute sleep restriction reduced insulin sensitivity in adolescent boys (34). Observations on sleep duration in healthy black and white adolescents show an inverse association between sleep duration and homeostasis model assessment of IR (HOMA-IR). Interventions to extend sleep duration may reduce diabetes and obesity risk in youth (35). A cross-sectional analysis from two examinations conducted in the Cleveland Children’s Sleep and Health Cohort (n 387; 43 % minorities) shows a quadratic U-shape association between sleep duration and HOMA-IR. When adjusted for age, sex, race, preterm status and activity, adolescents who slept 7-7.5 h had the lowest predicted HOMA-IR, while adolescents who slept 5-0 or 10-5 h had HOMA-IR indices that were approximately 20 % higher. It was concluded that shorter and longer sleep durations are associated with decreased insulin sensitivity in adolescents (33). Another lifestyle factor, namely physical activity, second for improving insulin sensitivity, may act directly as well as indirectly by its effects on sleep characteristics. With regard to food intake, studies have found associations between sleep deprivation and food choices (34–39). Sleep-deprived individuals appear more prone to choose unhealthy foods high in energy and fat content (34–39). Also, sleep-deprived individuals are reported to have more frequent meals or snacks between meals compared with individuals who had sufficient sleep (36). It has been assumed that sleep deprivation is associated with decreased leptin concentrations and increased ghrelin concentrations, thereby promoting the feeling of hunger and suppressing satiety (36,41). A reduced sleep duration, reduced quality of sleep and REM sleep, or fragmented sleep enhance a positive energy balance through altered substrate oxidation, hormone concentrations, sleeping metabolic rate, appetitive behaviours and stress (42). Circadian misalignment affects sleep architecture and the glucose–insulin metabolism, substrate oxidation, the HOMA-IR index, leptin concentrations and hypothalamic–pituitary–adrenal (HPA)-axis activity (42–45).

Sleep disruption, body weight and metabolic disorders in adults

Sleep and metabolism

Sleep and circadian rhythms have direct impacts on energy metabolism, and represent important mechanisms underlying the major health epidemics of obesity and
Sleep and body-weight management

Effects of changes in sleep duration during a dietary intervention for body-weight loss was assessed by Nedeltcheva et al. [46,56]. They showed that sleep restriction to 5.5 h sleep compared with 8.5 h sleep compromised the efficacy of a dietary intervention for weight loss. The combination of energy and sleep restriction in overweight adults resulted in decreased loss of fat and considerably increased loss of fat-free body mass. These results suggest that sleep plays a role in the preservation of human fat-free body mass during periods of reduced energy intake [46,56]. The effect on sparing fat-free mass was confirmed by Verhoef et al. [38] who assessed whether during a weight-loss weight-maintenance programme in overweight subjects, a possible increase in sleep duration would precede the diet-induced decreases in body weight. They observed a concomitant inverse correlation between changes in sleep duration and in body weight, and respectively fat mass.

In addition, Chaput et al. [59] observed that short-duration sleepers who maintained their short sleep duration habits experienced a greater increase in BMI and fat mass over a 6-year follow-up period compared with short-duration sleepers who increased their sleep duration, suggesting that shifting sleep duration from a short length to a healthier length is associated with lower adiposity gain [59]. Moreover, they showed that both sleep duration and sleep quality were significantly related to fat mass loss during dietary interventions in overweight and obese adults [60]. Despite these significant correlations it is not possible to determine any direction of causation.

Circadian alignment and energy balance

The significance of circadian alignment and energy balance implies assessment of the significance of circadian alignment for sleep, and sleep architecture, food-intake regulation, and physical activity. This is mainly assessed by circadian misalignment experiments. In the following sections, effects of circadian misalignment on sleep architecture and food-intake regulation are considered. In addition the significance of physical activity for circadian alignment will be highlighted.

Circadian misalignment and sleep

Circadian misalignment may reduce total sleep time, but mainly affects sleep architecture. The circadian phase at which sleep occurs affects the distribution of sleep stages. The preferential distribution of REM sleep towards the latter part of the night is linked to a circadian oscillator, while the preferential distribution of SWS towards the beginning of a sleep episode is mediated by homeostatic processes, i.e. the length of prior wakefulness [61]. Circadian misalignment resulted in disruption of the normal phase relationship between SWS and REM sleep, so that REM sleep is relatively phase advanced to SWS [44]. This abnormal circadian sequencing results in shortening of REM sleep latency and increasing REM sleep duration in a phase advanced stage. This short latency to REM sleep is typical of narcoleptic and depressive patients [62]. Mood disorders, especially unipolar depression and seasonal affective disorder, have been linked to circadian rhythm abnormalities [62]. Dysregulation in the HPA-axis, implying an overall increased cortisol secretion with a phase advance of the cortisol circadian rhythm is extremely frequent in individuals with depression [63,64]. Misalignment between timing of the clock and the timing of sleep, in either direction, has been associated with depression in vulnerable individuals [65].

Increased REM sleep during both a phase advance and a phase delay is not favourable [46,50,66–72], because this results in a relatively shorter REM sleep duration during the second part of the night, associated with higher cortisol concentrations, higher fasting insulin concentrations, and a higher HOMA-IR index [34,44,64,73,74]. Sleep during the circadian nadir (03.00–06.00 hours), is important in protecting normal physiological rhythms and function of the HPA-axis [34]. Circadian misalignment, both a phase advance and a phase delay results in dysregulation of the HPA-axis. All in all, circadian misalignment appears to affect sleep-architecture, namely the distribution of sleep stages. REM sleep then becomes
phase advanced to SWS with reduced REM sleep latency. REM sleep duration increases during phase advance, and during phase delay, resulting in a shorter REM sleep duration during the second part of the night.

Circadian misalignment, endocrinology, energy homeostasis and meal patterns

The daily patterns of feeding, energy utilisation, and energy storage across the daily 24-h cycle, is based upon a neuro-endocrinological system(75,76). Metabolically relevant hormones show circadian oscillation with different daily patterns. Cortisol secretion has a circadian rhythm with the nadir during the early biological night (i.e. a time according to the original circadian rhythm associated with the start of behavioural inactivity) and the peak in the biological morning (i.e. a time according to the circadian rhythm associated with the start of behavioural activity)(77). Glucose and insulin levels peak during the late biological night(78,79). Leptin, which suppresses appetite, is secreted in a circadian manner(80-83). In human subjects, night-time plasma leptin levels are high when appetite decreases, favouring fasting and nocturnal rest, and low during the day, when hunger increases. Gastric leptin levels oscillate in a circadian manner where leptin levels are high at night but low during the day(84-86).

Ghrelin, which is produced in the stomach, pancreas and hypothalamus(87,88), is involved in stimulating appetite via its action on neuropeptide Y in the lateral hypothalamus(89,90) and can also alter clock function in the SCN in vitro(91,92). Ghrelin oscillates with feeding(93), making this peptide a putative candidate for food-related entraining signals. In addition, elevated levels of ghrelin were found during the early part of the night in sleeping subjects, decreasing in the morning before awakening(93). Sleep deprivation can increase circulating ghrelin levels and this is accompanied by heightened hunger sensation(94). Thus, ghrelin may be a signal involved in the cross-talk between the peripheral and central circadian clock system.

In parallel to the circadian changes in neuropeptide levels and humoral signals from peripheral tissues, a circadian rhythm in macronutrient selection occurs. In human subjects, a carbohydrate-rich diet is favoured during breakfast and high-fat diets are preferred during evening meals(94). Carbohydrates are metabolised better during breakfast because, also in relation to the glucose-statistic theory, then the body metabolically responds more readily to a glucose stimulus, since the fasting glucose level then is relatively stable, and very clearly indicates the first transient glucose decline(95).

Disruption of the circadian system affects metabolic and cardiovascular changes(2,45,96-98). In relation to appetite, release of some endocrine products shifts with meal patterns, such as glucose, insulin, GLP-1, ghrelin and leptin concentrations. Independently, disruption of the circadian system was associated with a significantly increased insulin response(45), possibly related to hyperglycaemia associated with a progressing IR associated with sleep restriction, and to increased sympathetic nervous system activity(96). Changes in the magnitudes of glucose and insulin responses indicate a disturbed glucose and insulin metabolism(86,87) and decreased GLP-1 concentrations indicate decreased satiety(45).

Cortisol levels do not show a meal-related pattern during misalignment. During circadian misalignment the cortisol curve is flattened compared to 24-h cycles(11,45). In addition, with sleep loss, cortisol may exert its deleterious metabolic effects through remaining high night-time concentrations, which are associated with IR, suppressed immunity and increased inflammation(98).

Moreover, circadian disruption results in increased carbohydrate oxidation(45), probably due to both hyperinsulinaemia and hyperglycaemia(99). Often the increased carbohydrate oxidation occurs at the cost of protein oxidation, while fat oxidation remains constant(99).

The main effect of circadian misalignment, either phase advanced or phase delayed, is a concomitant disturbance of the glucose–insulin metabolism and substrate-oxidation. Chronically eating and sleeping at unusual circumadian times may create a health risk through metabolic disturbance(45).

Consequently, meals need to be aligned in a circadian fashion. This requires timing and regularity of meals, with respect to food selection, meal frequency, meal intervals and meal size(9,10,76). Beneficial metabolic effects of regular meal frequency on dietary thermogenesis, insulin sensitivity and fasting lipid profiles in healthy obese women align with effects of regular circadian patterns(42). After a regular v. an irregular meal pattern energy intake was lower, postprandial thermogenesis higher, and fasting total and LDL-cholesterol was lower(100). Peak insulin concentrations and area under the curve of insulin responses to the test meal were lower(100). Regular meal frequency creates more appropriate insulin sensitivity and lipid profiles compared with irregular meal frequency in healthy lean women(101), and irregular meal frequency led to a lower postprandial energy expenditure compared with the regular meal frequency, while the mean energy intake was not significantly different between the two(102). The reduced diet-induced thermogenesis with the irregular meal frequency may lead to weight gain in the long term(102). With a regular meal frequency glucose excursions are blunted, net insulin production is reduced, and LDL-cholesterol concentrations tend to be lowered, mainly due to gastric emptying slowing down, and insulin production being reduced(90-92). The net result is that lipid oxidation is favoured at the expense of glucose oxidation and lipid storage, and cholesterol synthesis is reduced. This may reduce adiposity and the level of circulating fatty acids, thereby leading to systematic, adaptive changes in both lipid and carbohydrate metabolism. Also examples of long-term responses to a sustained regular meal frequency such as improved glucose tolerance, and moderately reduced fasting plasma total and LDL-cholesterol, and a higher HDL:LDL cholesterol ratio are observed in normolipidaemic free-living subjects, as well as in type-II diabetes patients(103-111). Also for cholesterol synthesis, meal frequency-dependent control of cholesterogenesis appeared to be mediated via hormonal mechanisms(97).
Furthermore, circadian alignment including careful and fixed timing of food intake and meal frequency plays a role in substrate utilisation and in energy expenditure. Large metabolic fluctuations in carbohydrate and fat oxidation were shown in a gorging food-intake pattern, while in the nibbling pattern, carbohydrate and fat oxidation remained relatively constant during the active hours of the day\textsuperscript{[11]}. Also, the diet-induced thermogenic response was related to meal frequency\textsuperscript{[112]}. In a series of experimental studies, variation in energy intake was primarily explained by habitual meal frequency, macronutrient composition and number of blood glucose declines\textsuperscript{[114]}. The variation in habitual meal frequency was explained by percentage energy from carbohydrate or from fat in the diet, while the protein in the diet attenuates the metabolic amplitudes\textsuperscript{[115,116]}. Moreover the effect of protein intake on satiety is partly due to the optimal timing of protein intake\textsuperscript{[115,116]}. In healthy young men, habitual meal frequency appeared to be of greater significance in energy-intake regulation than forced meal frequency\textsuperscript{[117-120]}. Adioposity may increase when young lean male subjects switch from a four- to a three-meal pattern by removing their usual afternoon meal, partly mediated by a change in the macronutrient composition of the diet\textsuperscript{[122]}. Assessment of the effect of omitting or adding the third meal, revealing that eating three meals compared with two meals had no effects on 24 h energy expenditure, diet-induced thermogenesis, activity-induced energy expenditure and sleeping metabolic rate. However, eating the same amount of energy divided over three meals compared with over two meals, did increase satiety, particularly during the day, and did increase fat oxidation, particularly during the night in healthy, normal-weight women\textsuperscript{[122]}. 

**Circadian alignment and physical activity**

To include circadian rhythm in the assessment of circadian alignment and physical activity, wrist skin temperature has been used as a valid method of assessing circadian rhythms in human subjects\textsuperscript{[123]}. As a measure for circadianity, circadian temperature amplitude and stability have been used as variables. Tranell \textit{et al.}\textsuperscript{[123]} identified physiological and behavioural measures that were significantly associated with the circadianity of these temperature parameters. Moreover, they tested the hypothesis that circadian temperature amplitude and stability would significantly differ among groups of healthy young men of varying adiposities\textsuperscript{[124]}. Wrist skin temperatures taken at 10 min intervals for seven consecutive days were determined in eighteen optimal, twenty fair and twenty-one poor % body fat grouped consecutive days were determined in eighteen optimal, twenty fair and twenty-one poor % body fat grouped young men and subsequently analysed using available validated software. Body composition, cardiorespiratory fitness, actigraphy, daily nutritional and sleep data, and fasting lipid, insulin and glucose concentration measures were also determined\textsuperscript{[125]}. Subjects with one or more health problems had significantly lower temperature amplitude and stability\textsuperscript{[123]}. This occurred in subjects with a single metabolic syndrome risk factor compared to those with no metabolic syndrome risk factors, and in subjects with a poor % body fat\textsuperscript{[123]}. In addition, stepwise multivariate regression analyses showed that 50 % of the variance in temperature amplitude was explained by actigraphy (mean steps taken per day), cardiorespiratory fitness, and late night eating per week; and 57 % in temperature stability by mean steps taken per day, time spent in moderate-to-vigorous activity per day, fat mass, and late night eating per week\textsuperscript{[125]}. Physical activity was the most important measure associated with the differences in circadian rhythm parameters\textsuperscript{[123]}. 

**Genetic background for the amplitude and stability of circadian rhythm**

In order to shed light on the genetic component of the circadian marker described above, relative genetic and environmental influences on wrist temperature (WT) was determined using classical twin models\textsuperscript{[124]}\textsuperscript{[124]}. A study was performed in fifty-three pairs of female twins (twenty-eight monozygotic and twenty-five dizygotic), with a BMI 25-29 (SD 3-7) and mean age 52 (SD 6) years. The sample was selected from the Murcia Twin Register. Circadian patterns were studied by analysing WT during one week every 10 min using Circadianware\textsuperscript{[124]}. Genetic influences on WT variability were estimated by comparing correlations of monozygotic and dizygotic twin pairs and fitting genetic structural equation models to measured variables\textsuperscript{[124]}. Monozygotic twins showed higher intra-pair correlations than dizygotic twins for most of the parameters. Genetic factors were responsible for between 46 and 70 % of variance (broad sense heritability) in parameters such as mean temperature, mesor, acrophase, Rayleigh test, percentage of rhythmicity and 5 h of maximum temperature\textsuperscript{[124]}. The pattern of correlations and the genetic models point to moderate-to-high heritability for most of the WT parameters, suggesting a relevant genetic influence. The presence of these genetic factors points to endogenicity as the main cause of the coincidence of the WT rhythms\textsuperscript{[124]}. However, some WT parameters are still dependent on environment to a relevant extent and, hence, more amenable to change through external interventions\textsuperscript{[124]}. 

**Discussion**

Circadian alignment is crucial for body-weight management, and for metabolic health. In this context, circadian alignment consists of alignment of sleep, meal patterns and physical activity. Research on these topics mainly consists of research on misalignment. For instance, circadian misalignment appears to affect sleep-architecture in that REM sleep becomes phase advanced to SWS with reduced REM sleep latency. REM sleep duration increases during phase delay, resulting in a shorter REM sleep duration during the second part of the night. When sleep architecture is affected by circadian misalignment, it affects substrate oxidation, leptin- and ghrelin concentrations, appetite, food reward, HPA-axis activity and gut-peptide concentrations as such, that a positive energy balance is enhanced. Phase-advanced misalignment leads to
increased night-time cortisol exposure, increased HOMA-IR index, increased carbohydrate- and decreased protein-oxidation, as well as to food-reward deficiency(42,45). Phase-delayed misalignment increases REM sleep, glucose concentrations and carbohydrate oxidation, and decreased GLP-1 concentrations and protein-oxidation(42,45). The main effect of circadian misalignment, either phase advanced or phase delayed, is a concomitant disturbance of the glucose–insulin metabolism and substrate-oxidation. Chronically eating and sleeping at unusual circadian times may create a health risk through metabolic disturbance(45).

Since the relationship between circadian alignment and energy homeostasis appears in that daily patterns in activity, feeding, energy utilisation and energy storage are strongly synchronised by the SCN(4,5), and since the SCN clock is entrained by light–dark cycles as well as by daily feeding cycles, this close interaction is critical for circadian regulation of metabolism, and partly underlies the disruption of proper metabolic rhythms observed in metabolic disorders, such as obesity and type-II diabetes(4,10). Aligning meals in a circadian way requires timing of food intake, including regularity of meals, i.e. of meal frequency and meal intervals(9,10,76). Over the longer term, in the perspective of dietary intervention for body-weight loss, the combination of energy and sleep restriction in overweight adults resulted in decreased loss of fat and considerably increased loss of fat-free body mass(46,50). Moreover, a concomitant inverse correlation between changes in sleep duration and in body-weight, and respectively fat mass was shown, during weight maintenance, showing a concomitant improvement of body-composition and sleep duration(58,117).

The surprisingly strong effect of regular physical activity during the day on the stability and amplitude of circadian rhythm(123), may serve as an instrument to restore poor circadian rhythms. We suggest that primarily regular physical activity throughout and during the day stimulates the amplitude and stability of the circadian rhythm, which will be enhanced by a regular sleep pattern with sufficient sleep duration, taking into account the sleep hygiene(46), and a fixed and regular meal pattern. These environmental variables that support a stable circadian rhythm, likely operate in interaction with a genetic predisposition, suggested by a moderate-to-high heritability for most of the WT parameters indicating circadian rhythm(124).

Endogeneity may be the main cause of the coincidence of the WT rhythms(124). However, the dependence of these WT parameters on environment makes them amenable to change through external interventions(124).

In conclusion, notwithstanding the separate favourable effects of sufficient daily physical activity, regular meal patterns, sufficient sleep duration and Q5 on energy-balance, the overall effect of the amplitude and stability of the circadian rhythm, perhaps including genetic predisposition, may integrate the separate effects in an additive way.

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