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Artículo de revisión

The circadian control of eating

El control circadiano de la alimentación

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Abstract

Eating is a complex behavior that is primarily governed by energy homeostasis and modulated by hedonic cues. Eating is also structured in time, due to circadian clocks that control its daily rhythmicity. These circadian clocks are organized into a network of several oscillating structures, including a master clock in the suprachiasmatic nuclei of the hypothalamus and several secondary clocks in the brain and peripheral organs. The light-entrainable master clock is a conductor for the secondary clocks via neuroendocrine signals. In contrast to the master clock, most secondary clocks are sensitive to the synchronizing effect of meal time. Besides controlling the daily feeding/fasting cycle, several coupled secondary clocks in the brain defining a so-called "food clock" also adjust the timing of meal anticipation, a rhythmic behavior that mammals exhibit right before scheduled feeding time. There are reciprocal interactions between energy metabolism and circadian rhythmicity. On the one hand, metabolic alterations, like obesity and type 2 diabetes, are frequently associated with circadian disturbances. On the other hand, circadian disturbances have deleterious effects on metabolic health. Feeding cues, such as meal timing, nature of the diet and quantity of ingested food, are strongly involved in these circadian disturbances. For instance, eating many calories at the "wrong" phase of the living cycle (*e.g.*, at night for humans or during daytime in nocturnal animals) has obesogenic consequences. Besides management of total energy intake and expenditure, experimental evidence is given to show that daily timing of calorie intake, duration of eating window, together with a long enough nocturnal fasting are newly identified actors of energy balance. Accordingly, new nutritional strategies should be developed based on personalized chrononutrition.

Keywords: circadian clock, chrononutrition, metabolism

Resumen

Comer es un comportamiento complejo que es dirigido principalmente por la homeostasis energética y modulado por señales hedónicas. Comer es también una conducta estructurada en el tiempo, debido a los relojes circadianos que controlan su ritmicidad diaria. Estos relojes circadianos se organizan en forma de red en la cual participan diferentes estructuras oscilantes, entre lo que se incluye un reloj maestro, ubicado en los núcleos supraquiasmáticos del hipotálamo y varios relojes secundarios en el cerebro y los órganos periféricos. El reloj maestro, ajustado por la luz, coordina la actividad de los relojes secundarios a través de señales neuroendocrinas. A diferencia del reloj maestro, la mayoría de los relojes secundarios son sensibles al efecto sincronizador de la hora de comer. Además de controlar el ciclo diario de alimentación/ayuno, en el cerebro un grupo de relojes secundarios vinculados, que definen el llamado "reloj de la alimentación", también ajustan el momento de la anticipación de la comida, un comportamiento rítmico que los mamíferos presentan justo antes de la hora programada para comer. Existe una interacción recíproca entre el metabolismo energético y la ritmicidad circadiana. Por un lado, las alteraciones metabólicas, como la obesidad y la diabetes de tipo 2 están asociadas frecuentemente a alteraciones circadianas. Por otro lado, las alteraciones circadianas tienen efectos nocivos para la salud metabólica. Las señales marcadoras de la alimentación, como el horario de las comidas, la naturaleza de la dieta y la cantidad de alimentos ingeridos, están muy implicadas en estas alteraciones circadianas. Por ejemplo, ingerir muchas calorías en la fase "equivocada" del ciclo vital (por ejemplo, por la noche en el caso de los humanos o durante el día en los animales nocturnos) tiene consecuencias obesogénicas. Además de la gestión de la ingesta y el gasto totales de energía, se aportan evidencias experimentales que demuestran que el momento diario de la ingesta de calorías, la duración de la ventana de la alimentación, así como un ayuno nocturno lo suficientemente prolongado, son identificados como los nuevos actores del equilibrio energético. En consecuencia, deberían desarrollarse nuevas estrategias nutricionales basadas en la crononutrición personalizada.

Palabras clave: reloj circadiano, crononutrición, metabolismo

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Introduction

Food intake is governed by nutritional homeostasis and modulated not only by hedonic cues, but also by circadian mechanisms. These three processes interact on a daily basis to define what, how much and when we eat. Furthermore, emerging evidence suggests that dysregulation of these interactions leads to eating disorders and/or impaired metabolic health (Johnston et al., 2016; Ruddick-Collins et al., 2020).

The homeostatic aspects of food intake are mainly regulated by two brain areas, namely, the mediobasal hypothalamus and the caudal brainstem. Fasting-induced depletion of energy stores triggers orexinergic signals, such as ghrelin released from oxyntic mucosa of the stomach that will activate Agouti-related peptide (AgRP)- and neuropeptide Y (NPY)-containing neurons in the arcuate nuclei of the hypothalamus. These activated sensory neurons will then stimulate release of orexins and melanin-concentrating hormone (MCH) from the lateral hypothalamus (LHA). These and other neurochemical pathways trigger or facilitate foraging and ingestion of food. After food consumption, a number of neurohormonal changes occur to favor satiety. They include release of insulin from pancreatic β cells, leptin from the white adipose tissue, glucagon-like peptide 1 (GLP1) from the stomach and cholecystokinin (CCK) from the intestine (Figure 1) (Challet, 2019).

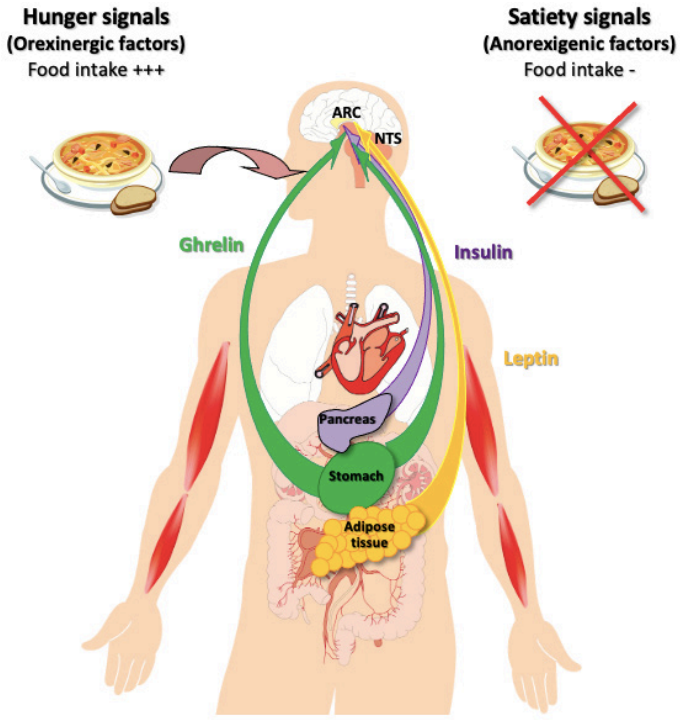

Figure 1. Hormonal regulation of food intake.
Eating behavior is regulated by a balance between orexinergic and anorexinergic factors. In the brain, a key structure is the arcuate nuclei of the hypothalamus that receives peripheral cues including circulating nutrients and hormones. Among the hormonal signals, ghrelin secreted from the stomach triggers food intake (i.e., is orexigenic; see the left side of the figure). After a meal, a number of hormones are released to inhibit food intake and favor satiety (see the right side of the figure). They include glucagon-like peptide 1 secreted from the stomach, insulin secreted from β cells of the pancreas, and leptin secreted from the white adipose tissue. The metabolic brainstem, including the nucleus of the solitary tractus also receives neuroendocrine cues regulating food intake. ARC, arcuate nuclei of the hypothalamus; GLP1, glucagon-like peptide 1; NTS, nucleus of the solitary tractus.

The hedonic aspects of eating involve the reward neurocircuit that enables ingestion of highly palatable food, eventually exceeding the metabolic need regulated by homeostatic mechanisms. Such reward circuit comprises limbic regions of the brain, including the ventral tegmental area (VTA) and its main projecting targets, the accumbens nucleus and amygdala, as well as cortical brain regions, like the prefrontal cortex (Reichelt et al., 2015). The temporal control of food intake relies for a large part on circadian clocks that favor or inhibit feeding according to the time of day (Figure 2). These regulatory mechanisms will be detailed below.

Regulation of circadian rhythms

A majority of functions and behaviors, whether it is feeding or sleep, exhibit endogenous rhythms close to 24 hours. These rhythms with a period close to the duration of the rotation of the Earth on itself are called "circadian" rhythms. They are distinguished from high-frequency biological rhythms, called "ultradian" rhythms, which have a period much shorter than 24 h (for instance, pulsatile secretion of hormones, heart rate, respiratory rate) and low-frequency biological rhythms, referred to as "infradian" rhythms, which are characterized by a period much longer than 24 h (for example, menstrual cycle, or seasonal rhythms of reproduction, hibernation or migration).

Circadian rhythms are generated by internal clocks that allow cells, organs and the whole body to anticipate and adapt to predictable changes in the environment. Specifically, circadian clocks depend on self-sustaining molecular oscillations, which involve specific genes, called clock genes. These approximately 24-hour oscillations produce an internal rhythm through the synthesis of target proteins that deliver intracellular and, possibly, extracellular temporal signals. At the scale of the whole body, circadian clocks are organized into a network of several oscillating structures, including a main clock in the suprachiasmatic nuclei of the hypothalamus and numerous secondary clocks in the brain and peripheral organs. Like a conductor who sets the tempo to all musicians of the orchestra, the phases of the secondary clocks are adjusted by the temporal signals emanating from the main suprachiasmatic clock (Albrecht, 2012). The internal synchronization set by the master clock involves neuroendocrine signals. The circadian nervous signals emitted by the suprachiasmatic nuclei are transmitted to the hypothalamic paraventricular nuclei, which connect them to the wiring of the autonomic nervous system and convey them to peripheral tissues (Buijs et al., 2006). Regarding circadian hormonal signals, two high-amplitude hormonal rhythms are tightly regulated by the suprachiasmatic clock. On the one hand, there is the rhythmic secretion of melatonin, released by the pineal gland every day at night (*i.e.*, during the sleep phase in humans and other diurnal species and during the activity phase in nocturnal animals)(Pevet & Challet, 2011). As a consequence, nocturnal melatonin is an internal time-giver (so-called *Zeitgeber* in German) for the secondary clocks which express melatonin receptors. Note that this hormone can also feed back to the main clock itself, in which it

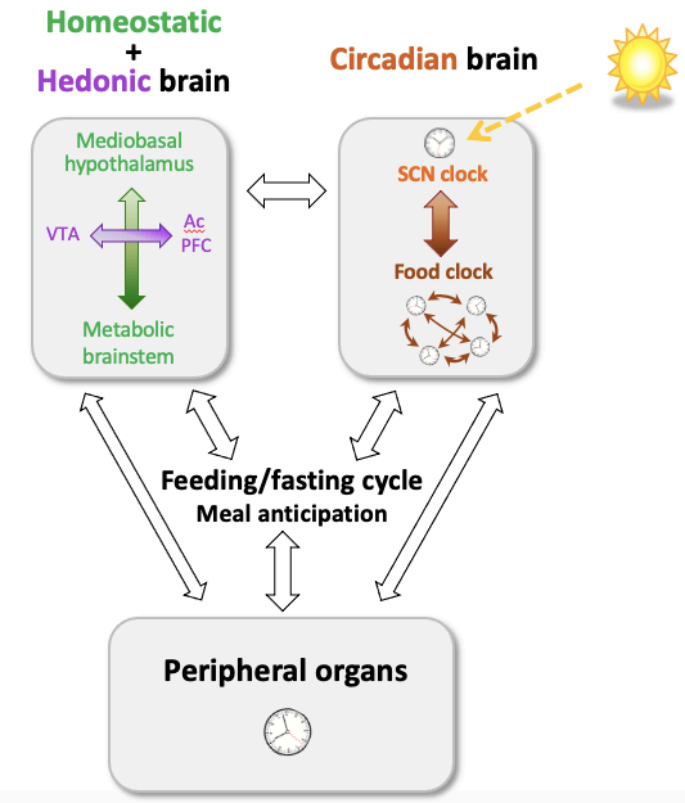

Figure 2. Central control of food intake by homeostatic, hedonic and circadian signals.
On a daily basis, food intake is regulated not ony by homeostatic and hedonic cues, but also by circadian signals from a multi-oscillatory system that controls the feeding/fasting cycle. The master clock in the suprachiasmatic nuclei of the hypothalamus is a light-entrainable clock. It is a rather "rigid" clock that tracks astronomical time via light cues perceived by the retina. The food clock is considered as a network of several meal-entrainable clocks located, among others, in the brain, including the mediobasal hypothalamus, the striatum, the cerebellum and the metabolic brainstem. The food-entrainable cerebral network constitutes a more "plastic" clock that tracks and adjusts its timing according to daily window of food availability. Ac, accumbens nuclei; PFC, prefrontal cortex; SCN, suprachiasmatic nuclei of the hypothalamus; VTA, ventral tegmental area.

induces changes in the rhythmic expression of clock genes (Agez et al., 2007). On the other hand, there is the rhythmic secretion of glucocorticoids by adrenal glands, with a daily peak of secretion occurring at the onset of the waking phase (*i.e.*, at dawn and dusk in diurnal and nocturnal species, respectively). The main glucocorticoids (cortisol in humans, corticosterone in rats and mice) are powerful time-givers of peripheral clocks, but not of the suprachiasmatic clock which does not express glucocorticoid receptors in adulthood. Resetting of the secondary clocks by glucocorticoids is carried out by a transcriptional modulation of clock genes (Oster et al., 2017). External synchronization allows organisms to be in sync with predictable cycles of the environment. The suprachiasmatic clock is essentially synchronized by ambient light (natural or artificial) detected by the retina and, more particularly, by a small population of ganglion cells which express a specific photopigment, called melanopsin. Besides its role in synchronizing the master clock, ambient light has also direct effects on food intake among other behaviors. In nocturnal rodents, acute light exposure during the usual active phase (nighttime) inhibits spontaneous food intake (Plata-Salaman & Oomura, 1987; Santoso et al., 2018). Conversely, acute dark exposure during the usual sleep phase (daytime) not only awakes them, but triggers food intake (Plata-Salaman & Oomura, 1987). Because such modulatory effects are more or less independent of circadian mechanisms, they are commonly called "masking" in the chronobiological field. Nevertheless, these findings indicate that the lighting conditions and times of day are important parameters to be taken into account in experimental investigations dealing with eating behavior (see below).

Circadian control of food intake

Food intake does not occur randomly over time, but it is structured throughout the 24 h cycle under the control of circadian clocks. In most animal species, indeed, there is a daily feeding/fasting cycle in parallel with a sleep/wake cycle and comprising a phase of foraging, feeding and wakefulness and a fasting concomitant with sleep (Armstrong, 1980). Among the experimental arguments supporting this notion, the daily feeding/fasting cycle is greatly reduced in amplitude, or even absent, in mice whose circadian clocks are damaged or genetically defective (Adamovich et al., 2014; Kettner et al., 2015; Sen et al., 2018; Stoynev et al., 1982). Furthermore, in rats, the amount of food eaten after a prolonged fast (more than two days) is not proportional to the duration of the fast, but is chronomodulated with a daily peak at dawn. In the same line, a 24-h fast started at different times of the day does not lead to identical food intake during refeeding, but is chronomodulated according to the time of refeeding, again with a peak at dawn (Rivera-Estrada et al., 2018).

In humans, the feeding/fasting cycle is also circadian in nature (*i.e.*, they are clock-controlled), as demonstrated in temporally isolated subjects who spontaneously ate 2-3 meals during their activity phase. Of note, this meal frequency is kept irrespective of large inter-individual variations in circadian periodicity and daily duration of waking period, that can range from a compressed interval of 12 h to an extended window reaching 30 h (Aschoff et al., 1986). A circadian rhythm of the feeling of hunger and appetite has been demonstrated in healthy subjects under laboratory controlled conditions, with peak and trough in the evening and morning, respectively (Sargent et al., 2016; Scheer et al., 2013). On the other side, there is a circadian rhythm of the sensation of fullness and satiety that is opposite in phase to that of hunger (Sargent et al., 2016). Thus, food intake in humans involves not only interacting homeostatic mechanisms (hunger and satiety), but also a temporal control by circadian mechanisms. As noticed by Scheer and colleagues (Scheer et al., 2013), this combination of two counterbalancing processes that regulate food intake throughout the 24 h cycle, is reminiscent of the two-process model already proposed and validated for sleep.

With respect to choice of macronutrients according to times of day, nocturnal rodents prefer to ingest protein and fat at the end of their active period (*i.e.*, dawn), while they preferentially select carbohydrates at the beginning of activity period (*i.e.*, dusk) (Leibowitz, 1988). Human subjects studied in laboratory controlled conditions display circadian variations of appetite for high-energy (starchy, sweet and salty) foods. These rhythms are

actually in phase with the circadian rhythm in hunger mentioned earlier (*i.e.*, with dawn trough and evening peak). In sharp contrast, appetite for low-energy food (*i.e.*, vegetable) does not show significant changes across the 24 h cycle (Scheer et al., 2013).

Within the multioscillatory circadian network, the suprachiasmatic clock regulates the wake/sleep cycle and hormonal rhythms (among others, cortisol and melatonin), and also participates in the daily rhythm of food intake. Several secondary circadian clocks in the hypothalamus and brainstem, which are timed by peripheral metabolic signals, likely contribute to the daily feeding/fasting cycle. Hypothalamic clocks may align homeostatic food intake with the sleep-wake cycle. The secondary circadian clock located in the arcuate nuclei is more specifically involved in the daily variations in hunger feeling and the integration of leptinergic signals (Cedernaes et al., 2019). As for the daily variations in hedonic food intake, they depend on the circadian clock within dopaminergic neurons in the VTA (Koch et al., 2020).

Synchronizing effects of timed meals

As clearly demonstrated in animals, meals timed at an atypical schedule (that is, when food access is limited to the usual phase of rest) can shift many secondary clocks located in peripheral organs and the brain, but not the suprachiasmatic clock. Accordingly, if animals are exposed to restricted feeding schedules under a light-dark cycle, the master clock will still remain synchronized to light cues, while peripheral clocks will be synchronized according to the time of food consumption (Aoyama & Shibata, 2020; Damiola et al., 2000; Stokkan et al., 2001). Similarly, in humans, scheduled meals can induce phase-shits of peripheral rhythms without affecting the phase markers of the main clock (Krauchi et al., 2002; Wehrens et al., 2017). Among the hormonal changes induced by restricted feeding schedules, pancreatic hormones may have some timing properties. Glucagon secreted before food access could serve as a pre-feeding timer of peripheral clocks (Ikeda et al., 2018; Mukherji et al., 2015). By contrast, insulin secreted during the post-prandial period could be a post-feeding timer (Crosby et al., 2019; Tahara et al., 2011).

Circadian control of meal anticipation

Meal anticipation is a rhythmic behavior that animals exhibit before scheduled daily feeding time. This behavioral arousal associated with increased glucocorticoid secretion and thermogenesis is most clearly induced when animals are fed during their usual phase of rest (Feillet et al., 2006a). Such rhythmic behavior persists in the absence of a functional suprachiasmatic clock and exhibits circadian properties. For instance, in response to an abrupt shift in the temporal window of food availability, food-anticipatory activity is resynchronized before food access only after several days. During these days, transient bouts of activity are progressively shifted from the previous to the new timing of food access. Such transient cycles are typical responses during re-entrainment of circadian clocks and cannot readily be explained by learning processes such as classical conditioning (Mistlberger, 1994). This and other features of food-anticipatory activity have led to the concept of a "food clock" that would control the timing of eating according to the availability of food. The current view of the food clock favors the idea of a multi-oscillating brain network involving secondary clocks in several structures of the mediobasal hypothalamus and brainstem in connection with the striatum and the cerebellum (Challet, 2019). Several works, including those of my team supports a role of the classical clock genes (*Per1*, *Per2* and *Rev-erba*) in the food clock (e.g., Chavan et al., 2016; Delezie et al., 2016; Feillet et al., 2006b; Mieda & Sakurai, 2011; Takasu et al., 2012). Nevertheless, the molecular mechanisms underlying meal-anticipation behavior remain a subject of controversy, particularly on the question of an involvement of clock genes (see also Pendergast et al., 2017; Storch & Weitz, 2009).

When they have free access to food, nocturnal laboratory rodents (rats, mice) feed primarily at night. A more detailed analysis of the daily periodicity reveals a frequently bimodal rate of nocturnal food intake, characterized by a first peak of intake in the early evening and a second at the end of the night (Strubbe & van Dijk, 2002). The evening peak which could depend more specifically on the food clock, is linked to the activation of the peripheral and central arousal systems, following the period of daytime sleep and fasting. On the contrary, the morning peak that anticipates the predictable period of fasting ahead would involve the suprachiasmatic clock. By analogy, in humans, it can be hypothesized that timing of breakfast and lunch might involve temporal signals linked to the food clock, while temporal cues from the suprachiasmatic clock might participate in timing the dinner (Challet, 2019). These assumptions, however, deserve further study to be tested experimentally.

Metabolic alterations and circadian rhythmicity

- Genetic models of obesity and diabetes

Genetic models of obesity and type 2 diabetes, such as Zucker (*fa/fa*) rats and *db/db* mice that bear mutations in the leptin receptor, display increased food intake during their resting phase, even when they are fed with chow diet (Grosbellet et al., 2015a; Mistlberger et al., 1998). An altered daily pattern of feeding is not observed in the hyperphagic *ob/ob* mice that are genetically obese and sometimes diabetic due to a mutated *ob* gene preventing leptin synthesis (Grosbellet et al., 2015a). This finding in *ob/ob* mice suggests that the abnormal feeding pattern in Zucker rats and *db/db* mice does not depend on their impaired leptin signaling. Other circadian disturbances in *db/db* mice include impaired responses to light and longer circadian period of the master clock (Grosbellet et al., 2016).

- High-fat-induced obesity and diabetes

Feeding rodents with a diet enriched in fat and sometimes also in sugar is a widely used procedure to induce obesity and diabetes after weeks or months. Strikingly, free access to high-fat diet is commonly associated with changes in the daily pattern of feeding/fasting. In nocturnal C57 mice, the most salient change in that

respect is a spontaneous increase in high-fat feeding during the usual rest phase. Of interest, increased feeding during daytime occurs in the first days of access to high-fat diet, well before the onset of metabolic disturbances (Kohsaka et al., 2007; Pendergast et al., 2013). Compared to males, female C57 mice are more resistant to diet-induced obesity and do not display increased daytime feeding, nor shift in their peripheral clocks. Resistance to diet-induced obesity in female mice relies on circulating estrogens that buffer against circadian disturbances of eating (Omotola et al., 2019; Palmisano et al., 2017). Furthermore, because limiting access to high-fat diet during the usual active phase (nighttime) markedly reduces the deleterious effects of the unbalanced diet in male C57 mice (Hatori et al., 2012), timing of eating should be considered as an important determinant of metabolic health (see below for details).

Other circadian disturbances have been highlighted in response to high-fat feeding. Although the master clock is not sensitive to the resetting of meal time (see above), it can receive metabolic cues that affect its function. Indeed, when high-fat diet is provided *ad libitum*, the circadian period of the master clock is lengthened, its synchronization to light is slowing down, and the amplitude of its clock-controlled rhythms (e.g. sleep-wake cycle, body temperature rhythm) is diminished (Kohsaka et al., 2007; Mendoza et al., 2008). In humans, obesity without type 2 diabetes is associated with higher nocturnal secretion of melatonin and higher secretion of leptin without sizeable phase-shifts (Mantele et al., 2012).

Furthermore, daily rhythms in expression of clock and metabolic genes can be dampened in white adipose tissue of obese subjects with type 2 diabetes as compared to lean control participants (Stenvers et al., 2019, but see also Otway et al., 2011). Alterations of clock and metabolic gene expression in white adipose tissue are normalized by body mass loss in overweight subjects (Pivovarova et al., 2016). It is also worth noting that several taxa of gut microbiota display disrupted rhythms in patients with type 2 diabetes (Reitmeier et al., 2020).

Circadian disturbances and metabolic health

- Altered daily pattern of eating

A number of mutations or knock-out of clock genes lead not only to altered, if not arrhythmic, patterns of food intake, but also to metabolic disturbances (Delezie et al., 2012; Lamia et al., 2008; Marcheva et al., 2010; Sen et al., 2018; Turek et al., 2005), even though the causal link between these alterations is not clearly established. If wild-type mice have access to chow diet only during 12 h per day, either during daytime or nighttime, they ingest spontaneously more energy and gain more body mass when food access is imposed during their usual resting phase (daytime) (Bray et al., 2013). When wild-type mice have access to an unbalanced (*i.e.*, high-fat) diet only during 12 h per day, either during daytime or nighttime, mice fed during the "usual" feeding phase (*i.e.*, nighttime in this nocturnal animal) gain less body mass than those fed only during daytime. Importantly, energy intake and levels of locomotor activity are comparable in the two groups, although additive effects of both variables may have contributed to the observed differences in body mass gain (Arble et al., 2009). The deleterious effects of obesogenic feeding at the "wrong" phase of the living cycle were confirmed and extended to mice with other obesogenic diets (Haraguchi et al., 2014; Yasumoto et al., 2016). Furthermore, rats fed with an obesogenic diet only during daytime gain more body mass per ingested calorie than those fed with same choice diet only at night (Oosterman et al., 2015).

In human chrononutrition, it is difficult to define and record meal characteristics, such as meal timing, composition and number. For many - including cultural and socio-professional - reasons, it is even more difficult to provide appropriate recommendations. In accordance with previous investigations dealing with timing of eating in humans (Gill & Panda, 2015; Zeron-Rugerio et al., 2019), the temporal window of eating can be used as a convenient marker of a subject's eating pattern. The longer duration of eating window is, the shorter nocturnal fasting will be. In a US survey performed in more than 150 subjects, daily food intake spreads mostly from 6 AM to 12 am (Gill & Panda, 2015), thus reducing the sleep/fasting duration to 6 h. The duration of nocturnal fasting overlapping the sleep period is important to take into account in a context of body mass management to prevent gain mass or improve mass loss because nocturnal fasting is a period of lipid oxidation.

Besides the duration of eating window, it is also important to consider its phase (*i.e.*, its temporal occurrence according to the ambient light-dark cycle). For instance, even if a long (*e.g.*, 12 h) nocturnal fasting is considered as beneficial for metabolic health, a long but delayed fast associating a late dinner and delayed (or absent) breakfast is correlated with increased body mass index (Makarem et al., 2020). Actually, both breakfast skipping and late dinner may contribute to this obesogenic effect (Figure 3).

Breakfast skipping increases postprandial glycemic response at lunch (Jakubowicz et al., 2017). Moreover, eating breakfast is correlated with improved lipid oxidation during overnight fast (Kelly et al., 2020). Within a sample of type 2 diabetes patients, those who self-reported missing breakfast have a higher body mass index (Reutrakul et al., 2014). A study reports that people having breakfast have a lower chance to be overweight compared to those skipping it (Batista-Jorge et al., 2016). Other works consider sustained morning fasting due to breakfast skipping does not markedly affect energy metabolism, at least in obese subjects (Chowdhury et al., 2019).

Late eating, defined here as a main meal after 3:00 pm, is associated with higher body mass index, and higher plasma triglycerides and lower insulin sensitivity (Dashti et al., 2020). There is an endogeneous peak in lipid oxidation during the first part of the night (Zitting et al., 2018). Snacking in the evening, however, lowers lipid oxidation during subsequent nocturnal fast (Kelly et al., 2020). Diet-induced thermogenesis after the same meal is lower in the evening compared to morning (Morris et al., 2015). Together, these findings suggest that subjects taking regularly a heavy and late dinner

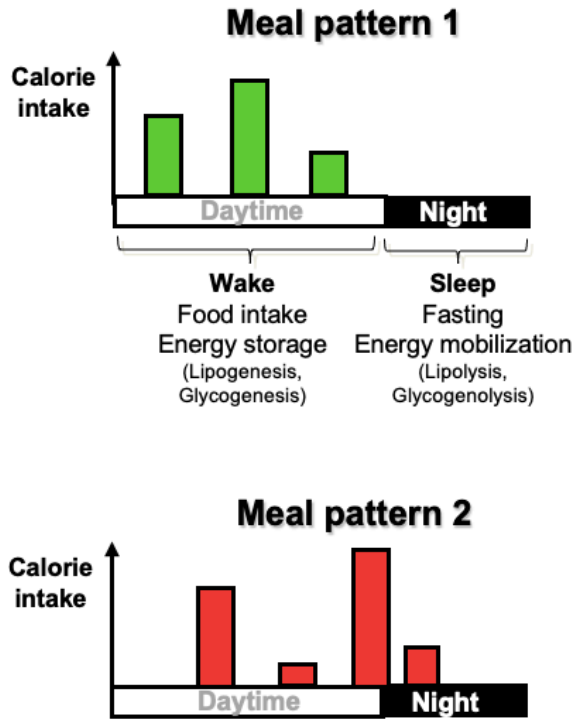

Figure 3. Examples of daily meal patterns in humans.
Meal pattern 1 is a classical distribution of meals with a solid breakfast, a large lunch and a light dinner. Such a meal schedule with a daily duration of about 12-h is recommended to maintain a stable energy balance or prevent body mass gain on the long-term. Meal pattern 2, including breakfast skipping, high-energy dinner, nocturnal snacking and/or a long (e.g., 18 h) window of eating, may favor a positive energy balance and accordingly, is not recommended for losing body mass.

may favor fat accumulation and reduce its mobilization during nocturnal sleep.

Recently, the notion of "eating jetlag" (Zeron-Rugerio et al., 2019), also called "metabolic jetlag" by others (Gill & Panda, 2015), has been defined as the variability of meal timing between working- and free-days. Eating jetlag is positively correlated with body mass index. Eating jetlag that likely triggers circadian misalignment in peripheral clocks, mostly results from shift in breakfast timing rather than shifts in lunch or dinner (Zeron-Rugerio et al., 2019).

- Erratic eating pattern

Providing six-meal schedule distributed over the light/dark-cycle (that is, giving a short access to food every 4 h) to rodents allows to eliminate the daily rhythm in feeding behavior. Such experimental paradigm markedly affects expression of metabolic genes in liver, brown adipose and muscles, without necessarily shifting circadian clocks. These findings highlight that erratic feeding pattern strongly impacts peripheral metabolism, eventually by bypassing peripheral clocks (de Goede et al., 2018; Greenwell et al., 2019). For more than half of participants in a US survey, eating behavior is considered as erratic (Gill & Panda, 2015). A comparable survey in India reaches the same conclusion (Gupta et al., 2017), raising the possibility that destructuration of the daily eating pattern in humans is likely a worldwide issue. As it will be evoked below, both shift-work and frequent jetlag promote this disturbance.

- Circadian misalignment

The number of people exposed to chronic jetlag and shift-work keeps rising nowadays. These socio-economical situations trigger several circadian alterations that all may affect metabolic health. They include irregular daily patterns of eating (see above), circadian misalignment, light at night and sleep curtailment. Circadian misalignment is due to a mismatch between the endogenous circadian timing and the external synchronizers, such as timing of light exposure and meal timing.

In animals, models of circadian misalignment and chronic jetlag lead to many metabolic disturbances such as increased obesity, impaired insulin secretion, reduced glucose tolerance and accelerated cellular aging (Bartol-Munier et al., 2006; Grosbellet et al., 2015b; Salgado-Delgado et al., 2010). Simulating night shifts and associated circadian misalignment can be achieved in subjects using the so-called forced desynchrony protocol under laboratory-controlled conditions. This protocol reveals that circadian misalignment in humans markedly modifies hormonal profiles, including decreased plasma leptin, increased plasma cortisol and insulin, and reduced glucose tolerance (Scheer et al., 2009). Circadian misalignment due to forced desynchrony or 8-h delay in bedtime also reduces total daily energy expenditure (McHill et al., 2014) and decreases insulin sensitivity (Leproult et al., 2014; Wefers et al., 2018). It also enhances mood vulnerability (Chellappa et al., 2020). There are gender differences in the metabolic responses to circadian misalignment, the neuroendocrine changes being higher in females (Qian et al., 2019). In parallel to these experimental findings, many epidemiological studies in various countries have highlighted significant associations between shift-work and a number of metabolic disturbances, such as obesity, high triglyceride levels, diabetes (Karlsson et al., 2003; Wyse et al., 2017), and prolonged daily eating duration (Lauren et al., 2020).

- Light at night

Light at night, sometimes called light pollution, is a direct consequence of the development of electrical light and the always increasing presence of outdoor and indoor artificial light. One of the best known physiological effect of light at night is a rapid and strong inhibition of melatonin synthesis and secretion by the pineal gland (Redlin, 2001). Furthermore, light at night will shift the master clock in the suprachiasmatic nuclei, leading either to phase-delay or advance depending on the timing of light exposure (Challet, 2007). In nocturnal animals, acute exposure to light at night reduces glucose tolerance (Opperhuizen et al., 2017). In mice, another deleterious consequence of prolonged light exposure, including at night, on metabolic health is a reduced activity of the brown adipose tissue that lowers energy expenditure and may favor increased adiposity (Kooijman et al., 2015).

Besides increased body mass index, elderly individuals regularly exposed to light at night display altered levels in circulating lipids, such as increased levels of triglycerides and low-density lipoprotein cholesterol, and reduced high-density lipoprotein cholesterol (Obayashi

et al., 2013). As a consequence, long-term light at night is associated with increased atherosclerosis (Obayashi et al., 2019).

- Sleep deprivation

Sleep loss has deleterious effects on glucose metabolism, notably through decrease in insulin sensitivity (Spiegel et al., 2009). Of note, this effect of sleep deprivation is additive to (*i.e.*, independent of) the decrease of insulin sensitivity due to circadian desynchronization (Leproult et al., 2014). Sleep reduction also increases appetite without necessarily increasing energy expenditure (St-Onge et al., 2011).

- Social jetlag

Chronic mild changes in timing of the sleep-wake cycle between working- and free-days, defining a so-called "social jetlag", may also have long-term metabolic consequences, such as increased body mass index (Mota et al., 2019; Parsons et al., 2015; Roenneberg et al., 2012). In keeping with these epidemiological studies in non-shift workers, animal research modeling social jetlag highlights deleterious effects of chronic shifts in timing of sleep-wake cycle on metabolic health (Espitia-Bautista et al., 2017).

Nutritional strategies based on chronobiology

Chronotherapeutics are treatments based on chronobiology, for instance, that target circadian clocks or take into account optimal times-of-day for improving efficacy and eventually reducing side-effects. In this last section, mention will be made of the expected benefit of respecting a temporal organization on a daily basis, combining a feeding phase more or less aligned to the solar phase (wakefulness phase) well separated from a phase of fasting and nocturnal sleep.

The first examples deal with parenteral nutrition that aims at providing continuous nutriments over 24 h in patients hospitalized in intensive care units. Although not commonly applied, it should be pointed out that as opposed to total parenteral nutrition, cyclical parenteral nutrition intended to mimic the daily feeding/fasting cycle, may have beneficial clinical outcomes that would not only favor metabolic health, but would also improve robustness of peripheral circadian rhythmicity (Matuchansky et al., 1992; Miki et al., 2003). The second examples concern laboratory (nocturnal) animals which spontaneously ingest a significant amount of food during the usual period of rest (daytime). As aforementioned, Zucker rats fed with a standard chow diet display binge eating during their rest phase. In these genetically obese rats, food access limited to the night leads to a reduction in body mass gain, despite the same caloric intake as measured in control rats fed *ad libitum*. Remember that C57 mice fed a diet enriched in fat become obese and spontaneously increase their ingestion of food during the usual resting phase (daytime), without necessarily increasing their daily energy intake (Hatori et al., 2012). If access to food is limited to 8 h per night, however, these mice gain much less body mass and do not exhibit fatty liver disease and hypercholesterolemia, unlike mice fed *ad libitum* with the same high-fat food and despite comparable daily energy intake (Hatori et al., 2012). The beneficial effects of time-restricted feeding for the metabolic health of mice is not limited to high-fat diet, but it is also efficient with other unbalanced diets such as high-fat plus high-sucrose or high-fructose diets (Chaix et al., 2014).

In relatively healthy subjects, consuming breakfast and having the largest meal early during the day (breakfast or lunch) may be efficient for preventing body mass gain (Hermenegildo et al., 2016; Kahleova et al., 2017). More and more studies support the efficacy of time-restricted eating to restore or maintain metabolic health, that is, to maintain a daily period of eating <12 h and a period of fasting (sleep) >12 h (Moon et al., 2020; Regmi & Heilbronn, 2020; Tippairote et al., 2020). For instance, when the temporal window of eating >14 h in overweight subjects is shortened to 10-11 h for four months, they lost body mass and reported improved sleep (Gill & Panda, 2015). In the same line, in patients with metabolic syndrome (body mass index of around 33), a three-month timed diet that combines a diurnal feeding window of 10 h and 14 h of daily fasting (including 7.5 h of sleep), induces a significant loss of mass and a drop in blood pressure (Wilkinson et al., 2020). In another study performed in men with prediabetes, feeding restricted to 6 h per day before 3:00 pm during five weeks leads to improved insulin sensitivity, blood pressure and appetite, without body mass loss (Sutton et al., 2018).

Moreover, in the case of a body loss diet (Mediterranean type, in this example), having the main meal earlier in the day improves the loss of body mass. In a sample of 270 patients that underwent bariatric surgery, body mass loss during post-surgery years is better in "early eaters" having a main meal around noon, compared to "late eaters" (main meal after 3 pm) (Ruiz-Lozano et al., 2016).

As evoked earlier with the concept of eating jetlag (Zeron-Rugerio et al., 2019), day-to-day regularity of meal timing is also a key point. Accordingly, on the long term, it is advisable to maintain daily meals at fixed times.

Conclusion

Current knowledge in chrononutrition suggests that in case of positive energy balance (*e.g.*, overweight, obesity) or to preclude its occurrence, besides the management of total energy intake, a greater daily calorie intake would preferably take place at the beginning of the active phase (breakfast/lunch), together with a nocturnal fasting long enough (12 h or more). By contrast, and for the same reasons as evoked above, in case of negative energy balance (*e.g.*, underweight, anorexia nervosa), greater daily caloric intake would favorably occur in the evening (dinner). Thus, new nutritional strategies based on personalized chronomedicine must be developed to limit, or even prevent, the harmful effects of circadian disturbances linked to diet. Based on experimental studies taking into account the timing and structure of meals, the amount and temporal distribution of calories ingested, and the choice of macronutrients, recommendations for daily eating regimens should soon emerge to improve metabolic health and help keeping a stable energy balance.

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