Trends in Endocrinology & Metabolism

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REVIEWS

Review

Eating Rewards the Gears of the Clock

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Eating behavior is regulated by metabolic and hedonic brain networks, which interact with each other to balance the physiological regulation of hunger and satiety. The daily balance of this regulation is controlled by the central circadian clock. Importantly, metabolic and reward properties of food impact the functioning of circadian clocks, altering the oscillatory activity of the molecular clockwork and circadian rhythms. However, when feeding (metabolic or reward) is timed, the whole circadian system is entrained. Furthermore, besides synchronizing the clock, the timing of both metabolic and reward eating might be crucial for health, to improve circadian physiology, as well as to treat metabolic (e.g., diabetes, obesity) and neurological diseases (e.g., mental, neurodegenerative).

Highlights

Eating behavior is centrally regulated by metabolic, hedonic, and circadian pathways which determine the quantity, quality, and time of food intake.

By contrast, time-restricted eating (TRE) is a powerful cue to synchronize body and brain clocks, including, under certain feeding conditions, the hypothalamic suprachiasmatic nucleus (SCN), the main mammalian brain timekeeper.

The central mechanisms to entrain the SCN by feeding are dependent mainly, but not exclusively, on metabolic hypothalamic (orexins) and hedonic mesolimbic (dopamine) molecules that impact the clockwork. Therefore, diet components that reach and trigger metabolic and hedonic brain changes might favor clock synchronization by TRE.

However, when eating is not timed, and it occurs at the rest phase of the organism, metabolic consequences (e.g., obesity, diabetes) or behavioral eating disorders (e.g., compulsive eating, binge eating) may appear. Thus, TRE aligned with the sleep–wake cycle might help to improve physiology and evade negative consequences in health induced by circadian disruptors (e.g., light pollution, social jetlag, shift work).

Clocking Food Intake

Food intake is a complex behavior that involves the participation of neural substrates that function in an interactive and balanced manner, in conjunction with peripheral physiology in various organs that indicate the energy state of the organism, in both hunger and satiety.

The classical mechanisms of the regulation of food intake involves two principal systems in the brain: (i) a metabolic system that regulates the amount of food necessary for the survival of the organism, and (ii) a hedonic or pleasure mechanism that regulates the quality and type of food selected and ingested [1]. While the metabolic mechanisms are mainly regulated by the **hypothalamus** (see Glossary) and brain stem, the hedonic processes are principally, but not uniquely, regulated by the dopamine (DA) system. Anatomically and functionally these centers in the brain are linked, and this gives a balanced regulation between the quantity and quality of what has to be eaten. In addition, food-related hormones (e.g., insulin, leptin, and ghrelin) have the ability to modulate the cellular activity of brain nuclei of both systems due to the presence of specific receptors. Therefore, the physiological regulation of food intake depends on the homeostatic interaction between the brain and the periphery. When this homeostasis is lost, metabolic pathologies appear.

Since physiology is clock controlled, food intake must be regulated in time. Therefore, centrally the circadian clock coordinates the time of metabolic and hedonic food intake, influencing the quality and quantity of food to be taken at a specific time of the day [2]. By contrast, the timing of food intake can either positively (**entrainment**) or negatively (misalignment) affect the circadian system. Furthermore, these effects may be even more evident when particular types of diets are eaten (e.g., high-fat, hypocaloric, **palatable diets**).

Timed Eating Behavior: Paced by the Clock(s)

Food intake is a robust **daily rhythm** accompanying increased locomotor activity around the event. Mammalian diurnal species, including humans, distribute food intake across the day or light phase of the light–dark (LD) cycle imposed by solar time [3,4], while nocturnal rodents eat higher amounts of food in the early night, with a second peak of feeding in the late night [5]. Essentially, daily variations of eating patterns are synchronized to the LD cycle through the

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Box 1. Molecular Clockwork

The molecular timekeeping of the SCN is dependent on the clock genes *Clock* and *Bmal1,* two transcription factors which are able to dimerize and bind to the enhancer box of other genes, such as *Period* (*Per1–3)* and *Cryptochrome* (*Cry1–2)*. PER–CRY, have the capacity to enter back into the nucleus to inhibit the activity of CLOCK–BMAL1, and thus their own transcription [75]. The final result is the oscillatory activity (around the 24 h) of these genes (excluding *Clock*) in the SCN, with peaks of activity during the light period for *Per1–3* and *Cry1–2* genes, and *Bmal1* with a peak during the dark period. Another group of genes oscillating in a circadian manner and dependent on the CLOCK–BMAL1 dimer are the nuclear hormone receptors *Rev-Erb* (α/β) and *Ror* (α, β, and γ). These genes induce the circadian rhythmicity of *Bmal1*: *Rev-Erbα* represses *Bmal1* during the day, while *Rorβ* activates it at night. Finally, clock output or clock-controlled genes (CCG) from the SCN signal the rest of the brain and body to give the timing cue required, and keep circadian synchrony in the whole body; vasopressin (*Avp*) is the principal SCN output signal. Moreover, other SCN output signals are humoral or paracrine. The peptides transforming growth factor alpha (TGFα), prokineticin 2 (PK2), and cardiotrophin-like cytokine (CLC) participate as temporal SCN signals for the circadian control of behavior [6]. The sophisticated clockwork enginery in the SCN has also been described in other tissues, such as the liver, heart, lung, kidney, pancreas, and adipose tissue; thus, despite the initial identification of a single body pacemaker in the brain, it is now well known that several organs in the whole body contain a circadian clock indispensable for the rhythmic functions accorded to each tissue [76].

suprachiasmatic (SCN) circadian pacemaker (and their molecular clockwork) (Box 1), which receives direct photic information from the retina (Box 2), and transmits this to brain structures that regulate feeding [2,6] (Figure 1).

The SCN projects to the metabolic hypothalamus via the subparaventricular zone, which then distributes timing information to the paraventricular (PVN), dorsomedial (DMH), and lateral hypothalamus (LH) [7] (Figure 1). Cells in the LH express the orexin (ORX) neuropeptides, which are involved in locomotion and feeding behaviors, and show daily (synchronized to the 24 h LD cycle) and circadian (self-sustained under constant light conditions) expression at both the gene and protein level. ORX release in nocturnal rodents peaks at the beginning of the night, the time at which the animals are awake and begin feeding [8,9]. Moreover, ORX have also been implicated in arousal and **reward** related to feeding [10]. Thus, the SCN communicates to the LH–ORX neurons to initiate rhythms of locomotion and metabolic–hedonic eating.

The SCN also provides timing information to brain regions regulating the **hedonic drive** of eating (Figure 1). In the midbrain, the DAergic ventral tegmental area (VTA) projects to the nucleus accumbens (NAcc) in the ventral striatum for the regulation of motivated behaviors [11,12]. In the NAcc, spiny gamma-aminobutyric acid-ergic (GABAergic) neurons contain DA receptors (D1 and D2 type), which are activated when eating, and this response is higher still if a palatable diet is ingested, leading to reinforcement of this behavior. Moreover, the DA tone in

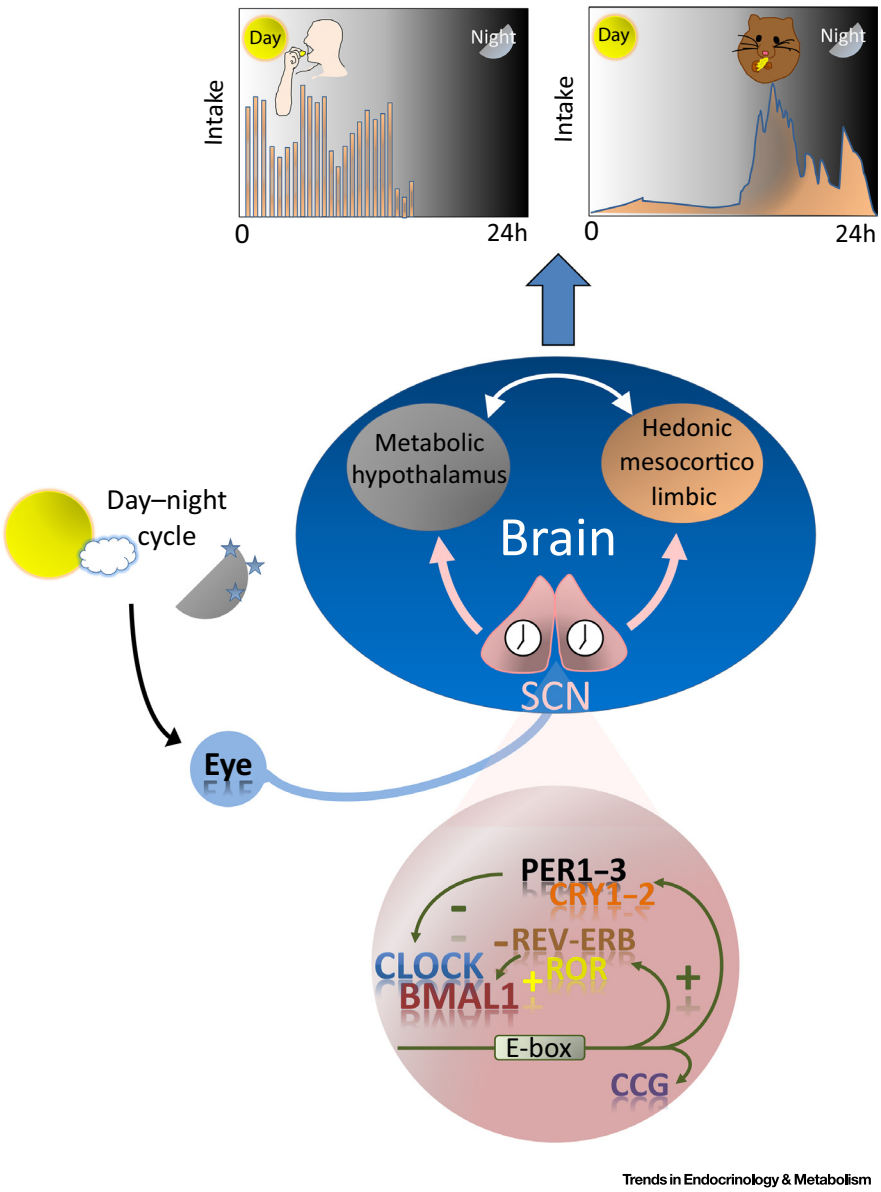
Box 2. Light-Synchronization of Circadian Clocks

The SCN is mainly synchronized to the day–night alternation [6]. Light is perceived in the eye by a particular layer of ganglion neurons containing the photopigment melanopsin, also called intrinsically photosensitive retinal ganglion cells (ipRGCs). These cells project to the SCN (in the ventral neurons), through the monosynaptic retinohypothalamic tract (RHT), for entrainment to the LD cycle [77]. At the cellular level, light signaling promotes an increase in the influx of Ca^{2+} in postsynaptic SCN cells, then an activation of protein kinases and CREB, which finally binds in the promoters of *Per1–2* genes, leading to the resetting of the phase and/or entrainment of the clock.

Moreover, since ipRGCs connect with other brain structures in the hypothalamus (e.g., LH, preoptic area) and epithalamus (perihabenular nucleus), light is able to modulate specific behaviors (e.g., sleep, feeding, motivation) [78]. Thus, the LD cycle may entrain brain circadian clocks and behavior directly and/or indirectly via the SCN. For peripheral oscillators, however, LD signals first entrain the SCN, and then the clock uses hormonal and neuronal pathways, behavioral (e.g., food intake, locomotor activity), or temperature cues to transmit the solar time information to the whole body [37].

Glossary

***Ad libitum*:** from the Latin 'at liberty', in feeding behavior it refers to a free-feeding or food-unlimited access situation of an organism.
Circadian rhythm: oscillations of biological functions within a period close to 24 h, which persist under conditions of constant light.
Daily rhythm: physiological 24 h rhythms expressed under entrainment condition, but might not sustain in constant conditions.
Entrainment: biophysical process by which external periodic cues (light–dark, feeding–fasting cycles) regulate the phase and period of an endogenous biological oscillator.
Hedonic drive: physiological forces acting within an organism to initiate behavior to obtain pleasure.
Hedonic eating: eating behavior of particular aliments to obtain pleasure without an energy deficit.
Hypothalamus: a group of nuclei in the ventral brain which regulates homeostasis and fundamental behaviors for survival, such as sleep, feeding, and drinking. For feeding behavior the hypothalamus senses the need for energy from the periphery (hormonal changes; glucose, insulin, leptin, glucagon) to induce or reduce the food intake.
Metabolic eating: eating behavior triggered by an energy deficit and necessary for survival.
Motivation: central processes driven by external or internal changes, which induce an organism to identify and exert effort to obtain goals (food, water).
Palatable diet: a diet containing particular foods with a high hedonic property able to induce the increase of eating in an organism.
Peripheral oscillator: circadian oscillators in the brain or periphery besides the suprachiasmatic nucleus.
Reward: any stimulus, situation, or object with a relevant salience value for the organism which promotes goal-directed behaviors.
Self-sustained oscillator: an oscillator capable of maintaining endogenous oscillations without any timing signal or the influence of another oscillator.
Slave oscillator: an oscillator which is driven and entrained by a self-sustained oscillator.



Suprachiasmatic (SCN): a pair of nuclei situated in the anterior hypothalamus, which contain a pacemaker in each cell and which serve as the principal circadian clock in mammals.
Synchronizer: an external or internal agent able to induce synchrony and coupling among oscillators.
Temporal calorie restriction: experimental paradigm in which the access to food sources is restricted in calories (66% of daily food intake) and time in the 24 h day cycle.
Time-restricted eating (TRE): experimental paradigm in which the access to food sources is restricted in time in the 24 h day cycle.

Figure 1. Daily and Circadian Rhythms of Eating Behavior Are Regulated Centrally by the Metabolic–Hedonic–Circadian Network. Food intake is controlled by specific brain sites driving the metabolic and hedonic pathways of eating in the hypothalamus and mesocorticolimbic system respectively. Accompanying these two pathways, the suprachiasmatic (SCN) clock, and its molecular machinery (Box 1), dictate the time of both the need and pleasure of eating. The SCN receives direct projections from retinal ganglion cells, allowing the synchronization to the light–dark cycle (LD). Thus, daily hedonic and **metabolic eating** is time controlled, and synchronized to the LD cycle (Box 2), giving a robust food intake by daytime for diurnal species (including humans) and at nighttime for nocturnal animals (e.g., rats, mice, hamsters). The SCN sends neural and paracrine timing signals to both hedonic and metabolic centers of food intake to impose rhythms of eating. Interestingly, despite the fact that the functional clockwork of the SCN between diurnal and nocturnal species is similar, food intake is opposite during the 24 h day, suggesting that the time of eating behavior may reside somewhere in these brain feeding centers (i.e., metabolic, hedonic). E-box, enhancer box; CCG, clock-controlled genes.

VTA cells might be modulated by metabolic factors, such as ghrelin and leptin, to promote and inhibit, respectively, reward eating [12,13].

DA release and content in the striatum is rhythmic, in nocturnal rats and mice higher levels occur at night, and in the day for diurnal rodents; hence, higher levels of DA occur at the time of locomotion and feeding for both nocturnal and diurnal rodents [14–16]. Thus, DA rhythms are likely participating in the modulation of locomotion and feeding rhythms. Anatomically, the SCN projects to the VTA indirectly via the medial preoptic nucleus (MPON) of the hypothalamus [17]. Thus, VTA–DA **circadian rhythms** related to feeding might be induced or at least regulated by the SCN; at first, to initiate locomotion at the right time for food-seeking behaviors, and secondly, to modulate circadian food-reward at night for nocturnal species [18] or by day in diurnal species. This last point might be crucial to facilitate and promote reinforcement and conditioned learning associated to food intake.

Accordingly, the control of food intake in the brain is dependent on this balanced metabolic–hedonic–circadian circuit [2]. However, when one of these components is out of balance food intake is altered, often leading to overconsumption and weight gain. The exposure to and intake of high-caloric diets induces several changes in all of these brain centers regulating feeding, including those from the circadian system.

The ***ad libitum*** intake of high-caloric diets leads to alterations in circadian rhythms of behavior, and on the expression of clock genes and those regulating energy balance in the hypothalamus and peripheral tissues [19]. Furthermore, the behavioral and molecular entrainment to light is affected in mice fed with a high-fat diet [20]. Taken together, these results indicate that high-fat feeding alters the functioning and light synchronization of the mammalian circadian clock.

In an experimental model in which rodents were given the choice between a high-caloric diet versus a normocaloric diet, animals showed 'snacking' feeding behavior and preference for the high-caloric diet along the whole 24 h LD cycle, disrupting the daily rhythm of eating and leading to rapid weight gain [21,22]. Thus, beyond the type of diet, the loss of daily rhythms of feeding becomes an important factor in inducing obesity and metabolic diseases.

Centrally, in animals exposed to the protocol of diet choice, the day–night expression of the clock proteins PER2 and BMAL1 in the mouse lateral habenula (LHb) is disrupted by the intake of the caloric diet [21]. The LHb is an epithalamic nucleus, which is relevant for the control of monoamines and the regulation of palatable food intake [23,24]. Interestingly, sleep deprivation, a condition that increases caloric intake and body weight gain [25], disrupts clock gene expression in the LHb [26], while a perturbation of the LHb clock by high-caloric diets might lead to disruption of the sleep–wake cycle. This highlights a specific circadian role of the LHb in rhythmic caloric intake, likely via its control on DAergic hedonic centers [27]. Accordingly, it was recently reported that rhythms of DA release in the SCN are disrupted in an animal model of obesity [28]. Therefore, DA rhythms in the SCN and the rest of the forebrain could be necessary to maintain a healthy metabolic condition and proper food intake.

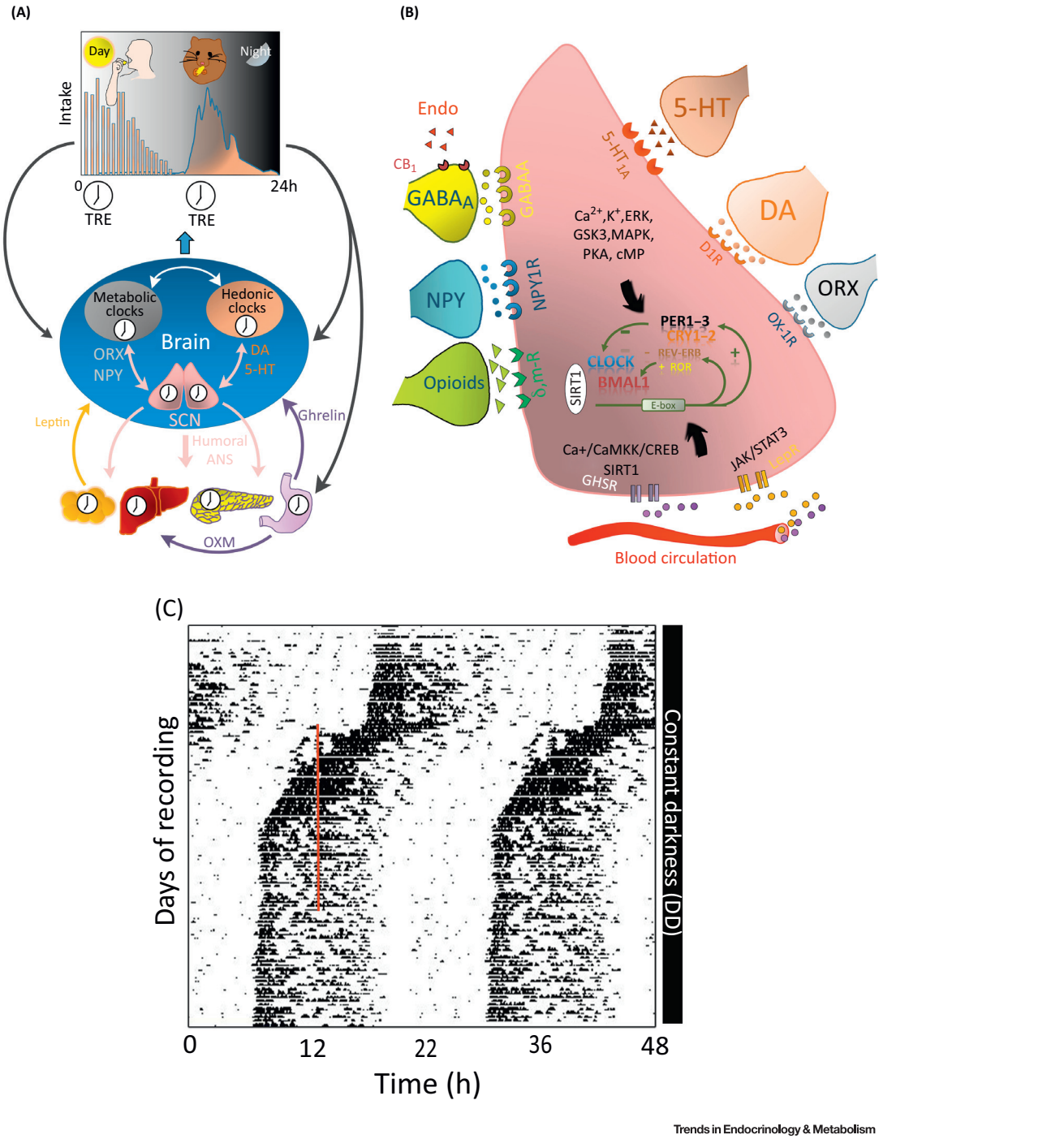
Timed Eating Behavior: Pacing Clock(s)

Time-Restricted Eating, a Good or Bad Clock Aligner? A Matter of Time

Time-restricted eating (TRE) induces an increase in the locomotor activity pattern in anticipation of meal access and the synchronization of physiological rhythms and metabolic activity, indicating that feeding time is a strong **synchronizer** of circadian rhythms [29,30] (Figure 2A, Key Figure). Nevertheless, the SCN (clock gene expression) remains entrained to the LD cycle, thus TRE uncouples rhythms of clock genes in peripheral [31] (liver, lung) (Box 3),

Key Figure

Time Eating Behavior Drives Brain and Peripheral Clocks and Circadian Rhythms



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Box 3. Peripheral Circadian Oscillators

Several years have passed since the first discovery of the expression of clock genes oscillating in the liver [31,79,80]. The liver is a peripheral circadian clock which plays an important role in physiology and metabolism. Interestingly, the first reports on the circadian activity of liver were made serendipitously by the group of Prof. Ueli Schibler. In the interest of studying the albumin gene, authors isolated the transcription factor D-element-binding protein (DBP), with the surprising result that accumulation of *Dbp* in the liver is 100-times more at night than by day, and is independent of the SCN and/or rhythmic hormone release [81]. How important is the rhythmic gene expression in the liver? A specific *Bmal1* deletion in the liver clock alters glucose metabolism, inducing a decrease in the levels of circulating glucose in blood at daytime, thus, altering the endogenous rhythm of glucose production necessary for the metabolic challenges during sleep/fasting conditions [82].

In the pancreas, β-cells exhibit rhythmic expression of circadian genes, which induces diurnal insulin secretion [83,84]. Considerably, clock capacity in islet pancreas cells is dependent on clock genes, since when one of the principal actors of the molecular clockwork, such as *Clock* or *Bmal1,* is lacking, the insulin secretion is altered, leading to possible development of diabetes [85]. Thus, the pancreatic circadian clock locally regulates insulin release in time; a circadian dysfunction of it leads to metabolic pathology.

In the cardiovascular system, a circadian clock regulates daily changes in blood pressure (BP) and heart rate (HR). Clock genes and proteins (*Bmal1*, *Per2*, *Rev-Erbα*) and clock output genes (*Dbp*) are rhythmically expressed in the heart, and these rhythms persist *ex vivo*, indicating the presence of an autonomous circadian clock within cardiac cells [86]. Moreover, global and specific mutations of the BMAL1 clock gene lead to alterations in cardiovascular functions (BP, HR), bradycardia, and depressed systolic function. In humans, cardiovascular incidents (myocardial infarction) show a higher frequency in the morning (06.00–12:00 h), which can be correlated to the circadian variations of cardiac functions (BP, HR, blood consistency) [87]. The clock in the cardiovascular system is synchronized by the SCN via the autonomous nervous system [88], therefore, a misalignment between the SCN and the heart clock by circadian disruptions (jetlag, shift work) may potentiate the risk for cardiovascular diseases [87].

and extra-SCN [32] (hypothalamic and limbic) oscillators (Box 4) from the main SCN pacemaker. However, the uncoupling of daily feeding rhythms from the LD cycle can lead to negative metabolic consequences. Actually, in laboratory animals, mainly mice and rats, TRE has been imposed in the light phase (when nocturnal rodents sleep), which perturbs their sleep–wake cycle. Metabolically, when mice are fed with a high-fat diet only during the light phase of the LD cycle, body weight increase is significantly higher than in animals fed at the dark phase [33].

Conversely, TRE at night, when nocturnal rodents are active, leads to diverse effects in metabolism and physiology, improving circadian rhythms even in clock gene mutant mice [34–36]. TRE protects against obesity induced by diet in double global *Cry1-2* mutants and in mice carrying a liver-specific deletion of *Bmal1* and/or *Rev-Erbα/β*. More importantly, effects of

Figure 2. (A) Time-restricted eating (TRE) is a strong synchronizer for extra-suprachiasmatic (extra-SCN) oscillators in the brain and periphery. TRE aligned with the active phase of the organism (by daytime for diurnal species, and at nighttime for nocturnal) favors synchronization and improves physiology and health. However, when time of feeding is misaligned to the sleep–wake cycle, metabolic, behavioral, and physiological consequences emerge (e.g., body weight gain, glucose metabolism dysregulation). TRE coupled to a hypocaloric condition, or with a strong hedonic background, entrains the main SCN clock. The SCN projects to the metabolic and hedonic brain feeding centers, and to peripheral oscillators via the autonomous nervous system (ANS). However, viewed another way, the SCN is innervated by these structures and peripheral hormones, which will affect the clock in food entrainment. (B) At the SCN level, feeding time might affect the physiology and molecular properties of the clock through the release of diverse neurotransmitters and the activation of diverse receptors and the intercellular pathways. In addition, peripheral hormones (e.g., ghrelin, leptin) synchronized by feeding time may act directly on their receptors localized in the SCN and other brain circadian clocks to potentiate food synchronization. (C) Representative actogram of the behavioral circadian rhythm (in constant darkness, DD) of wheel running activity of a mouse synchronized to daily palatable meal (chocolate) intake without food restriction (red vertical line). Abbreviations: 5-HT, serotonin; 5-HT_{1A}, serotonin 1A receptor; Ca^{2+}, calcium; CaMKK, Calcium/calmodulin-dependent protein kinase; CB_1, cannabinoid 1 receptor; CREB, cAMP-response element-binding protein; D1R, dopamine 1 receptor; DA, dopamine; δ-R, δ-opioid receptor; E-box, enhancer box; ENDO, endocannabinoids; ERK, extracellular signal-regulated kinase; $GABA_A$, $GABA_A$ receptor; GHSR, growth hormone secretagogue receptor; GSK3, glycogen synthase kinase-3; JAK, Janus kinase; K^+, potassium; LepR, leptin receptors; MAPK, mitogen-activated protein kinase; μ-R, μ-opioid receptor; NPY, neuropeptide Y; NPY1R, neuropeptide Y1 receptor; ORX, orexin; OX-1R, orexin 1 receptor; OXM, oxyntomodulin; PKA, protein kinase A; SIRT1, sirtuin 1; STAT3, signal transducer and activator of transcription.

Box 4. Extra-SCN Brain Circadian Oscillators

In the brain, extra-SCN structures have been identified as circadian oscillators with self-sustained ability that are synchronized by the SCN. These are the olfactory bulb (OB) [89] and the LHb [90,91]; both are good examples of **self-sustained oscillators**, independent of, but entrained by the SCN, and dependent on clock genes. The clock in the OB controls the circadian rhythms in odor detection, and this behavior might be relevant in nature for foraging and optimizing the quality of food sources. The LHb has been revealed as a relevant structure for the control of monoamines. Moreover, it has been implicated in the regulation of palatable and caloric food intake [23,24]. In the hypothalamus, beyond the SCN, the arcuate and DMH nuclei have circadian activity in the firing rate and clock gene expression, and these are importantly affected by feeding status in mice [92]. However, these have been classified as **slave oscillators**.

TRE at night against obesity, hyperinsulinemia, and inflammation are observed in animals fed with a high-caloric diet, even if these eat the same number of calories as those exposed *ad libitum* to the diet. In both clock altered mice and/or those exposed to hypercaloric diets, TRE at night modifies gene rhythms in the liver, permitting better energy utilization and expenditure, and avoiding the development of obesity or metabolic syndrome [34,35]. Thus, TRE might have both beneficial or negative consequences in physiology; the difference is in the time of feeding aligned with the sleep–wake cycle [33] (Figure 2A).

What are the signals by which TRE entrains peripheral clocks? Body temperature, hormones, and peptides related to feeding are important candidate signals for the entrainment of **peripheral oscillators**, and even circadian clocks in extra-SCN brain sites [37]. Recently, it was reported that oxyntomodulin (OXM) is the principal signal, induced by feeding, that entrains the circadian clock in the liver through activation of *Per1* [38]. Importantly, the effect of OXM on the liver is clock-dependent. When mice are treated with OXM by day, the liver clock shifts, but not when OXM is given at night [38]. It will be interesting to determine whether OXM can entrain other peripheral oscillators, and to identify new peripheral or central signals that specifically entrain peripheral and central oscillators by feeding time (Figure 2A).

Time-Restricted Eating for the Master Clock: A Matter of Time and Calories

Circadian rhythms of locomotion, body temperature, hormonal release (all of them SCN outputs), and SCN clock gene expression are phase-shifted or entrained when TRE is coupled to a caloric restriction (CR) in nocturnal and diurnal rodents. This suggests that in addition to feeding time, a caloric condition promotes resetting of the SCN circadian clock [4,39].

CR has beneficial effects on health and lifespan through the activation of the sirtuin 1 (SIRT1) and mitochondrial oxidative metabolism [40]. Interestingly, at the clock level, SIRT1 regulates the circadian rhythms of peripheral tissues and central structures, having as molecular targets BMAL1 and PER2 clock components, deacetylating both proteins [41]. Thus, by changing the cellular metabolic state of the SCN, CR can entrain the molecular clockwork (Figure 2B).

By contrast, SIRT1 in the ventromedial hypothalamus (VMH) is relevant for the control of energy balance, mainly sensing feeding and metabolic cues. The VMH projects directly to the SCN, thus CR might induce the expression of SIRT1 in the VMH, and then, indirectly, alter the molecular timekeeping in the SCN [42]. However, as the SCN clock receives direct projections from other hypothalamic and non-hypothalamic structures related to feeding, it is highly likely that entrainment of the SCN by feeding is dependent on several inputs from the whole brain.

Time-Palatable Eating: Rewarding the Clock

Food intake induces the activation of the regions of the hedonic reward system. The intake of palatable diets triggers the release of DA from the VTA in the midbrain to the ventral NAcc [12].

Moreover, DA release might also target other brain sites containing DA receptors, such as the prefrontal cortex, the striatum, and importantly, the SCN [43]. The VTA projects a functional pathway directly to the SCN, targeting D1-type receptors in clock cells to facilitate the re-entrainment of behavioral rhythms to a new LD cycle [43]. Activation of DA receptors leads to intracellular changes in the mitogen-activated protein kinase (MAPK) and cAMP-response element-binding protein (CREB), and finally an increase in the expression of *Per* genes [44]. Then, DA release by feeding time can induce *Per* gene expression in the SCN clock via these pathways (Figure 2B). Furthermore, when feeding is highly palatable, DA release is enhanced, having a major impact on the control of behavior (e.g., learning, reinforcement), including circadian behavior (synchronization) [12,45].

In animals fed with a daily palatable diet, without food restriction, circadian rhythms of locomotor activity (Figure 2C) and clock gene expression are synchronized to the time of feeding [45,46]. Moreover, in arrhythmic *Per* mutant mice a daily palatable snack is able to rescue and entrain behavioral rhythms [47]. Altogether, the effects of daily palatable meal to entrain and rescue circadian rhythms are certainly dependent, in part, on DA activity. DA release at the level of the forebrain (e.g., striatum, NAcc, SCN) is rhythmic [14,28], and synchronized by feeding (palatable or regular diet); hence, feeding time can reach SCN clock (via D1 receptors), inducing the synchronization of molecular, behavioral, and physiological rhythms (Figure 2A–C). However, the neural mechanisms of palatable food entrainment become more complex when we add other systems, substrates, and molecules participating in the regulation of hedonic feeding, and that can affect the SCN.

Serotonin (5-HT) from the raphe nuclei is an important internal synchronizer for the SCN since the clock contains diverse types of 5-HT receptors (5-$HT_{1A, 1B, 2A, 2B}$, and $_7$). 5-HT has been implicated in the nonphotic synchronization of the clock via 5-HT_{1A} and 5-HT_7 receptors, the activation of both the protein kinase A (PKA) and K^+ channels, and changes in *Per* gene expression [48]. Intake of meals rich in carbohydrates increases hypothalamic 5-HT release, and 5-HT neurons in the raphe nuclei show c-Fos expression in animals synchronized to daily palatable meals [46,49]. Thus, 5-HT may be involved in the food-reward entrainment of the SCN clock (Figure 2B).

ORX are able to shift molecular and electrical activity of the SCN through the activation of ORX-1 and ORX-2 receptors, changing intracellular Ca^{2+} levels and leading a suppression of *Per* genes [50]. In the entrainment of circadian rhythms and molecular clock gene expression in the SCN by daily access to a palatable feeding, ORX cells are significantly activated (c-Fos expression) [46]. In addition, a molecular disruption of the clock, which leads to compulsive intake of palatable food, upregulates ORXergic activity [9]. Thus, ORX are another internal time cue with the ability to entrain the clock when palatable feeding is timed by changing *Per* gene expression (Figure 2B).

Endocannabinoids are involved in the central regulation of feeding at both levels, metabolic and hedonic [51]. 2-arachidonoylglycerol (2-AG) and N-arachidonoylethanolamide (AEA), the two principal ligands of the endocannabinoid receptors (CB1 and CB2) show circadian variations in the brain, and CB1 receptors are expressed in the SCN nuclei [52,53]. CB1 receptors in the SCN presynaptically regulate GABAergic transmission; thus, cannabinoids upregulate the firing rate of SCN cells and modulate the light entrainment of the clock by a presynaptic mechanism [53]. Therefore, during palatable feeding time, CB might impact the SCN clock as an entraining signal via the modulation of the GABAergic neurotransmission and clock gene expression (Figure 2B).

Similarly, the opioid circuitry, implicated in food-reward related behaviors, might affect the circadian system [54]. **Motivation** for the intake of palatable foods is modulated by opioid (enkephalin) action in the forebrain. μ-opioid receptors are contained in the forebrain, including the SCN, which is reset by selective agonists of these receptors via the ERK1/2 and glycogen synthase kinase-3β (GSK3β) signaling pathways [54,55]. Thus, opioid signals rising after palatable feeding might be able to time code the SCN to potentiate and induce entrainment to timed food-reward.

Additionally, from the periphery, the metabolic reward hormones, leptin and ghrelin, may impact the SCN to reinforce or coordinate entrainment to feeding time. *In vitro*, both leptin and ghrelin reset the circadian electrical and clock gene activity in the SCN [56,57], likely via direct actions on leptin and ghrelin receptors, respectively [58,59]; hence, in TRE, high levels of ghrelin and leptin after and before feeding, respectively, are important physiological signals for the entrainment of circadian clocks, bolstering the brain metabolic and hedonic drives of feeding for SCN synchronization (Figure 2B).

In summary, when the clock is entrained to food with a strong palatable and reward content, several brain circuits give timing information to the SCN. The summation and temporal coordination (before, during, and after feeding) of these might lead to the entrainment of the clock and the expressed behavioral and physiological rhythms.

Circadian Food Entrainment in Humans: Physiology, Behavior, and Gene Expression

The knowledge in relation to the effects of food entrainment on the circadian physiology of rodents has advanced profoundly, highlighting that feeding time synchronizes behavior, physiology (hormonal rhythms), and gene expression in the brain, including the SCN and peripheral tissues.

However, there is still much to be understood with regard to the effects of meal timing on the human circadian system and health. This has become a subject of scientific and societal interest due to the increasing epidemic of metabolic diseases worldwide, such as obesity and diabetes, but also due to eating disorders (e.g., compulsive feeding, binge eating, night eating disorder).

In healthy conditions, human feeding behavior follows a daily and circadian rhythm [3]; however, this may be disrupted under particular conditions of overeating, malnutrition, or by shifting the time of feeding. Accordingly, calorie intake at different times of day differentially impacts energy balance and metabolism [60]. Humans, being a diurnal species, have to distribute calorie intake mainly in the early day and reduce it at night. Unfortunately, this is not the current situation in human eating behavior. Healthy subjects without a phase shift condition (e.g., shift work, jetlag) show aberrant eating behavior with a principal caloric intake at night and less by day [61].

Similar to what has been reported in rodents, when mealtime is out of phase with the sleep–wake cycle, the human circadian system is in a state of internal misalignment between central and peripheral clocks, which could lead to pathology (e.g., obesity, diabetes) [62]. Previous studies have reported that eating late at night increases the risk of obesity. In addition, the risk is higher still when eating earlier in the day (breakfast) is omitted [63].

Certain social conditions in which people are exposed to circadian disruptions, such as shift work or social jetlag, lead to an increased calorie intake at night, which is significantly correlated with obesity [64,65]. Calorie intake at night leads to clock gene expression changes in

peripheral oscillators (adipose tissue), hormonal release (leptin, insulin), and changes in plasma glucose rhythms and glucose tolerance, which altogether may induce increased appetite and food intake [66]. In shift work conditions, the daily oscillations of the hunger hormone ghrelin are shifted with a postprandial increase, which might trigger (via VTA–DAergic neurons) **hedonic eating** at night [67].

Contrary to this, when feeding happens at early times of day, physiological responses are different. Gastrointestinal absorption is higher during the day, thus calorie intake by day improves glucose tolerance and plasma insulin levels during fasting conditions. Moreover, feelings of hunger are reduced when calorie intake is principally in the day than at night [60]. Importantly, a group of subjects with prediabetes exposed to **temporal calorie restriction** during the day, showed improvements in insulin sensitivity, β-cell responsiveness, blood pressure, and appetite, indicating the beneficial effects, even in a pathological condition, of TRE early in the day [68].

Timing of caloric intake affects brain DA and 5-HT metabolism in both rodents and humans [12]. In obese subjects, caloric intake in the early morning increases the binding of the DA (DAT) and serotonin (SERT) transporters in the ventral striatum and thalamus respectively. This effect was diminished when the subjects' caloric intake was higher at night (dinner) [69].

A reduction in the dopamine D2 receptors availability in the striatum has been associated with body weight increase and obesity [70]. DA cell activity shows daily variations, hence, the effects of mealtime in the day on DA metabolism might be dependent on the rhythmic properties of the DAergic system. Moreover, hormonal changes (leptin and ghrelin) by timed calorie intake in the early morning could potentiate DA metabolism and contribute to reduced food intake and body weight.

Altogether, the important data on the effects of food entrainment in the human circadian system and metabolism indicate that a timed food intake aligned with the sleep–wake cycle and other hormonal rhythms improves and maintains healthy physiology. In mealtime synchronization, both central systems controlling eating (metabolic and hedonic) are importantly implicated.

Concluding Remarks and Future Perspectives

In this review, some of the most important, but unfortunately not all, discoveries of the effects of feeding behavior on circadian rhythms and clocks have been highlighted, as well as how food intake affects the main clock in the SCN when the caloric content and/or the hedonic value of the food changes. The neural and molecular mechanisms of food entrainment of circadian clocks are not yet fully described; nevertheless, important advances indicate that the central pathways underlying food intake (metabolic and hedonic) must be involved.

However, there are still several questions regarding the mechanisms of entrainment of peripheral oscillators and the SCN clock to food timing with or without palatable diets. For example, how do reward components of palatable diets (e.g., sucrose, fat) reach the brain and then the SCN? Are these effects clock-dependent? If so, what are the optimal times to affect the SCN clock by feeding? Are clock genes implicated in SCN food entrainment (see Outstanding Questions)?

The timing of eating has an important clinical application in human health. Thus, new proposals in research are necessary to understand the central and peripheral (circadian and non-circadian) mechanisms that underlie the effects of meal timing in physiology, and how the principal SCN clock, which was neglected as a 'food-entrainable oscillator', is entrained by the time of eating.

Outstanding Questions

How does the SCN circadian clock connect with the metabolic and hedonic brain centers for the control of feeding?

How are peripheral circadian clocks entrained to the LD cycle?

How are peripheral clocks synchronized to feeding–fasting cycles?

Can the brains extra-SCN circadian oscillators regulate rhythms of eating behavior?

At the central level, what are the mechanisms underlying eating disorders?

Is the principal SCN circadian clock a 'food-entrainable oscillator'?

What are the consequences of the circadian clock's misalignment on food intake and metabolism?

What is the relevance of knowing these mechanisms? If we determine how feeding time synchronizes the clock in the SCN, it would be feasible to think that 'feeding time therapy' can be used in chronobiology to treat circadian and non-circadian pathologies in which the oscillatory capacity of the clock is compromised.

When the SCN clock is genetically altered, this becomes highly sensitive and responsive to time feeding–metabolic–hedonic cues, even more than to LD cycles [71–73]. Thus, in circadian pathological conditions (e.g., shift work, social, jetlag, seasonal depression) in which light has been used as treatment, feeding time might replace it as a 'new medication' to rescue SCN circadian rhythms. Moreover, it will not be surprising or unreasonable to think that food entrainment can be used to treat obesity, diabetes, eating disorders [74], and also other mental illnesses, such as depression or neurodegenerative diseases (e.g., Parkinson's, Alzheimer's, Huntington's diseases) [72], in which a disturbed clock has to be readjusted.

Further, even more interesting is the proposition of combining light and feeding therapies, to set in time circadian clocks and improve health. For this, it is first necessary to understand the putative circadian and brain mechanisms shared by light and food to potentiate and facilitate the entrainment of the circadian system.

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