Epigenetic control and the circadian clock: Linking metabolism to neuronal responses

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Abstract
Experimental and epidemiological evidence reveal the profound influence that industrialized modern society has imposed on human social habits and physiology during the past 50 years. This drastic change in life-style is thought to be one of the main causes of modern diseases including obesity, type 2 diabetes, mental illness such as depression, sleep disorders, and certain types of cancer. These disorders have been associated to disruption of the circadian clock, an intrinsic time-keeper molecular system present in virtually all cells and tissues. The circadian clock is a key element in homeostatic regulation by controlling a large array of genes implicated in cellular metabolism. Importantly, intimate links between epigenetic regulation and the circadian clock exist and are likely to prominently contribute to the plasticity of the response to the environment. In this review, we summarize some experimental and epidemiological evidence showing how environmental factors such as stress, drugs of abuse and changes in circadian habits, interact through different brain areas to modulate the endogenous clock. Furthermore we point out the pivotal role of the deacetylase silent mating-type information regulation 2 homolog 1 (SIRT1) as a molecular effector of the environment in shaping the circadian epigenetic landscape.

Abbreviations
AMPK, AMP-activated protein kinase; α-MSH, alpha-melanocyte-stimulating hormone; ARC, arcuate nucleus; BAT, brown adipose tissue; BMAL1, Brain and Muscle ARNT-Like 1; COXIV, cytochrome c oxidase subunit IV; DBH, dopamine β-hydroxylase; DIO1, dihydroxyphenylalanine decarboxylase; DIO2, thyroxine deiodinase 2; DIO3, triiodothyronine deiodinase 3; DNL, de novo lipogenesis; ghrelin; IR, insulin resistance; IGF1, insulin-like growth factor 1; IRS-1, insulin receptor substrate 1; KAT2A, histone acetyltransferase 2A; KDM4C, lysine (K)-specific demethylase 4C; LKB1, liver kinase B1; LKB2, lung kinase B2; LRRK2, leucine-rich repeat kinase 2; MAOA, monoamine oxidase A; MEF2A, myocyte enhancer factor 2A; NCOA4, nuclear receptor coactivator 4; PARP1, poly(ADP-ribose) polymerase 1; PGC-1α, peroxisome proliferator-activated receptor γ coactivator 1α; PGC-1β, peroxisome proliferator-activated receptor γ coactivator 1β; PPARγ, peroxisome proliferator-activated receptor gamma; SIRT1, silent mating-type information regulation 2 homolog 1; SIRT3, silent mating-type information regulation 2 homolog 3; TET, ten-eleven translocation; TRIB1, tribbles homolog 1; TRIB2, tribbles homolog 2; TRIB3, tribbles homolog 3; UCP1, uncoupling protein 1; VAST, very abundant small transcript; WADE, Wnt-activated deacetylase enhancer; ZFAND3, zinc finger andaneino/DOX-dependent protein 3; ZNF743, zinc finger protein 743.
Like 1; BNST, bed nucleus of the stria terminalis; BST, basal forebrain in the nucleus of the stria terminalis; CCG, clock-controlled gene; CLOCK, Circadian Locomotor Output Cycles Kaput; Cry, Cryptochrome; DARPP-32, dopamine-regulated and cyclic-AMP-regulated phosphoprotein; DBP, D-box binding protein; DMH, dorsomedial hypothalamus; DRN, dorsal raphe nucleus; E2f1, E2F transcription factor 1; EZH2, enhancer of zeste homolog 2; FAA, food anticipatory activity; FEO, food-entrainable oscillators; FOXO1, forkhead box O1; HAT, histone acetyl-transferase; HDAC, histone deacetylase; JARID1a, jumonji, AT rich interactive domain 1A; JMJD5, jumonji domain containing 5; LSN, lateral septal nucleus; NA, nucleus accumbens; NAD*, nicotinamide adenine dinucleotide; NAMPT, nicotinamide phosphoribosyltransferase; PAS, PER ARNT Single minded protein; Per, Period; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PI3K, phosphatidylinositol 3-kinase; POA, preoptic area; POMC, proopiomelanocortin; PP1, protein phosphatase 1; PPARγ, peroxisome proliferator-activated receptor gamma; PT, parataenial nucleus; PVH, paraventricular hypothalamus; p53, transformation related protein 53; RE, nucleus reuniens; REV-ERBa/β, Reverse Erithroblastosis Virus α and β; RORα, Retinoic Acid-Related Orphan Receptor alpha; SCN, suprachiasmatic nucleus; SCREBP-1c, sterol regulatory element binding protein 1c; SF-1, steroidogenic factor-1; SIRT1, silent mating-type information regulation 2 homolog 1; STAT3, signal transducer and activator of transcription 3; TEF, Thyrotroph Embryonic Factor; VMH, ventromedial hypothalamus

Key words
epigenetic mechanism; clock; SIRT1; metabolism; social zeitgebers; nutrients

Modern life-style and disruption of the clock

The highly accelerated industrialization and urbanization during the past 50 years has imposed drastic changes in social life-style. This has been particularly significant in urban zones, where the sleeping period has been reduced by ~2 h in the last 50 years (Misra and Khurana, 2008 and Lucassen et al., 2012). These new environmental conditions have been associated to chronic stress, which in turn generate certain neuropsychiatric disorders, such as anxiety, depression, cognitive dysfunction and sleep disorders, all of which are linked to the disruption of circadian rhythms (Chrousos, 2009). The recent development of telecommunications and internet has further expanded these alterations in individual habits and promoted sleep disorders. These modern life-style rhythms are known as ‘social zeitgebers’, and include work and social demands on interpersonal relationships. The new social zeitgebers have forced the population to adapt to specific types of food consumption, as well as the feeding and sleep schedules, according to their current needs (Mistlberger and Skene, 2004 and Soria and Urretavizcaya, 2009). The consequent alteration of circadian rhythms correlates with the increase in predisposition to develop a variety of chronic diseases, mostly cardiovascular, metabolic and neuropsychiatric. These illnesses are particularly evident in night and shift workers. The environment-morbidity relationship is not well understood; however, studies in humans and animal experimental models are providing evidence toward the identification of molecular and cellular mechanisms involved in these pathologies. In this review we summarize the key molecular mechanisms of the circadian clock and the link with epigenetic control. Specifically, we expand on the critical role of silent mating-type information regulation 2 homolog 1 (SIRT1) in the modulation of the circadian clock and metabolic homeostasis, as well as its central role in cognitive functions. Finally, we highlight the influence that feeding may have on the central clock at the behavioral and molecular levels.

The central clock

All functions of the central nervous system have evolved in a circadian environment,
generating responses essential to adapt and anticipate environmental fluctuations. Circadian clocks are organized hierarchically, with the central clock localized in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks localized in other brain regions and peripheral tissues (Cermakian and Sassone-Corsi, 2002).

The SCN consists of a bilateral nucleus with about 20,000 neurons. It is located in the anterior hypothalamus above the optic chiasm and receives the light input from the retina through the retino-hypothalamic tract (RHT) (Moga and Moore, 1997). Light functions as a prominent zeitgeber, adjusting the endogenous rhythms to maintain the 24-h-period oscillation. The role of the SCN as master clock was first illustrated in rodents where bilateral destruction of the SCN abolished circadian rhythms (Stephan and Zucker, 1972), whereas transplanting fetal SCN restored the circadian rhythms at behavioral and hormonal levels (Drucker-Colin et al., 1984). This was further sustained from studies in hamsters, in which the altered behavior from tau mutant animals was recovered by transplantation of SCN from wild-type animals (Amir et al., 2004). In addition to the SCN, other brain regions show circadian rhythms including the substantia nigra (SN), the nucleus accumbens (NA) and the ventromedial hypothalamus (VMH) (Dibner et al., 2010). Surgical ablation of the SCN abolishes the rhythmicity of the extra-hypothalamic nuclei (Inouye and Kawamura, 1979). Thus, the SCN appears to orchestrate circadian rhythmicity in other brain nuclei, possibly through both synaptic connections and diffusible molecules. Finally, physiological communication between the SCN and peripheral clocks by autonomic innervations and endocrine signaling has been postulated (Buijs and Kalsbeek, 2001).

Interactions of the SCN with other brain areas

Although light is the dominant zeitgeber and the SCN is the light-entrainable oscillator (LEO), some evidence suggests that the central clock could also be influenced by non-photic inputs including behavior, nutritional intake, restricted exercise and social contact (Hastings et al., 1998 and Challet, 2010). Thus, the SCN may be considered as an element of a neuronal network in which signals are received from, and sent to other brain regions, including nuclei from the limbic cortex, the basal forebrain, the hypothalamus, the brainstem and the midline thalamus (Moga and Moore, 1997). The afferent projections of the SCN come from six areas: the retina, the limbic system, the hypothalamus, the raphe nuclei, the paraventricular thalamus and the extraretinal visual system. Furthermore, these connections arrive into two main subdivisions of the SCN: (i) the core, which contains neurons producing vasoactive intestinal peptide (VIP) and gastrin-releasing peptide (GRP). It receives dense visual afferents projections from the retino-geniculo and pretectohypothalamic tracts and non-photic inputs from the raphe and midline thalamus (Leak et al., 1999). (ii) The shell that surrounds the core and receives inputs from non-visual sources, including limbic areas (infralimbic cortex, ventral subiculum and lateral septal nucleus (LSN)), basal forebrain, hypothalamus, brainstem and thalamus and contains neurons producing arginine vasopressin (AVP) as neurotransmitter and calretinin (Leak and Moore, 2001). The core is densely projected to the shell with sparsely reciprocal innervation (Leak et al., 1999). In the case of the efferent projections from the SCN, the core and the shell also differs in the innervated targets, for instance the core connects with the hypothalamus within nuclei including the perisuprachiasmatic nucleus (PSCN), the lateral subparaventricular area (LSPVZ), the ventral tuberal area (VTU), the basal forebrain within the LSN, and the thalamus in nuclei such as the parataenial nucleus (PT) and the nucleus reuniens (RE). The shell mainly controls the hypothalamic nucleus including the preoptic area (POA), the dorsomedial hypothalamic nuclei (DMH), the paraventricular hypothalamic (PVH), medial subparaventricular area (MSPVZ) and the thalamic regions which include the paraventricular thalamic nucleus (PVT), the zona incerta (ZI), the PT, the RE and the basal forebrain in the nucleus of the stria terminalis (BST) (Moga and Moore, 1997, Leak et al., 1999 and Leak and Moore, 2001). Hence the core might compute dense light and serotonergic inputs, meanwhile the shell further modulates the central clock by weak...
inputs from a wide array of brain areas from the limbic system and the hypothalamus. Interestingly experimental evidence has supported this anatomical organization, for example, acute increase in SCN serotonin released from the dorsal raphe nucleus (DRN) is induced by sleep deprivation, which is mediated by the suppression of DRN GABAergic tone, inducing phase resetting of the central clock (Glass et al., 2003). Hence, it has been postulated that serotonin might modulate the excitability of the SCN to afferent inputs at three levels, (i) modulation of afferent visual or non-visual pathways regulating the phase of circadian response, (ii) modulation of the excitability of the SCN to afferent photic or non-photic inputs, (iii) modulation of the responsiveness of efferent targets to circadian signals (Lowry, 2002) (Fig. 1A).

**Fig. 1.** The SCN interacts with several brain areas. (A) Representative schema depicting the efferent and afferent signaling to the suprachiasmatic nucleus (SCN) from different brain regions. These include limbic structures such as infralimbic cortex (LC), lateral septal nucleus (LSN), basal forebrain of the stria terminalis (BST), ventral subiculum (VS), paraventricular thalamic nuclei (PVT), accumbens nucleus (NA), dorsal raphe nucleus (DRN), median raphe nucleus (MRN), and hypothalamic nuclei such as ventromedial hypothalamus (VMH), dorsomedial hypothalamus (DMH), paraventricular hypothalamus (PVH), and the retino-hypothalamic tract (RHT). (B) Schema representing the possible link between the hypothalamic clocks and the metabolic sensors influencing the clock in peripheral tissues (see also Table 1).

Regarding the connections between the SCN and other hypothalamic nuclei controlling food intake and body weight, the ventral part of the arcuate nucleus (ARC) sends peripheral information to the SCN such as feeding-related signals (Yi et al., 2006). Hence, ARC lesions induce arrhythmic food intake when animals are exposed to constant darkness (Li et al., 2012). Furthermore, lesions in the SCN in rats decrease the activation of the ARC and alpha-melanocyte-stimulating hormone (α-MSH) neuronal activity (Guzmán-Ruiz et al., 2013) and result in uninterrupted feeding (Kalra et al., 1999) and altered diurnal pattern of plasmatic leptin levels (Kalsbeek et al., 2001). This evidence suggests that the hypothalamic nuclei involved in feeding behavior acts in synchrony with the SCN to generate feeding rhythms entrained to photic cues. Furthermore, it has been observed in animals and humans that the preference for certain kinds of food change within the hour of the day. For example in rats the preference of carbohydrates and proteins increases at the onset of the activity period at night, and by the end of their activity phase, the preference for fats is increased (Cagampang and Bruce, 2012). This is also observed in humans, where carbohydrates are preferred during the breakfast, and high-fat diet is preferred during the evening (Westerterp-
Interestingly, the SCN shares connections with limbic brain areas involved in motivation and reward responses such as the bed nucleus of the stria terminalis (BNST) and the NA (Watts et al., 1987 and Amir et al., 2004). This stress out the role of other brain regions of the reward system that have been implicated in both, drugs and food addiction as discussed in the following sections. The hypothalamus also controls the energy balance by modulating the energy expenditure as heat production. For example, the VMH which receives neuronal afferents from the SCN and PVH has been implicated in the control of the thermogenesis by the brown adipose tissue (Amir, 1990). Interestingly, the stimulation of the SCN by glutamate, activates brown adipose tissue (BAT) thermogenesis and this effect is mediated by the VMH (Amir et al., 1989).

Finally, the DMH which also receives indirect and direct inputs from the SCN has been implicated in several circadian rhythms such as wakefulness, feeding, locomotor activity, and serum corticosteroid and glucose levels (Nagai et al., 1988, Chou et al., 2003 and Cailotto et al., 2005).

The core cellular clock

In virtually every cell of the body, the molecular clock “ticks” through a complex molecular mechanism consisting on a network of interlocked transcriptional-translational feedback loops. Central to the circadian machinery are the core clock proteins Circadian Locomotor Output Cycles Kaput (CLOCK) and Brain and Muscle ARNT-Like 1 (BMAL1). These transcription factors dimerize through their PER ARNT Single minded protein (PAS) domains and subsequently bind E-box promoter elements, thereby activating the transcription of clock-controlled genes (CCGs). The genes Period 1–3 (Per1, Per2 and Per3) and Cryptochrome 1–2 (Cry1 and Cry2) are core clock genes and their products heterodimerize to repress CLOCK–BMAL1, inhibiting their own expression and forming a negative autoregulatory feedback loop (Sahar and Sassone-Corsi, 2009). A number of CCGs encode for transcription factors, including D-box binding protein (DBP), Thyrotroph Embryonic Factor (TEF), Retinoic Acid-Related Orphan Receptor alpha (RORα) and Reverse Erithroblastosis Virus α and β (REV-ERBα/β). DBP and TEF bind D-boxes, while RORα and REV-ERBα/β bind the Reb-Erb/ROR promoter elements, ensuring additional circadian waves in the expression of downstream genes. It is estimated that the circadian machinery controls the cyclic expression of about 10–20% of genes in the cell (Aguilar-Arnal and Sassone-Corsi, 2013). Importantly, epigenetic control plays a central role in the harmonic organization of circadian transcription.

Epigenetics: How the environment shapes the circadian response

Epigenetic control involves a variety of mechanisms, including chromatin remodeling through post-translational modifications of the N-terminal tails of histones. These include methylation, acetylation, ubiquitination, and phosphorylation (Borrelli et al., 2008 and Aguilar-Arnal and Sassone-Corsi, 2013). The transcriptional control of a significant fraction of the genome by the clock invokes genome-wide mechanisms of chromatin remodeling. Early findings supported this concept by showing that chromatin remodeling in the SCN is triggered in response to light input (Crosio et al., 2000). Further observation revealed that activation of CCGs by CLOCK–BMAL1 is coupled to circadian changes in histone acetylation at their promoters (Etchegaray et al., 2003). Subsequent studies confirmed and expanded these observations showing that in addition to histone acetylation, histone methylation is also important for clock function (Etchegaray et al., 2003, Curtis et al., 2004, Naruse et al., 2004 and Etchegaray et al., 2006). The discovery that the core protein CLOCK has itself intrinsic histone acetyl-transferase (HAT) activity, targeting histone H3 K9 and K14 at CCG promoters, paved the way to unravel the function and structure of the circadian chromatin complex (Doi et al., 2006a). First, CLOCK acetylates its molecular partner BMAL1 at the single aminoacid K537, an event essential for circadian rhythmicity (Hirayama et al., 2007). Moreover, it has been demonstrated that the histone methyltransferase MLL1 directs the cyclic tri-methylation of the H3K4 on CCGs promoters, directing the recruitment of the dimer CLOCK:BMAL1
to genomic targets and promoting transcriptional activation (Katada and Sassone-Corsi, 2010). Other proteins are able to interact with the clock machinery and promote circadian epigenetic changes. The methyl transferase enhancer of zeste homolog 2 (EZH2) interacts with CLOCK and BMAL1, promoting H3K27 di- and tri-methylation and enhances the transcriptional repression mediated by CRY (Etchegaray et al., 2006). The histone demethylases jumonji, AT rich interactive domain 1A (JARID1a) and jumonji domain containing 5 (JMJD5) have also been implicated (DiTacchio et al., 2011), whereas other studies further indicated intercorrelations and dynamics within different epigenetic circadian events (Koike et al., 2012 and Vollmers et al., 2012). Thus, the core circadian clock appears to be coupled to a variety of epigenetic mechanisms, including the modulation of the nuclear organization (Aguilar-Arnal et al., 2013). These molecular mechanisms might be coupled to changes in the environment through signaling pathways. In this respect, the nicotinamide adenine dinucleotide (NAD⁺)-dependent SIRT1 histone deacetylase (HDAC) plays a pivotal role, linking the circadian clock to the intracellular energetic environment.

SIRT1: A deacetylase at the interface between metabolism and circadian control

The enzyme SIRT1, is a NAD⁺-dependent deacetylase, (Bellet et al., 2011). SIRT1 has a wide variety of targets, including histone and non-histones proteins. Because of this, SIRT1 influences several cellular and physiological processes, including DNA repair, cell cycle arrest, cell survival, gluconeogenesis, lipid metabolism, insulin sensitivity, and has been related with both, healthy aging and control of lifespan. Moreover, SIRT1 exerts control on metabolism by deacetylating key metabolism-regulatory factors such as forkhead box O1 (FOXO1), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), transformation related protein 53 (p53), E2F transcription factor 1 (E2F1), peroxisome proliferator-activated receptor gamma (PPARγ), signal transducer and activator of transcription 3 (STAT3) and sterol regulatory element binding protein 1c (SCREBP-1c) (Brooks and Gu, 2009 and Peek et al., 2012).

The HDAC activity of SIRT1 oscillates in a circadian manner, rhythmically deacetylating the histone H3K9/K14 at the promoters of CCGs, and the non-histone proteins BMAL1 and PER2 (Asher et al., 2008 and Nakahata et al., 2008). Additionally, genetic ablation of Sirt1 or pharmacological inhibition of SIRT1 provokes disturbances in circadian cycles, both in cultured cells and in vivo (Nakahata et al., 2009). It has been suggested that the activity of SIRT1 counterbalances the rhythmic HAT function of CLOCK, although other HATs are likely to be implicated (Masri and Sassone-Corsi, 2010). Importantly, the cyclic activity of SIRT1 is modulated by the circadian levels of its cofactor NAD⁺ (Nakahata et al., 2008). NAD⁺ can be synthesized de novo from tryptophan or by the salvage pathway (Revollo et al., 2004). NAD⁺ can be used for energy transferring with the subsequent production of ATP in the mitochondria, or it is used in regulatory functions as a cofactor for NAD⁺-consuming enzymes. Remarkably, the circadian clock acts on the synthesis of NAD⁺, controlling the circadian expression of the nicotinamide phosphoribosyltransferase (NAMPT) gene, a CCG that encodes a key enzyme in the salvage pathway (Nakahata et al., 2009 and Ramsey et al., 2009). Thus, the circadian feedback transcriptional loop is tightly linked to an enzymatic feedback loop (Fig. 2). This regulatory pathway appears to be functional in peripheral clocks as well as in the central clock. Indeed, SIRT1 modulates the central clock in a process that appears to become less efficient in aged animals, as observed in jet-lag experiments and gene expression studies. This modulation comprises a direct activation of BMAL1 by SIRT1 through PGC-1α and NAMPT (Chang and Guarente, 2013). Furthermore, it has been demonstrated that SIRT1 has tissue-specific functions on different metabolic tissues such as liver, skeletal and cardiac muscle, pancreas and adipose tissue (Rodgers et al., 2008). For example, SIRT1 is necessary for the adaptations to fasting, and in conditions of caloric restriction SIRT1 triggers lipid mobilization from adipose tissue, a switch from glucose to lipid oxidation in skeletal muscle and liver and an increase in hepatic glucose production (
These observations suggest the importance of SIRT1 in the control of both central and peripheral clocks, where it might modulate in a circadian manner a plethora of physiological outputs.

Fig. 2. The NAD⁺ salvage pathway is controlled by the circadian clock. The biosynthesis of NAD⁺ follows a circadian pattern, which is caused by the circadian expression of NAMPT, a rate-limiting enzyme in the NAD⁺ biosynthetic salvage pathway. The Nampt gene contains E-boxes in its promoter, leading to direct transcriptional control by the dimer CLOCK:BMAL1. The fluctuating levels of NAD⁺ modulate the activity of SIRT1 which in turn regulate the transcriptional activity of CLOCK:BMAL1 on their targets genes.

Control of energy balance by SIRT1

The central nervous system (CNS) directs both behavioral and metabolic responses in peripheral tissues to adapt quickly to the changing environment. Specifically, the hypothalamus computes the metabolic information from the body and responds accordingly to meet the body’s energy balance requirement, through the melanocortin system (Cone, 2005, Morton et al., 2006 and Dietrich and Horvath, 2013).

Since food consumption in mammals follows a circadian rhythm, it is expected that the neuroendocrine mechanisms controlling feeding behavior will also coherently display daily oscillations. There is growing evidence that the circadian clock directly participates in the hypothalamic control of food intake and energy homeostasis. In the ARC, the expression of the orexigenic Npy/Agrp and anorexigenic Pomc/Cart genes are rhythmic (Xu et al., 1999, Lu et al., 2002 and Stutz et al., 2007), an event which is correlated with daily rhythms in food intake. While it is unclear whether the molecular clock controls the expression of these neuropeptides, studies in mouse show that animals with a disrupted clock display hyperphagia, accompanied with altered rhythms in the expression of Cart and ghrelin genes. Both genes contain E-box elements in their promoters, and are thereby bona fide CLOCK–BMAL1 targets (Turek et al., 2005). Control of food intake by the hypothalamus involves the action of metabolic sensors such as the AMP activated protein kinase (AMPK) and SIRT1 (Minokoshi et al., 2004, Cota et al., 2006 and Çakir et al., 2009), which control the circadian clock in peripheral tissues (Nakahata et al., 2008, Lamia et al., 2009 and Giebultowicz and Kapahi, 2010). Recently, using two-photon laser microscopy on organotypic slices of SCN, it has been observed that the redox state in the SCN oscillates daily in wild-type mice but not in Bmal1−/− mice (Wang et al., 2012). In the hypothalamus the redox state has been implicated in the control of food intake (Benani et al., 2007). The redox state has been also correlated with the daily energetic status of the cell in the hypothalamus and peripheral tissues, such as the liver and adipose tissue. Particularly, the NAD⁺/NADH ratio changes with feeding in the hypothalamus and
SIRT1, has been also implicated in neurogenesis, synaptic formation, and exerts protective action against Alzheimer, amyotrophic lateral sclerosis and axonal degeneration (Ramadori et al., 2008 and Michan, 2013). SIRT1 has been also linked to the rewarding processes related to drugs of abuse. Accumulating evidence indicates that mechanisms of drug addiction involve epigenetic changes within brain reward regions (Feng and Nestler, 2013). During repeated cocaine administration, Sirt1 expression increases and is associated to an increment in electrical excitability of the NA, potentiating the rewarding effects of cocaine (Renthal et al., 2009). Moreover, SIRT1 modulates not only the homeostatic process but also non-homeostatic process. Hence, it was shown that SIRT1 regulates anxiety and exploratory behavior by activating Mao-A transcription, a gene that encodes the enzyme monoamine oxidase A (MAO-A), which in turn degrades serotonin and noradrenaline. This effect is obtained through direct deacetylation by SIRT1 of the transcription factor NHLH2 that controls Mao-A expression (Libert et al., 2011). Interestingly it has been observed that the expression of Mao-A follows a circadian rhythm which is controlled by the clock machinery (Hampp et al., 2008). However, whether SIRT1 participates in the circadian control of Mao-A expression remains unexplored.

Addiction and the circadian clock

Experimental and epidemiological studies have linked the circadian clock with addiction to drug, alcohol and food. Addict patients show disruption in sleep and circadian rhythmicity, whereas experiments of drug self-administration in rodents show circadian patterns of drug ingestion (Terman and Terman, 1970 and Kosobud et al., 2007). The use of mouse models of clock disruption has revealed an increase in cocaine reward and excitability of dopamine neurons in brain reward regions. These effects are associated to an increase of dopamine release and turnover and an increment in dopamine receptors sensibility (Spencer et al., 2012). Similarly, clockΔ19 mutant mice – which express a truncated, inactive form of the CLOCK protein – exhibit an increase in ethanol intake, an effect which is mediated by the ventral tegmental area (VTA) dopamine system. Moreover, chronic alcohol treatment leads to changes in Clock gene expression in the VTA and in the SCN, which could be linked to the pervasive disruption in rhythm and sleep in alcoholics (Chen et al., 2004 and Ozburn et al., 2013).

Disruption of circadian behavior is also intimately associated to social stress (Tornatzky and Miczek, 1993 and Holmes et al., 1995). For example activation of the stress system stimulates arousal and suppresses sleep (Chrousos, 2007). Importantly, it has been suggested that psychological distress can be reduced by eating highpalatable food (Maniam and Morris, 2012), a notion that is supported by some experimental evidence (Dallman et al., 2005). The reward system has been implicated in the development of eating disorders, including bulimia, anorexia, and binge and night-eating disorder (Tanofsky-Kraff and Yanovski, 2004, Adam and Epel, 2007 and Zheng et al., 2009). Hence, it is plausible that feeding disorders might have a circadian component, since the...
feeding regimen and the scheduled feeding are capable to control the endogenous clock. Furthermore, alteration of circadian rhythms caused by mutation of clock genes also leads to changes of normal feeding schedule (Turek et al., 2005, Kohsaka et al., 2007, Challet and Mendoza, 2010, Mendoza et al., 2010 and Volkow et al., 2011).

It has been postulated that, as in the addiction to drugs of abuse, the consumption of highly palatable food results in an increased reinforced value of food. Importantly, reinforcement learning elicited by either drugs of abuse as well as food, promotes the nuclear accumulation of the ‘dopamine-regulated and cyclic-AMP-regulated phosphoprotein’ (DARPP-32), mediated by a signaling cascade triggered by the dopamine D1 receptor. Consequently DARPP-32 inhibits protein phosphatase 1 (PP1), resulting in events of chromatin reorganization characterized by an increment of H3 phosphorylation (Stipanovich et al., 2008). Interestingly, DARPP-32 also participates in central clock entrainment by photic inputs (Yan et al., 2006). Importantly, signaling, molecular and behavioral connections between dopamine regulatory pathways and the circadian clock have been revealed (Doi et al., 2006b, Yujnovsky et al., 2006 and Zocchi and Sassone-Corsi, 2010). These and additional experimental evidence suggest that the reward system might entrain the endogenous clock. For example, some reports have shown that animals fed scheduled highly palatable food under ad libitum standard chow are capable to entrain the SCN clock in constant darkness (Challet and Mendoza, 2010).

Indeed, the SCN receives inputs from three areas in the limbic system, namely the infralimbic cortex, the LSN and the ventral subiculum (Moga and Moore, 1997). Furthermore, the SCN might receive dopaminergic signals indirectly through the paraventricular thalamic nuclei that projects directly to the SCN or via orexinergic neurons (Bubser et al., 2005).

**Food as a zeitgeber**

Since the circadian machinery serves to anticipate changes in the environment and consequently to adapt to daily variations in food availability, the clock is not only synchronized by the day/night cycle, but also by the feeding schedule. While the light-entrainable oscillator (LEO) is well characterized (the SCN), the exact localization within the brain of the food-entrainable oscillators (FEOs) remains a subject of debate. The behavioral manifestation of the FEO corresponds to changes or adaptation toward food consumption that have been extensively studied in rodents. When food is administered at specific times of the day, the animal displays an increase in locomotor activity few hours before the feeding time. This phenomenon, known as FAA, is accompanied by several physiological changes such as the rise of corticosterone and insulin secretion, body temperature, gastrointestinal motility and activity of digestive enzymes. FAA influences the oscillation of clock genes in peripheral tissues but not in the SCN (Stephan, 2002 and Froy, 2007). Thus, FAA appears to function as a zeitgeber since it is characterized by a limited time-frame of entrainment, the persistence of oscillation, and transient resetting after a change in meal time (Screaton et al., 2004 and Buhr et al., 2010). Remarkably, neither SCN-ablation nor constant darkness inhibits the FAA and its associated rhythms in peripheral tissues, suggesting the existence of the FEO outside of the SCN. Attempts to localize the FEO in the central nervous system have been carried out by targeting specific nuclei in the hypothalamus including the VMH, PVH, ARC, lateral hypothalamus (LH) and DMH.

The DMH is a possible candidate. Indeed, a compact part of the DMH shows oscillation in Per2 expression under scheduled feeding, which persists 2 days after entrainment by feeding restriction. Furthermore, DMH-lesioned mice fail to anticipate feeding time and premeal rise in body temperature (Gooley et al., 2006), and restoration of Bmal1 in the DMH is able to rescue the FAA (Fuller et al., 2008). Yet, contradictory data contrast the notion that the DMH is necessary for FAA generation (Landry et al., 2006 and Moriya et al., 2009). Another hypothalamic nucleus considered to be part of the circuits controlling the FAA is the VMH. This is the first nucleus activated during feeding restriction, and
lesions in the VMH abolish the ability to anticipate a food-restricted meal (Ribeiro et al., 2007). Moreover, since feeding is a highly reinforcing behavior, the NA has been postulated to be part of the FEO. Hence, a lesion in the core part of the NA reduces the FAA. In agreement with these results, highly palatable food is also able to induce FAA even under conditions of ad libitum food access (Challet and Mendoza, 2010). One attractive hypothesis is that the FEO is not localized in one nucleus. Rather, it is distributed in various hypothalamic nuclei and extra hypothalamic areas, such as the NA, the amygdala, the BNST, and the POA nucleus of the solitary tract (Mistlberger, 2011). This would allow a more pleiotropic control of the neuronal pathways involved in FAA.

At molecular level, the core clock has been implicated in the development of FAA. Under restricted feeding clock gene expression is shifted in non-SCN brain regions. Also, mutations in clock genes are able to affect the development of the FAA. For example, brain-specific Bmal1-null mice display a deficit in the development of FAA, accompanied by a reduced food consumption (Mieda and Sakurai, 2011). As mentioned above, the generation of FAA needs an entrainment in a limited window of time. Hence, mice lacking Cry1 (which shows a shorter circadian period than Cry2−/− mice) are entrained only to a shorter period of feeding cycles compared with the Cry2−/− animals. This implies that the intrinsic rhythmicity controlled by the core clock machinery could be a component for the entrainment of FAA (Takasu et al., 2012). However, contrasting results in mice lacking Cry1/Cry2, Bmal1, Per1/Per2, or in the ClockΔ19 mutant mice, show maintenance of the FAA rhythm. (Storch and Weitz, 2009) Thus, it has been suggested that FAA may be independent of the clock system and that it has rather emerged because of the rhythms of metabolic gene expression (Mistlberger, 2011). Interestingly, food entrainment, when accompanied with caloric restriction, causes a shift in the circadian gene expression in the SCN (Mendoza et al., 2005). All together, these observations suggest that the nutritional input acts as a powerful zeitgeber which modulates the core clock system within cells residing in the SCN as well as the peripheral clocks. Moreover, under certain conditions, the food input and the reward inputs might converge to override the dominating effect of light on the central clock.

Finally, most of the molecular mechanism governing the hypothalamic clocks by non-photic cues remains to be analyzed. The hypothalamic responses to the nutritional and metabolic conditions of the body through hormones such as leptin, ghrelin, insulin, or metabolites including glucose, aminoacids, lipids, NAD+ and AMP are triggered by metabolic sensors and signaling pathways including the AMPK, SIRT1, PI3K, PPARγ, etc., (Table 1) which modulate the neuronal responses to body needs. Importantly, these factors are also known to control the circadian clock in peripheral tissues such as liver, muscle, white and brown adipose tissue. The coordinated circadian regulation between the metabolic pathways and transcriptional networks achieved by the nutritional sensors in peripheral tissues (Desvergne et al., 2006, Asher and Schibler, 2011, Eckel-Mahan et al., 2012 and Eckel-Mahan et al., 2013), also might be modulating the circadian clock in the different hypothalamic nuclei that compute the metabolic information. Therefore, the understanding of how the circadian clock within these hypothalamic nuclei is modulated by non-photic inputs, to respond to the metabolic necessities is of pivotal importance for the development of treatments against metabolic diseases such as type 2 diabetes, obesity and feeding disorders (Fig. 1B).

<table>
<thead>
<tr>
<th>Protein</th>
<th>Hypothalamic function</th>
<th>Clock function</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>ROCK (Rho-associated protein kinase)</td>
<td>Mediates leptin action in the ARC</td>
<td>Modulates the circadian rhythmicity of the sensitivity of myofilaments to Ca2+</td>
<td>Huang et al., 2012, Su et al., 2012 and Saito et al., 2013</td>
</tr>
<tr>
<td>AMPK (AMP-activated protein kinase)</td>
<td>Its activity is modulated by metabolic signals in the hypothalamus and it</td>
<td>AMPK phosphorylates and destabilizes CRY1, thereby regulating the molecular</td>
<td>Minokoshi et al., 2004 and Lamia et al., 2009</td>
</tr>
</tbody>
</table>
is essential for the control of food intake. Activated by L-leucine, mTOR inhibits food intake.

In the SCN mTOR shows rhythmic activity, and participates in the entrainment of the central clock.

Cota et al., 2006 and Cao et al., 2013

SIRT1 (silent mating-type information regulation 2 homolog 1) Protects against diet that induces obesity acting in signaling pathways in POMC and SF1 hypothalamic neurons.

Regulates the circadian clock thought BMAL1 and PER2 deacetylation.

Asher et al., 2008, Nakahata et al., 2008, Ramadori et al., 2010 and Ramadori et al., 2011

PPARγ (peroxisome proliferator-activated receptor gamma) Leads to positive energy balance through hyperphagia.

Its expression is circadian in peripheral tissues. Participates in the reprogramming of the circadian clock by nutritional stress.

Yang et al., 2006, Ryan et al., 2011 and Eckel-Mahan et al., 2013

PI3K (phosphatidylinositol 3-kinase) Needed for the anorexigenic effect of leptin and insulin in the VMH.

Participates in the circadian regulation of L-type voltage-gated calcium channel in the retina.

Ko et al., 2009, Xu et al., 2010 and Klockener et al., 2011

Conclusive remarks

Environment has changed during the past 50 years at a pace that has had a tremendous impact on the physiology and metabolism of all life forms. When considering the varied cycles of activity and resting, the feeding schedule, the transformed diet, the social stressors, alcohol or drug abuse, it is essential to consider how all these may have a zeitgeber effect. This is a very exciting time as we are starting to gain insight within the molecular and epigenetic mechanisms that control these processes. Hence, new insights will allow the design of more effective strategies and pharmacological approaches targeting key proteins and pathways to resynchronize the endogenous clock, and treat the wide spectrum of pathologies such as obesity, type 2 diabetes, cardiovascular disease, mental illness such as depression, drug, alcohol or food addiction and feeding and sleep disorders (Fig. 3).
These stressors in turn might alter the endogenous clock generating a plethora of circadian-related diseases.

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