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Central Circadian Clock Regulates Energy Metabolism

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Abstract

Our body not only responds to environmental changes but also anticipates them. The light and dark cycle with the period of about 24 hours is a recurring environmental change that determines the diurnal variation in food availability and safety from predators in nature. As a result, the circadian clock is evolved in most animals to align locomotor behaviors and energy metabolism with the light cue. The central circadian clock in mammals is located at the suprachiasmatic nucleus (SCN) of the hypothalamus in the brain. We here review the molecular and anatomic architecture of the central circadian clock in mammals; describe the experimental and observational evidence that suggests a critical role of the central circadian clock in shaping systemic energy metabolism; and discuss the involvement of endocrine factors, neuropeptides, and the autonomic nervous system in the metabolic functions of the central circadian clock.

Keywords

Circadian clock; energy metabolism; SCN; hormone; autonomic nervous system

1. Introduction

Metabolic disorders, including obesity and type 2 diabetes, have reached pandemic levels in modern human societies. The underlying etiology was assumed to be an imbalance between total calorie intake and total energy expenditure. However, recent studies have suggested that the temporal pattern of calorie intake plays a critical in the pathogenesis of metabolic disorders. Restricting feeding exclusively to the active/dark phase almost eliminated high fat diet-induced metabolic disruption without changing total calorie intake in mice (Hatori et al., 2012; Tsai et al., 2013). Conversely, restricting feeding exclusively to the normal sleep phase disturbed metabolism in animals (Bray et al., 2010, 2013). In human, shiftwork has

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been associated with increased susceptibility to many metabolic disorders (Karlsson et al., 2001; Kubo et al., 2011; Suwazono et al., 2008). It has also been recognized that patients with cardiovascular diseases have a higher risk of heart attacks in the early morning compared to other times of the day (Takeda and Maemura, 2016) and that many diabetes patients display the dawn phenomenon, abnormal elevation of blood glucose in the early morning (Monnier et al., 2013). These findings not only demonstrate that time of the day is a critical factor in metabolism, but also pose a challenge to the homeostasis concept in physiology. Instead of homeostatic, many biological processes are actually homeodynamic.

The biological system is intrinsically rhythmic rather than trying to stay in a steady state. Robust rhythmic patterns, on a time scale ranging from milliseconds to months, are observed in many biological processes such as neuronal firing, heartbeat, breathing, sleeping, feeding, reproduction, molting, and migration, across a variety of animals in nature. Circadian rhythms, with a period of about 24 hours, is fundamental biological rhythms that are essential for normal energy metabolism. Most living animals sleep in a circadian pattern, with the body rotating between anabolism during the active/feeding phase and catabolism during the sleep/fasting phase.

The circadian rhythm is manifested at multiple levels. (1) At the whole-organism behavioral level, both consummatory behaviors and locomotor activities exhibit robust rhythm, which leads to diurnal patterns of calorie intake and energy expenditure. This behavioral rhythm is controlled by the central nervous system and is directly entrained by light that is perceived by the eye. (2) At the tissue and organ level, metabolic organs such as liver, muscle, and adipose receive or release different metabolites depending on the time of the day. The direction and the rate of metabolic fluxes within the metabolic organs are driven by two sets of mechanisms: anticipatory mechanism governed by the endogenous circadian clock within the metabolic tissue and responsive mechanisms that react to external neuronal, behavioral, or endocrine factors. (3) At the cellular and molecular level, many intracellular signaling pathways are involved. The anticipatory mechanism is controlled by the molecular clock machinery that, through various transcription factors and coregulators, orchestrates rhythmic gene expression of many metabolic enzymes. The responsive mechanisms, on the other hand, are initiated by binding of an external signaling molecule to its cellular receptor. For example, the insulin receptor at the cell membrane initiates cytosolic kinase cascades in response to elevated blood insulin levels during feeding, while the glucocorticoid receptor in the cell nucleus alters gene expression in response to oscillating glucocorticoid levels that are dictated by the central nervous system (Oster et al., 2017). We will review recent findings on these mechanisms, with an emphasis on how the central circadian clock controls systemic energy metabolism.

2. Intrinsic rhythm of energy metabolism

Glucose is a major fuel source for many cells and the body has developed intricate regulatory mechanisms to maintain normal blood glucose levels. Within the normal range, blood glucose levels exhibit a clear daily rhythm in healthy human subjects as well as in animals (Kalsbeek et al., 2014; La Fleur, 2003). The basal fasting glucose levels peak at the onset of locomotor activities during the transition from the sleep phase to the active phase

(Cailotto et al., 2005; Challet et al., 2004; La Fleur et al., 1999). Interestingly, glucose tolerance also shows rhythm, with the highest glucose tolerance in the morning and the lowest tolerance at evening or night in human (Leung et al., 2017). In one study addressing rhythmicity in glucose tolerance, blood insulin and glucose levels were measured continuously for 24h in normal healthy human subjects under a constant glucose infusion. Blood glucose levels display around 15% elevation at around the middle of the sleep as compared to daytime levels in all subjects. The results are not confounded by the infusion rate or on the time elapsed since the beginning of the infusion because the timing of initiation of the infusion was varied to differentiate effects of the circadian time from effects of the infusion duration (Van Cauter et al., 1989).

Insulin is the major hormone controlling blood glucose levels. Both secretion of insulin from the pancreas and the systemic insulin sensitivity display circadian rhythm (Kitazawa, 2013). In one study addressing rhythmicity of insulin throughout the circadian cycle, rats were subjected to a feeding regimen of six identical meals equally distributed over a 24h period in order to remove the entraining capacity of food (Kalsbeek A., 1998). Under these conditions, basal blood glucose levels peak at the onset of the active phase while basal insulin levels peak at the late sleep phase. Food-induced increase in blood glucose levels is almost identical across different times. Food-induced increase in insulin levels is the most dramatic during the early active phase and clearly diminished during the second half of the sleep phase (Kalsbeek A., 1998). These results show that the circadian regulation of basal blood glucose and feeding-induced insulin responses is independent of the feeding schedule.

Insulin lowers blood glucose levels by suppressing endogenous glucose production (EGP) from the liver and promoting glucose rate of disposition (Rd) through uptake by the muscle and adipose tissues. The glucose tolerance reaches the highest point of the day at the activity onset. This diurnal variation in glucose tolerance is unlikely to be caused by variations in insulin secretion because glucose-induced insulin secretion is almost identical across different time points in rats (la Fleur et al., 2001a). This suggests that the circadian rhythm of insulin sensitivity underlies the diurnal variation in glucose tolerance. Hyperinsulinemic euglycemic clamp analysis, the gold standard assay for systemic insulin sensitivity, has been performed at different times of the day. Zeitgeber time (ZT) is used to indicate the time of the day during the normal 12h light/12h dark cycles with ZT0 indicating the onset of light and ZT12 indicating the onset of darkness. Clamp analysis of mice showed that the glucose infusion rate (GIR) at ZT18 is higher than ZT6 in mice. This is mainly contributed by lower EGP under the hyperinsulinemic condition at ZT18 than ZT6 because blood glucose Rd does not show changes between ZT6 and ZT18 (Coomans et al., 2013a). Consistent with this study, a separate study found that fasting glucose at ZT7 is higher than that at ZT1, ZT13, or ZT19 in mice, while GIR at ZT7 is lower than GIR at ZT1, ZT13, or ZT19 (Shi et al., 2013). Glucose Rd change is minimal, with a slightly higher Rd at ZT14 than ZT2 in rats. However, in another study, mice displayed higher glucose tolerance at ZT11 than ZT1 (Arble et al., 2015).

3. The molecular circadian clock

At the molecular level, what gives rise to the circadian rhythm is a cell-autonomous transcription-translation feedback loop that exists in most cells of the body (Takahashi, 2017). The core molecular clock is composed of multiple transcription factors with short half-lives. In mammals, CLOCK and BMAL1 (brain and muscle ARNT-like 1) forms a heterodimeric complex and transcriptionally activates the expression of Cryptochromes (CRYs), Periods (PERs), and REV-ERBs (nuclear receptor subfamily 1, group D, member 1 and 2) (Figure 1) (Albrecht et al., 1997; Balsalobre et al., 1998; Bunger et al., 2000; Gekakis et al., 1998; Kume et al., 1999; Shearman et al., 1997, 2000; Shigeyoshi et al., 1997; Sun et al., 1997; Tei et al., 1997; Vitaterna et al., 1994). Once the PERs and CRYs proteins have reached a critical concentration, they directly bind to the CLOCK/BMAL1 complex and block their transactivation activities. REV-ERBs, on the other hand, bind to the BMAL1 promoter and transcriptionally suppress BMAL1 gene expression (Preitner et al., 2002). Once the CLOCK/BMAL1 activity is suppressed, CRYs, PERs, and REV-ERBs themselves start to decay because their own gene expression is shut down. Once the decay induces the protein levels to drop below a certain threshold, their inhibition on CLOCK/BMAL1 is disarmed, allowing CLOCK/BMAL1 to be reactivated. Such negative feedback regulation forms a self-sustainable cycle that repeats itself every 24h. These genes described above are referred to as core clock genes because they are required for the molecular clock to generate circadian rhythm. Depletion of these genes and their paralogs renders the clock non-functional and causes loss of intrinsic behavioral circadian rhythm in the absence of external light cues (Takahashi, 2017).

Most of the central circadian clock genes in mammals exist as paralogs including PER1/2/3, CRY1/2, and REV-ERBα/β. The transcription factor NPAS2 (neuronal PAS domain protein 2) is able to functionally substitute for CLOCK in the central clock in mice to regulate circadian rhythmicity, suggesting that CLOCK and NPAS2 can independently heterodimerize with BMAL1 to maintain molecular and behavioral rhythmicity (DeBruyne et al., 2007). Generally, all paralog genes need to be knocked out to confer arrhythmicity under constant darkness. The only exception is BMAL1, whose single knockout confers arrhythmicity, despite the presence of its paralog BMAL2 (Bunger et al., 2000). BMAL1 knockout mice also display hypoinsulinemia and glucose intolerance as well as abnormal locomotor activities and feeding behaviors (Marcheva et al., 2010). Interestingly, constitutive expression of BMAL2 rescued the behavioral and metabolic phenotypes of BMAL1 knockout mice (Shi et al., 2010). It was postulated that BMAL2 is regulated by BMAL1 and that BMAL1 knockout actually results in dysfunction of both BMAL1 and BMAL2 (Shi et al., 2010). REV-ERBα/β belong to the nuclear receptor superfamily of ligand-regulated transcription factors (Dumas et al., 1994; Lazar et al., 1989; Miyajima et al., 1989). REV-ERBα/β compete with RORα/β/γ (retinoic acid-related orphan receptors) for DNA binding (Preitner et al., 2002; Sato et al., 2004), which further regulates other rhythmic transcription factors including NFIL3 (nuclear factor, interleukin-3 regulated; also known as E4BP4), DBP (D-box binding protein), TEF (thyrotroph embryonic factor), and HLF (hepatic leukaemia factor) (Gachon et al., 2004; Mitsui et al., 2001).

The phase, period, and amplitude for the oscillation of the core clock genes are subject to modulation by multiple environmental factors. This allows the molecular clock to be aligned with the environment, a process referred to as entrainment. Many signaling molecules can respond to environmental cues and regulate the activity or stability of the proteins encoded by the core clock genes. Currently known regulators include casein kinase 1 (CK1) (Lee et al., 2001), phosphoprotein phosphatase (Lee et al., 2011), FBXL3 (an F-box-type E3 ligase) (Busino et al., 2007; Godinho et al., 2007; Siepka et al., 2007), FBXW7 (another F-box protein E3 ligase) (Zhao et al., 2016), O-GlcNAc transferase (OGT) (Kaasik et al., 2013), sirtuins (Asher et al., 2008; Nakahata et al., 2008), and AMP-activated protein kinases (AMPK) (Um et al., 2007; Lamia et al., 2009).

In addition to the upstream cytosolic signaling pathways, a number of chromatin remodelers and epigenome modifiers work closely with the core clock machinery and serve as output mechanisms for the clock to regulate gene expression (Mendoza-Viveros et al., 2017). The CLOCK/BMAL1 complex directly associates with various histone acetyltransferases, including p300, CREB-binding protein (CBP) and p300/CBP-associated factor (PCAF), to promote histone acetylation and transcription activation (Curtis et al., 2004; Etchegaray et al., 2003). CLOCK also has histone acetyltransferase activity by itself (Doi et al., 2006). CLOCK/BMAL1 also recruits histone methyltransferases and demethylases, such as mixed lineage leukemia 1 (MLL1) and Jumonji/ARID domain-containing protein 1A (JARID1a), which contributes to rhythmic histone methylation (DiTacchio et al., 2011; Katada and Sassone-Corsi, 2010). CRY proteins can recruit enhancer of zeste homolog 2 (EZH2), a histone methyltransferase of the polycomb repressive complex 2 (PRC2), that contributes to transcriptional repression (Etchegaray et al., 2006). PER proteins can recruit histone deacetylase 1 (HDAC1) and methyltransferase such as SUV39h (Duong and Weitz, 2014). REV-ERBs can recruit nuclear receptor corepressors (NCORs) and HDAC3 that regulates expression of many metabolic enzymes in the liver and muscles (Feng et al., 2011; Hong et al., 2017; Sun et al., 2013; Yin and Lazar, 2005).

4. Neural anatomy of the central circadian clock

Although the molecular clock machinery operates in almost all cells throughout the body, the master circadian clock that dictates the behavioral rhythm is within the brain. The suprachiasmatic nucleus (SCN) of the hypothalamus is the site of the central circadian clock in mammals. Bilateral SCN lesions cause locomotor arrhythmicity under even the normal light/dark cycle (Ibuka et al., 1977). Grafting of the SCN into arrhythmic animals restores normal circadian rhythmicity that exhibited the period of the donor genotype (Lehman et al., 1987; Ralph et al., 1990), demonstrating that the SCN is the *bona fide* location of the central clock. Interestingly, grafting SCN even within a semipermeable polymeric capsule is able to restore locomotor rhythm, suggesting that diffusive factors contribute to SCN-originated signals during the control of locomotor rhythm (Silver et al., 1996). The SCN is a paired structure with a ventral core region receiving photic input and a dorsal shell region receiving non-photic input. Most SCN neurons are positive with γ-aminobutyric acid (GABA). The core region is enriched with neurons expressing vasoactive intestinal polypeptide (VIP) and the shell region is enriched with neurons expressing arginine vasopressin (AVP) (Welsh et al., 2010). The core region projects to the shell region as well as the lateral

subparaventricular zone (SPZ) while the shell region projects to the dorsomedial hypothalamus (DMH) and medial SPZ (Leak et al., 1999) (Figure 2).

The SCN receives many afferent neural connections (Morin, 2013). The best-characterized one originates from the retina and targets the SCN with a distinct projection of the optic nerve known as the retinohypothalamic tract (RHT). This projection allows photic information, received by rod or cone photoreceptors or intrinsically photoreceptive retinal ganglion cells (ipRGCs), gains access to the central clock (Lucas et al., 2012; Pickard, 1982). This photic information influences phase and period of the central circadian clock, a process referred to as photoentrainment. SCN in both diurnal and nocturnal is the same for the astronomical times (Challet, 2007; Dardente et al., 2004). It is therefore believed that the downstream polysynaptic relay mediates the activity difference between diurnal and nocturnal animals (Smale et al., 2003). Actually, some animal species can switch between diurnal and nocturnal behaviors (Hut et al., 2012).

Another robust afferent projections to the SCN is the geniculohypothalamic tract (GHT) from the thalamic intergeniculate leaflet (IGL) and ventral lateral geniculate nucleus (vLGN), regions that receive projections from retinal ipRGCs (Mikkelsen, 1992; Moore et al., 2000). It has been postulated that the GHT mediates non-photic arousal-inducing phase shifts of circadian rhythms (Harrington, 1997). Recently, it was shown that optogenetic activation of GHT neurons suppresses SCN responses to retinal input in a time-dependent manner, suggesting that the GHT allows the thalamic activity to gate retinal input to the SCN according to the time of day (Hanna et al., 2017). A third well known afferent projection to the SCN is serotonergic neurons originating from the median raphe (MnR). Disruption of this input causes an earlier onset and later offset of the active phase as well as increased SCN sensitivity to photoentrainment, which demonstrates a critical role of the MnR in modulating the light sensitivity of the SCN central clock (Mistlberger et al., 2000; Morin, 1999). Pharmacological blockade of the serotonin signaling within the SCN renders mice unable to be synchronized by wheel running without changing the overall locomotor activity, suggesting that the serotonin afferents are required for physical activity-mediated entrainment of the SCN central clock (Edgar et al., 1997).

The SCN receives projections from the dorsomedial hypothalamus (DMH), an input that plays a role in food anticipatory activities (FAA). When nocturnal animals anticipate the scheduled food in the light cycle when they would otherwise normally sleep, the DMH neuronal activities increased and inhibited the SCN neuronal activity through the GABAergic inhibitory input into the SCN. DMH lesions diminished FAA while double lesions of the DMH and SCN restored FAA. These findings suggest that DMH-mediated inhibition of the SCN activity overrides clock-controlled sleep and permits locomotor activity in the sleep phase (Acosta-Galvan et al., 2011). In addition to the projections described above, the SCN has been found to be directly innervated by over 35 anatomical routes (Morin, 2013), which allows the central clock to integrate multiple signals received from different brain regions.

The SCN neurons send efferent projections to multiple regions of the brain. The two subdivisions of the SCN project to different hypothalamic areas, with the core projecting to

the lateral SPZ and the shell to the DMH and the medial SPZ (Leak and Moore, 2001; Leak et al., 1999). The SPZ of the hypothalamus is the main efferent target of neural projections from the SCN and an important relay for the circadian timing system. The ventral SPZ (vSPZ) is critical for rhythms of sleep and locomotor activity. Interestingly, anterograde tracing with biotinylated dextran amine (BDA) showed that the anatomic architecture from the SCN to the vSPZ are highly conserved between diurnal Nile grass rats and nocturnal lab rats despite distinct oscillation phases of the vSPZ neuronal activities, suggesting that the neural basis for a diurnal or nocturnal phase preference is independent of the anatomic structures (Schwartz et al., 2011). Unlike the vSPZ, the dorsal SPZ (dSPZ) relays signals from the SCN in controlling body temperature rhythms (Lu et al., 2001).

The SCN projects to the paraventricular nucleus (PVN) of the hypothalamus, which dictates the circadian rhythm of circulating glucocorticoids. Anterograde tracing revealed a direct connection between the SCN and the PVN neurons producing corticotropin-releasing hormones (CRH) (Vrang et al., 1995). AVP released from the SCN during the light cycle represses CRH releases in the PVN in nocturnal animals. In diurnal animals, AVP stimulates CRH releases, suggesting a neurochemical difference in the PVN interneurons between different chronotypes (Oster et al., 2017). In addition to the direct projection to the PVN, diffusive endocrine effects of the AVP, indirect multi-synaptic projections from the SCN to the PVN, as well as neuronal routes connecting the SCN with the adrenal cortex could all play important roles in the glucocorticoid rhythm (Buijs et al., 1998).

The SCN also projects to the arcuate nucleus (ARC), a hypothalamic region that controls feeding and energy expenditure. A robust circadian rhythm was observed in the firing activity of the ARC neurons expressing α-melanocyte-stimulating hormone (α-MSH), with the peak activity in the late dark cycle in rats. Bilateral SCN lesions blocked this rhythm and a direct projection from the SCN to the ARC was identified by neuronal tracing (Guzmán-Ruiz et al., 2014). This finding suggested a potential time-dependent regulation of the appetite by the central circadian clock. The ARC also projects to the SCN. Surgical micro-cuts that eliminate these reciprocal connections lead to arrhythmicity in locomotor activities, corticosterone levels, and body temperature in the constant darkness condition in rats. Interestingly, the SCN clock gene rhythmicity was not altered by these micro-cuts while the ARC gene rhythmicity was disrupted (Buijs et al., 2017). These findings suggest that the autonomous clock in the SCN controls the molecular clock in the ARC and potentially other brain regions through a complex neuronal projection network.

Although neurons have been considered as the major pacemaker for the central clock, astrocytes also contribute to circadian rhythms. All the core clock genes are expressed in astrocytes. Depletion of either BMAL1 or CK1ε specifically in the SCN astrocytes increased the period of both the SCN molecular clock rhythm and the locomotor behavioral rhythm (Tso et al., 2017). Pharmacological modulation of a GABA receptor rescued the behavioral phenotype, suggesting the involvement of the GABA signaling (Barca-Mayo et al., 2017). In contrast to the SCN neurons, SCN astrocytes are more active at night as measured by intracellular calcium imaging. The SCN astrocytes suppress SCN neuronal activity by regulating extracellular glutamate levels that are sensed by a pre-synaptic glutamate receptor complex in the SCN neurons (Brancaccio et al., 2017).

5. Evidence supporting a role of central clock in energy metabolism

Lesion

The SCN lesion caused arrhythmicity in sleep and wake behaviors, consummatory behaviors, and energy expenditure (Meyer-Bernstein et al., 1999; Coomans et al., 2013b; Malloy et al., 2012). The SCN lesion also abolished daily change in plasma free fatty acids, disrupted the circadian rhythm in glucose tolerance, and blocked hyperglycemic effects of GABA-A antagonist at the PVN (Kalsbeek et al., 2008a). Bilateral SCN lesion dramatically reduced GIR and increased EGP without changing glucose Rd (Coomans et al., 2013b). Transplant of the fetal SCN into the 3rd ventricle of the SCN-lesioned animals, reinstated locomotor rhythm, although did not restore the rhythm of glucocorticoids or melatonin (Lehman et al., 1987; LeSauter et al., 1997; Silver et al., 1996). Parabiosis between the SCN-lesioned and SCN-intact mice showed that circulating factors or behavioral cues are sufficient to maintain the clock gene expression rhythms in liver and kidney, but not in heart, spleen, or skeletal muscle, indicating that the central clock communicates with different peripheral tissues through distinct mechanisms (Guo et al., 2005). Bilateral SCN lesion eliminated circadian rhythms of blood glucose and insulin, and abolished time-dependent responses to 2-deoxy-D-glucose, an inhibitor of glucose utilization (Nagai et al., 1994). The SCN-lesioned rats did not show the glucose rhythm even on a scheduled feeding regimen (La Fleur et al., 1999). The rhythm of glucose tolerance was also lost in SCN-lesioned rats (la Fleur et al., 2001a).

Light and feeding

Nighttime light, shift work, and social jetlag have become prevalent since industrialization, which could disrupt our central circadian clock and contribute to the pandemic of metabolic disorders (Fonken and Nelson, 2014; Roenneberg and Merrow, 2016). Shift workers who work from 10 pm to 6 am make up about 20% of working force in modern society (Antunes et al., 2010) and have a higher prevalence of obesity and heart disease (Karlsson et al., 2001; Kubo et al., 2011; Suwazono et al., 2008). Dim light at night or prolonged daily light exposure promotes obesity and metabolic disorders in animal models (Aubrecht et al., 2015; Kooijman et al., 2015; Opperhuizen et al., 2015). Housing mice under constant light caused arrhythmicity in locomotor activity, increased food intake, reduced energy expenditure, increased body fat mass, and impaired insulin sensitivity (Coomans et al., 2013a; Shi et al., 2013). Although blood glucose displays robust diurnal changes in constant darkness in rats, light exposure at any circadian time could increase blood glucose, suggesting that light can directly regulate blood glucose independently of the circadian clock (Challet et al., 2004).

In addition to light, feeding is an important factor that entrains the peripheral circadian clocks in metabolic tissues. On one hand, feeding is not required for rhythmic glucose or insulin responses in the normal physiological condition because a regimen of 6 identical meals per day did not disrupt rhythmic glucose or insulin responses (Kalsbeek A., 1998). On the other hand, food can cause profound remodeling of the molecular clock in metabolic tissues (Eckel-Mahan et al., 2013; Tognini et al., 2017). Scheduled feeding in particular can reverse the changes in the amplitude or phase of the peripheral clocks that were altered by the constant light housing in mice (Hamaguchi et al., 2015). Restricting feeding only within

the active phase almost eliminated high fat diet-induced metabolic disruption without changing total calorie intake in mice (Hatori et al., 2012; Tsai et al., 2013). Conversely, restricting feeding in the normal sleep phase disturbed metabolism in animals (Bray et al., 2010, 2013; Yasumoto et al., 2016). These studies suggest that the feeding schedule and the light schedule need to be aligned with each other to maintain metabolic health. Night-eating syndrome (NES) is characterized by a delayed circadian pattern of food intake and is defined by consumption of 25% or more of the total daily calories after the evening meal (Allison et al., 2010). With disrupted rhythmic patterns of sleep and eating, NES is strongly associated with metabolic disorders, with a particularly high prevalence among individuals seeking gastric bypass surgery (Gallant et al., 2012; O'Reardon et al., 2004).

Sleep disturbance

Circadian clock disruption is intertwined with sleep disturbance (Tsuneki et al., 2016). Human epidemiology studies have found that lack of sufficient sleep or poor sleep quality is associated with diabetes, metabolic disorders, increased appetite, obesity, and disrupted hormone levels (Koren et al., 2016). In addition to the observational studies, experiments have also been performed in human subjects. Restricting sleep to 5h per day for 5 days caused ~20% reduction in oral and intravenous insulin sensitivity in normal healthy human subjects (Eckel et al., 2015). In another human study, restricting sleep to 4h per day for 5 days reduced systemic insulin sensitivity by 25%, which was mostly due to non-hepatic insulin resistance and was associated with increased fasting nonesterified fatty acids (NEFA) levels in the blood (Rao et al., 2015). Actually, loss of one-night sleep was sufficient to cause glucose intolerance in human (Cedernaes et al., 2016). Elevated sympathetic tone, glucocorticoids levels, and growth hormone levels could all contribute to the sleep restriction-induced metabolic disruption.

Neurectomy and pharmaceuticals

The SCN innervates both the sympathetic and parasympathetic nervous systems (SNS and PSNS) (Bartness et al., 2001; Buijs and Kalsbeek, 2001). Virus-mediated neuronal tracing revealed that the SCN innervated the liver via both the SNS and PSNS. Administration of GABA-A or VAP antagonists at the PVN elevated blood glucose levels in rats, which was blocked by hepatic sympathectomy, but not hepatic parasympathectomy. Silencing neuronal firing by tetrodotoxin administration at the SCN, but not the PVN, elevated blood glucose levels (Kalsbeek et al., 2004). Consistent with this finding, tetrodotoxin administration at the SCN, but not at the PVN, increased EGP in the glucose clamp analysis (Foppen et al., 2016). Considering the direct projection from the SCN to the PVN and the high basal blood glucose levels in anti-phase with the SCN neuronal firing activity in rats, these findings support a role of the SCN-PVN-SNS-EGP signaling in governing the rhythmic blood glucose levels under the normal physiological condition. Interestingly, hepatic sympathectomy in combination with a non-circadian feeding regimen disrupted the blood glucose rhythmicity without disrupting the clock gene expression rhythmicity in the liver, suggesting the molecular clock in the liver is not sufficient for generating the blood glucose rhythmicity (Cailotto et al., 2005). Of note, simultaneous hepatic sympathectomy and parasympathectomy in combination with a non-circadian feeding regimen did not abolish

the blood glucose rhythmicity, suggesting that unbalanced interplay between the SNS and PSNS accounts for the elevated glucose levels (Cailotto et al., 2008).

In addition to the liver, the SCN also innervates white adipose tissues (WAT) and brown adipose tissues (BAT) through sympathetic nerves as shown by retrograde tracing from adipose tissues (Bartness et al., 2001). BAT is a major thermogenetic tissue critical for maintaining the body temperature that has a clear circadian rhythm culminating in the dark cycle in nocturnal animals. The thermoregulatory median preoptic nucleus (MnPO) is innervated by both VAP-expressing SCN neurons and α-MSH-expressing ARC neurons. Administration of AVP into the MnPO decreased body temperature in the dark phase, while an AVP receptor antagonist increased body temperature in the early light cycle. Conversely, administration of a melanocortin receptor agonist into the MnPO prevented the diurnal drop in body temperature, while a melanocortin receptor antagonist induced a nocturnal decrease in body temperature. These findings suggest that the opposite effects of VAP and α-MSH govern the body temperature rhythm through the MnPO (Guzmán-Ruiz et al., 2015). The ventromedial hypothalamus (VMH) is another brain region that controls BAT activity and body temperature. VMH-specific depletion of BMAL1 in mice increased nocturnal expression of thermogenic genes in the BAT, enhanced BAT lipid oxidation, and increased body temperature especially in the dark cycle, without affecting the clock gene oscillation in the BAT. Administration of a β3 adrenoreceptor antagonist rescued the phenotype, demonstrating a role of the SNS in relaying the circadian signals into the BAT (Orozco-Solis et al., 2016).

Genetic animal models

Knock-out or mutation knock-in of core clock genes in mice altered glucose or lipid metabolism, which has been summarized recently (Eckel-Mahan and Sassone-Corsi, 2013). Genetic deletion of core clock genes, including CLOCK, BMAL1, PERs, CRYs, REV-ERBs, or RORs led to several metabolic abnormalities and disrupted glucose homeostasis. In addition to the core clock genes, genetic manipulation of clock-controlled output mediators could specifically affect metabolism without altering the clock itself or other clock-controlled biological processes, which has therapeutic implications. REV-ERBs recruit the NCOR/HDAC3 complex to the chromatin on a genome-wide scale in a rhythmic manner in the liver and skeletal muscles, regulating the diurnal metabolic fluxes in lipid anabolism in the liver and amino acid catabolism in the muscle. Depletion of HDAC3 in the liver or muscle disrupted the rhythmic metabolic flexibility and caused unique metabolic disorders (Feng et al., 2011; Sun et al., 2012, 2011; Hong et al., 2017). In addition to the molecular output mediators, the SNS is an important anatomic mediator that connects the central clock with metabolic processes in the liver, BAT, and other peripheral tissues through adrenergic receptors in the target tissue (Yi et al., 2010; Zhang and Bi, 2015). Recent studies have demonstrated diverse metabolic functions of adrenergic receptors using genetic mouse models (Table 1).

Human genetics

Smith-Magenis syndrome (SMS) is a rare genetic disorder characterized by intellectual disability, sleep disturbance, obesity, metabolic changes, multiple congenital anomalies, and

psychiatric behaviors. It is caused by a heterozygous microdeletion on chromosome region 17p11.2 containing the retinoic acid-induced 1 (RAI1) gene or mutations within RAI1. RAI1 is a transcription factor and was shown to regulate expression of CLOCK as well as other circadian clock genes. Dysregulation of the molecular clock is therefore considered as an underlying cause of many abnormalities in SMS patients (Chen et al., 2015).

Genetic association studies have identified the association of BMAL1 polymorphism with hypertension ($P = 0.0042$ for rs9633835) and diabetes ($P = 0.0036$ for rs7947951) (Diabetes Genetics Initiative of Broad Institute of Harvard and MIT, Lund University, and Novartis Institutes of BioMedical Research et al., 2007; Scott et al., 2007; Woon et al., 2007). A series of CLOCK polymorphisms have also been associated with susceptibility to nonalcoholic fatty liver disease, metabolic syndrome ($P = 0.0015$ for rs1801260), overweight ($P < 0.001$ for combined rs1554483G and rs4864548A), or small dense low-density lipoprotein levels in the circulation (Sookoian et al., 2007; Scott et al., 2008; Sookoian et al., 2008; Tsuzaki et al., 2010). A recent GWAS has identified a missense polymorphism (rs10462020; Gly639Val) of PER3 associated with type 2 diabetes (Below et al., 2011). Another meta-analysis of multiple GWAS studies identified CRY2 associated with fasting glucose levels (Dupuis et al., 2010). Genetic variants in the gene melatonin receptor 1B (MTNR1B) have been consistently shown to have a robust association with diabetes, although how it contributes to diabetes pathophysiology remains unclear (Bouatia-Naji et al., 2009; Lyssenko et al., 2009; Prokopenko et al., 2009; Bonnefond and Froguel, 2017).

6. Hormones and neuropeptides in metabolic functions of the central clock

Hormones play pivotal roles in metabolic homeostasis. A common feature for many hormones is the robust circadian rhythm that is not only due to responsiveness to environmental or behavioral variations associated with the sleep/wake cycle but also is regulated by the anticipatory circadian clock under the normal physiological condition (Gamble et al., 2014). When the normal circadian rhythm is disrupted by irregular light or feeding schedules, the endocrine system is also altered and can contribute to the metabolic derangement in these conditions (Bedrosian et al., 2016). Neuropeptides and neurotransmitters are involved at all levels of the SCN clock functions, including receiving the upstream input from environmental entraining cues, synchronizing different neurons within the SCN, and relaying the SCN efferent information to other parts of the body (An et al., 2013; Reghunandanan and Reghunandanan, 2006). Understanding how hormones and neuropeptides contribute to the clock function is important for successful manipulation of the clock with therapeutic implications.

Melatonin is released from the pineal gland and is unique in that it peaks in the dark phase in both diurnal and nocturnal animals, while other hormones display the opposite circadian phase between nocturnal and diurnal animals. Melatonin release is controlled by the SCN. GABA release from the SCN inhibits the PVN-originated projections to the pineal gland during the light cycle. This rhythmic GABAergic inhibitory signal, in combination with a

constant glutamatergic excitatory projection from the SCN, restricts the melatonin release from the pineal gland only during the dark cycle (Kalsbeek and Fliers, 2013). Suppression of melatonin secretion by pinealectomy abolished the blood glucose circadian rhythm in rats under a non-circadian scheduled feeding regimen without altering blood insulin levels (la Fleur et al., 2001b). Pinealectomy impaired glucose tolerance, which could be corrected by exogenous melatonin administration (Forrestel et al., 2017). The chronic melatonin administration was shown to improve insulin sensitivity and ameliorate obesity in some animal models (Agil et al., 2013; Nduhirabandi et al., 2011), but was also shown to cause glucose intolerance in other studies (Cagnacci et al., 2001; Rubio-Sastre et al., 2014). Many inbred mouse strains including the C57BL/6J mice have no detectable levels of melatonin due to genetic mutations (Kasahara et al., 2010; Roseboom et al., 1998). However, the depletion of melatonin receptor type 1 or type 2 in mice abolished the blood glucose circadian rhythm without altering the rhythmic expression of clock genes in the skeletal muscle, liver, or adipose tissue (Owino et al., 2016).

Glucocorticoid is another class of hormones with robust circadian rhythm and pivotal roles in energy metabolism. The blood glucocorticoid level peaks at the activity onset, which is regulated by the hypothalamic–pituitary–adrenal (HPA) axis. The corticotrophin-releasing hormone (CRH) from the PVN stimulates adrenocorticotropic hormone (ACTH) from the pituitary (Kalsbeek and Fliers, 2013). The SCN rhythmically releases vasopressin during the light in rats, which inhibits CRH neurons in the PVN. This control could be through diffusive vasopressin via the cerebrospinal fluid (CSF) or through the SCN to PVN neural projections (Vrang et al., 1995). PVN neurons in nocturnal animals respond to vasopressin differently from diurnal animals (Kalsbeek et al., 2008b). Glucocorticoid can partially restore the peripheral circadian rhythm due to the SCN lesion, suggesting that it could relay signals from the SCN to peripheral tissues (Reddy et al., 2007; Pezük et al., 2012). Within the target tissue, glucocorticoid binds to the glucocorticoid receptor and regulates glucose utilization as well as hepatic gluconeogenesis (Oster et al., 2017).

Orexin is a neuropeptide secreted by the lateral hypothalamus (LH) with low levels in the CSF during sleep and high levels during wake (Chieffi et al., 2017). Darkness activates orexin neurons in nocturnal rodents (Marston et al., 2008), while orexin suppresses the SCN neurons either directly or indirectly through augmenting the IGL-mediated suppression of the SCN neurons (Belle et al., 2014; Palus et al., 2015). Activation of the orexin at the onset of the active phase not only facilitates wakefulness but also adapts the peripheral glucose metabolism to the active phase (Kalsbeek and Fliers, 2013). Orexin deficiency caused sleep disorders, obesity, and glucose intolerance in human and mouse models (Chemelli et al., 1999; Hara et al., 2005; Lin et al., 1999; Tsuneki et al., 2008). Overexpression of orexin protected mice from diet-induced obesity and glucose intolerance, mainly through the orexin receptor 2 (OX2R). Pharmacological activation of the LH neurons or orexin ICV administration increased EGP in rats, an effect that can be blocked by orexin receptor 1 (OX1R) antagonist or hepatic sympathectomy (Yi et al., 2009). Although ICV administration of orexin during the day increased blood glucose levels in mice, orexin administration at night decreased blood glucose levels associated with reduced gluconeogenesis gene expression, an effect that can be blocked by hepatic parasympathectomy (Tsuneki et al., 2015). Thus, orexin bidirectionally regulates hepatic

gluconeogenesis through an OX2R-sympathetic pathway in the day and an OX1R-parasympathetic pathway at night.

Acetylcholine is a major neurotransmitter of the PSNS through activation of muscarinic acetylcholine receptors (mAChRs) in target tissues. The subtype M3 is the only mAChR expressed in the mouse hepatocytes. Interestingly, knockout of the mAChR-M3 did not alter glucose tolerance or hepatic expression of metabolic enzymes in mice fed either normal chow or high-fat diet, suggesting that metabolic effects mediated by hepatic vagal nerves are acetylcholine independent (Li et al., 2009).

7. Concluding remarks

Energy metabolism is a biological process with intrinsic circadian rhythms at multiple levels, which is orchestrated by both the anticipatory mechanism from the central circadian clock and the responsive mechanism that reacts to the sleep/wake cycle or fasting/feeding cycle. The molecular clock is composed of a handful of transcription factors in negative feedback loops that exist in the brain as well as in the peripheral tissues. The central clock in the SCN of the hypothalamus is entrained by light and synchronizes with oscillators in other brain regions through neuronal projections or neuropeptides. The central clock regulates systemic metabolism through the autonomous nervous systems and endocrine factors. Disruption of the circadian clock system by irregular light or feeding schedules contributes to metabolic disorders such as obesity and diabetes. Harnessing the circadian clock system with chronotherapy or lifestyle intervention is a promising strategy combating against these metabolic diseases.

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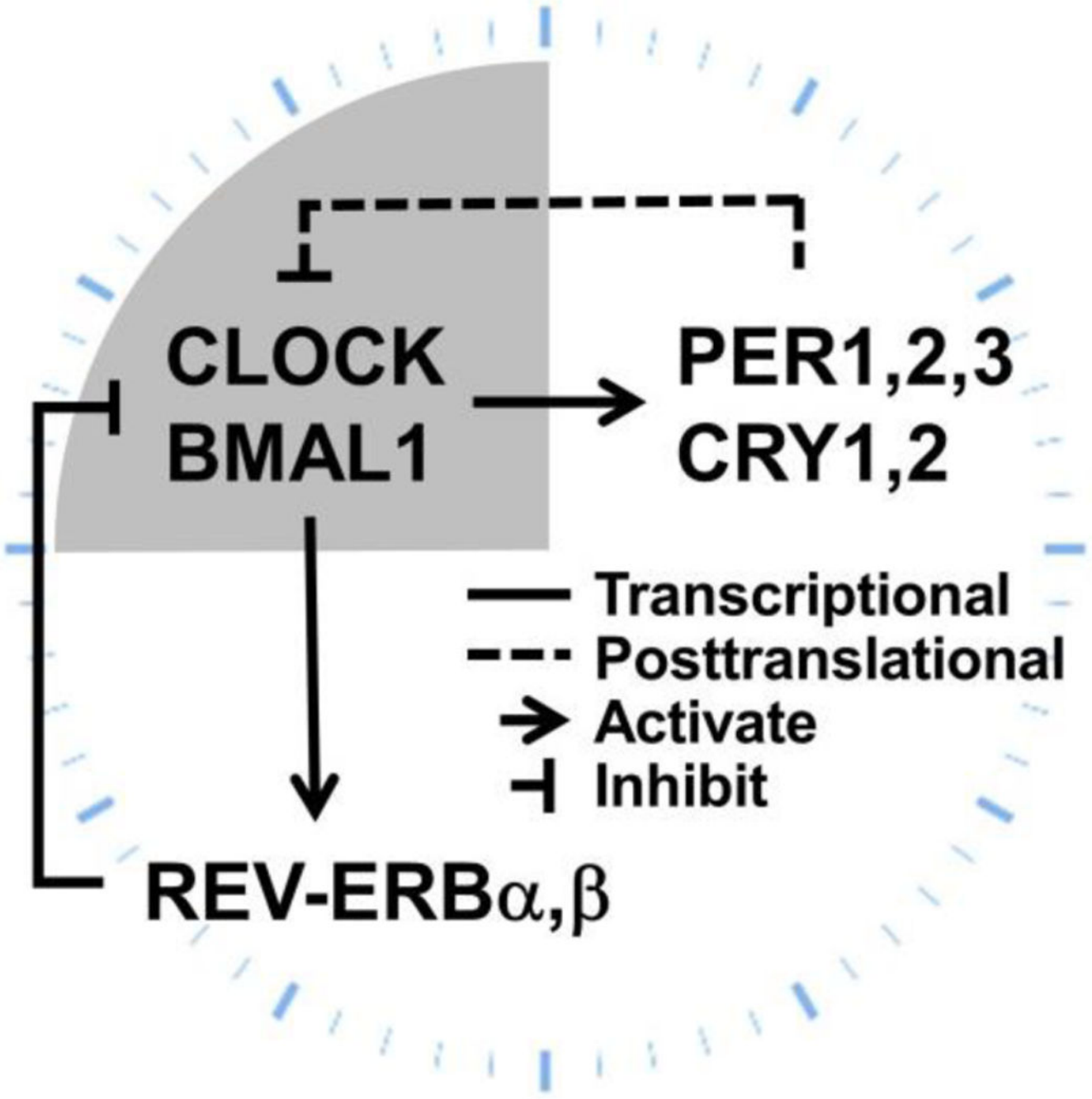

Figure 1.
The molecular circadian clock machinery.

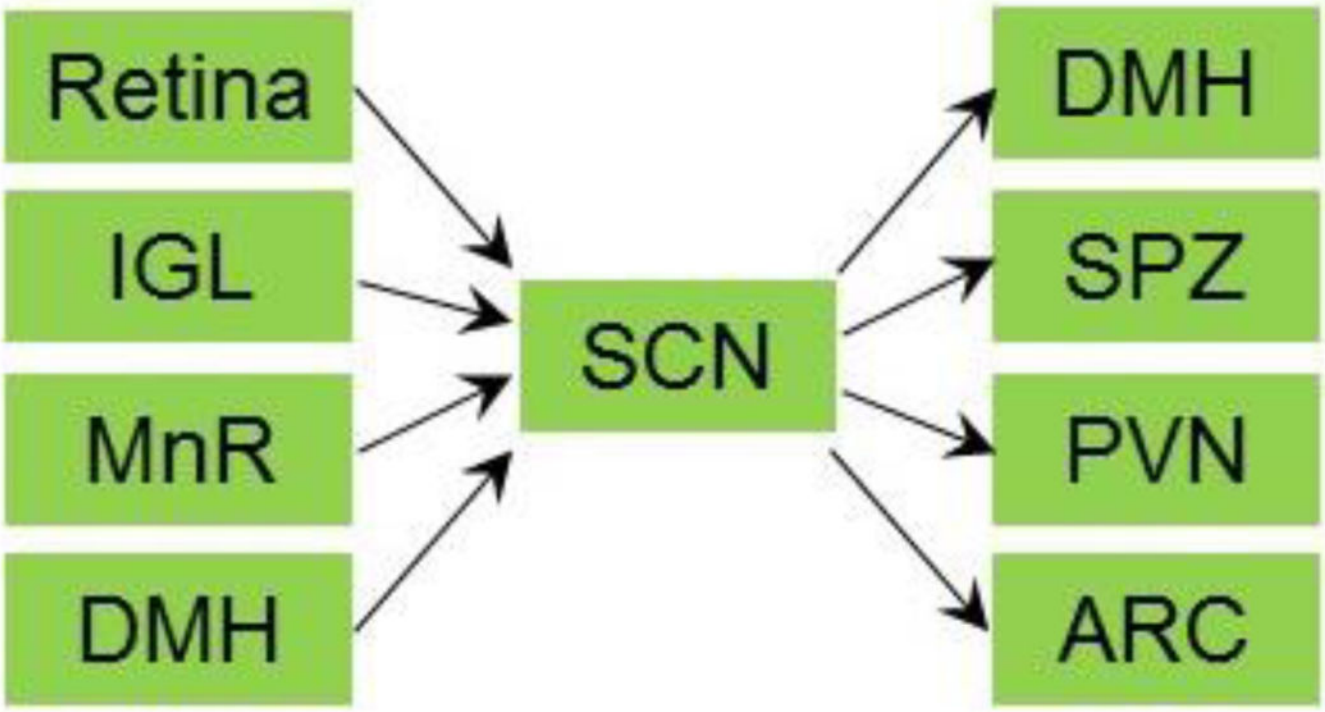

Figure 2. Major inputs and outputs of the SCN.

The suprachiasmatic nucleus (SCN) receives projections from retina, the thalamic intergeniculate leaflet (IGL), the median raphe (MnR), and the dorsomedial hypothalamic nucleus (DMH). The SCN projects to the DMH, the lateral subparaventricular zone (SPZ), the paraventricular nucleus (PVN), and arcuate nucleus (ARC).

Table 1.

Genetic mouse models of adrenergic receptors (AR).

KO, knockout; DKO, double knockout; TKO, triple knockout; OE, overexpression.

Model	Metabolic phenotypes compared to control wild-type (WT)	Reference
α1A-AR KO	Lowered glucose uptake and GLUT translocation in the adult heart	(Shi et al., 2016a)
α1A-AR OE	Increased glucose uptake, increased GLUT1 and GLUT4 membrane translocation in the adult heart	(Shi et al., 2016a)
α1B-AR KO	Higher blood glucose and insulin levels during the transition from fed to fasting, higher leptin levels in the fed state, insulin resistance with impaired suppression of EGP, higher susceptibility to diet-induced obesity and glucose intolerance	(Burcelin et al., 2004)
α2A-AR KO	Lower basal glucose levels, abolished effects of dexmedetomidine and atipamezole on blood glucose or insulin levels	(Fagerholm et al., 2004)
α2A-AR KO	Hyperinsulinaemia, lower blood glucose levels, improved glucose tolerance	(Savontaus et al., 2008)
α2C-AR KO	Impaired glucose tolerance that was reversed by pretreatment with propranolol, higher adrenaline secretion, unaltered insulin secretion	(Ruohonen et al., 2012)
α2A/α2C-AR DKO	Similar glucose and insulin phenotype as knock-out α(2A)-AR alone, but more sensitive to the glucose-lowering effect of insulin than WT mice.	(Ruohonen et al., 2012)
α2A, α2B, or α2C-AR KO	Ex vivo experiments demonstrating that α2A and α2C mediate the inhibitory effects of adrenaline on pancreatic insulin release	(Peterhoff et al., 2003)
β1-AR KO	Hypothermia during cold exposure and reduced BAT thermal response to norepinephrine; more susceptible to diet-induced obesity, hypercholesterolemia, hypertriglyceridemia, glucose intolerance, hyperglycemia, and steatohepatitis; defective diet-induced thermogenesis	(Ueta et al., 2012)
β2-AR KO	Lower hepatic triglyceride content and body weight during aging, lower glucose tolerance in young age and improved glucose tolerance in old age	(Shi et al., 2016b)
β2-AR KO	Fasting hyperinsulinemia; higher PEPCK (PCK1) gene expression in the liver; similar glucose intolerance, body weight gain, and liver lipid content as WT on high fat diet	(Fernandes et al., 2014)
β3-AR KO	Normal BAT thermogenesis, increased susceptibility to diet-induced obesity, elevated inflammation, similar glucose tolerance as WT, ameliorated hypertriglyceridemia and hypercholesterolemia on high fat diet	(Preite et al., 2016)
β1,2,3-AR TKO (beta-less mice)	Increased fat mass, glucose intolerance, impaired glucose-induced insulin secretion, higher liver PEPCK gene expression in the fed state, enhanced insulin sensitivity	(Asensio et al., 2005)