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[REVIEW]

Resetting Mechanism of Central and Peripheral Circadian Clocks in Mammals

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ABSTRACT—Almost all organisms on earth exhibit diurnal rhythms in physiology and behavior under the control of autonomous time-measuring system called circadian clock. The circadian clock is generally reset by environmental time cues, such as light, in order to synchronize with the external 24-h cycles. In mammals, the core oscillator of the circadian clock is composed of transcription/translation-based negative feedback loops regulating the cyclic expression of a limited number of clock genes (such as *Per*, *Cry*, *Bmal1*, etc.) and hundreds of output genes in a well-concerted manner. The central clock controlling the behavioral rhythm is localized in the hypothalamic suprachiasmatic nucleus (SCN), and peripheral clocks are present in other various tissues. The phase of the central clock is amenable to ambient light signal captured by the visual rod-cone photoreceptors and non-visual melanopsin in the retina. These light signals are transmitted to the SCN through the retinohypothalamic tract, and transduced therein by mitogen-activated protein kinase and other signaling molecules to induce *Per* gene expression, which eventually elicits phase-dependent phase shifts of the clock. The central clock controls peripheral clocks directly and indirectly by virtue of neural, humoral, and other signals in a coordinated manner. The change in feeding time resets the peripheral clocks in a SCN-independent manner, possibly by food metabolites and body temperature rhythms. In this article, we will provide an overview of recent molecular and genetic studies on the resetting mechanism of the central and peripheral circadian clocks in mammals.

Key words: circadian clock, oscillation, phase resetting, suprachiasmatic nucleus, light

INTRODUCTION

According to the rotation of the earth on its axis, most organisms living in this world exhibit daily changes in physiology and behavior (Pittendrigh, 1993; Hastings *et al.*, 2003). For example, the pineal gland, a neuroendocrine organ, produces and secretes melatonin actively during night in vertebrate species (Klein *et al.*, 1997). Many of the daily rhythms persist with the intrinsic period lengths close to 24 h even under the constant condition without any external time cues, indicating the presence of autonomous time-measuring system in each organism. Such a system is called circadian clock, where “circadian” is a coined word of *circa* (about) and *dies* (day) in Latin. Because the period lengths of the circadian clocks generally deviate from 24 h, the clocks have an important ability to reset (shift) the phase

in response to environmental time cues, such as light, and synchronize with the ambient 24-h cycles.

In mammals, the circadian clocks are present in a variety of tissues and cells, and these cell-autonomous oscillators appear to be organized in a hierarchical manner (Reppert and Weaver, 2002; Schibler and Sassone-Corsi, 2002) (Fig. 1). The master pacemaker controlling the behavioral rhythm is localized in the hypothalamic suprachiasmatic nucleus (SCN) that consists of densely packed ~20,000 neurons. This central clock is reset mainly by external light signal captured by the retina. On the other hand, the clocks in peripheral tissues such as liver and heart are called peripheral clocks. In the absence of the SCN, the oscillation of peripheral clocks damps within several cycles, and hence the peripheral clocks are considered as slave oscillators that regulate local rhythms of each tissue. A forced change of feeding time synchronizes peripheral clocks independently of the central clock, suggesting that non-photic signals such as the feeding signal may be a dominant time cue for

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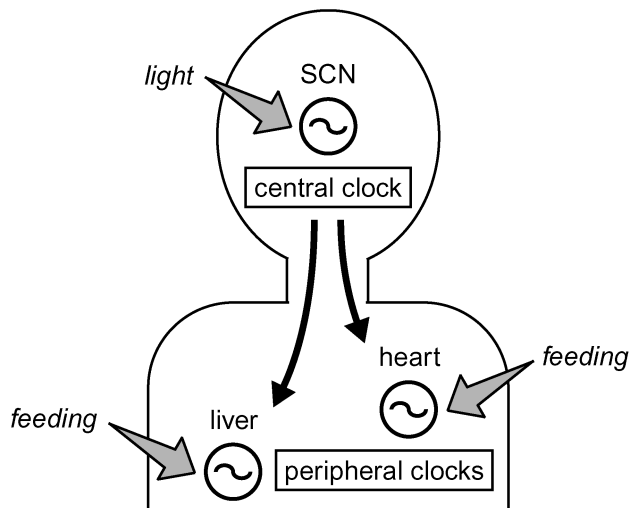


Fig. 1. Central and peripheral clocks in mammals. SCN, suprachiasmatic nucleus.

peripheral clocks. In this review, we focus on recent progress in the understanding of the resetting mechanism of the central and peripheral clocks in mammals.

OSCILLATION OF MAMMALIAN CIRCADIAN CLOCK

The circadian clock system is genetically programmed, and the “clock genes” constituting the oscillator have been pursued primarily by using model organisms such as cyanobacteria, *Neurospora*, *Drosophila*, and mice (Dunlap, 1999). The genetic and molecular analyses identified several clock genes forming a well-conserved transcription/translation-based negative feedback loop in each organism. In mammals, basic helix-loop-helix-PAS transcription factors CLOCK and BMAL1 act as positive regulators, and three PERIOD proteins (PER1, PER2, and PER3) and two CRYPTOCHROME proteins (CRY1 and CRY2) operate as negative regulators (King and Takahashi, 2000; Reppert and Weaver, 2002) (Fig. 2). CLOCK-BMAL1 heterodimer binds to E box enhancer to activate the transcription of *Per* and *Cry* genes (Fig. 2, red arrows). This activation involves association of CLOCK with histone acetyltransferase p300 and acetylation of H3 histone in the promoter region of target genes (Etchegaray *et al.*, 2003). PER and CRY proteins thus translated in the cytoplasm are transported to the nucleus and inhibit the CLOCK-BMAL1-dependent transcriptional activation, resulting in a decrease in their own transcripts. After that, regulated degradation of PER and CRY proteins leads to a restart of the activation and inhibition cycle of E box-mediated gene expression, allowing the circadian oscillations of mRNA and protein levels of both *Per* and *Cry*. The mammalian homolog of *Drosophila* clock protein TIMELESS (TIM) also seems to play a role in the clock oscillation by interacting with PER (Barnes *et al.*, 2003). In addition, basic helix-loop-helix transcription factors DEC1 and DEC2 inhibit the CLOCK-BMAL1 function, and the expression of *Dec1* gene is controlled by CLOCK-BMAL1,

suggesting that DEC proteins act as additional negative regulators in the feedback loop (Honma *et al.*, 2002; Gréchez-Cassiau *et al.*, 2004; Kawamoto *et al.*, 2004). On the other hand, the transcription of positive regulator gene *Bmal1* is repressed by an orphan nuclear receptor REV-ERB α , whose mRNA expression is activated by CLOCK-BMAL1 (Preitner *et al.*, 2002; Ueda *et al.*, 2002) (Fig. 2, green arrows). This regulation results in circadian oscillation of *Bmal1* expression in antiphase with the rhythm of *Per* expression. These two loops of negative and positive regulators are tightly coupled with each other (Fig. 2, red and green arrows) and constitute the core of the circadian oscillator. In addition to the core loops, basic leucine zipper transcription factors DBP and E4BP4 form secondary loops by regulating *Per1* gene expression antagonistically through DBP-binding site (Yamaguchi *et al.*, 2000; Mitsui *et al.*, 2001) (Fig. 2, dark blue arrows). Such a transcription/translation-based oscillatory mechanism appears to be common to the central and peripheral clocks in mammals (Yagita *et al.*, 2001). To control the circadian changes in physiology and behavior, the core and secondary loops regulate the expression of the output genes (also called clock-controlled genes). For example, E box enhancer regulates gene expression of a variety of factors that include a neuropeptide arginine vasopressin (Jin *et al.*, 1999), a secreted protein prokineticin 2 (Cheng *et al.*, 2002), a serine protease inhibitor plasminogen activator inhibitor-1 (Maemura *et al.*, 2000), a transcription factor c-Myc (Fu *et al.*, 2002), and the Cdc2 kinase WEE1 (Matsuo *et al.*, 2003). Recent studies using DNA microarray technology identified a large number of rhythmically expressed genes (Grundschober *et al.*, 2001; Akhtar *et al.*, 2002; Duffield *et al.*, 2002; Humphries *et al.*, 2002; Kita *et al.*, 2002; Panda *et al.*, 2002a; Storch *et al.*, 2002; Ueda *et al.*, 2002; Oishi *et al.*, 2003). Some of these genes may be regulated directly by the transcription factors involved in the oscillatory loops through the upstream *cis*-elements, such as E box, REV-ERB α /ROR response element, and DBP-binding site (Ueda *et al.*, 2002).

Once the clock genes are translated, their products (clock proteins) undergo post-translational modifications such as phosphorylation and ubiquitination (Lee *et al.*, 2001; Akashi *et al.*, 2002; Yagita *et al.*, 2002). Casein kinase I ϵ (CKI ϵ) and mitogen-activated protein kinase (MAPK) phosphorylate several clock proteins to modulate their stability and/or function (Keesler *et al.*, 2000; Takano *et al.*, 2000; Vielhaber *et al.*, 2000; Akashi *et al.*, 2002; Eide *et al.*, 2002; Sanada *et al.*, 2002) (Fig. 2, light blue arrows). In the mammalian SCN, phosphorylation levels (*i.e.*, activities) of MAPK exhibit circadian rhythm (Obrietan *et al.*, 1998; Coogan and Piggins, 2003; Lee *et al.*, 2003; Nakaya *et al.*, 2003). The rhythm of MAPK activity might be controlled by SCOP, a rhythmically expressed gene product acting as negative regulator of the Ras-MAPK pathway (Shimizu *et al.*, 2003). JNK and p38, two other members of MAPK superfamily, are also rhythmically phosphorylated in the hamster SCN (Pizzio *et al.*, 2003). In contrast to accumulating evidence for the

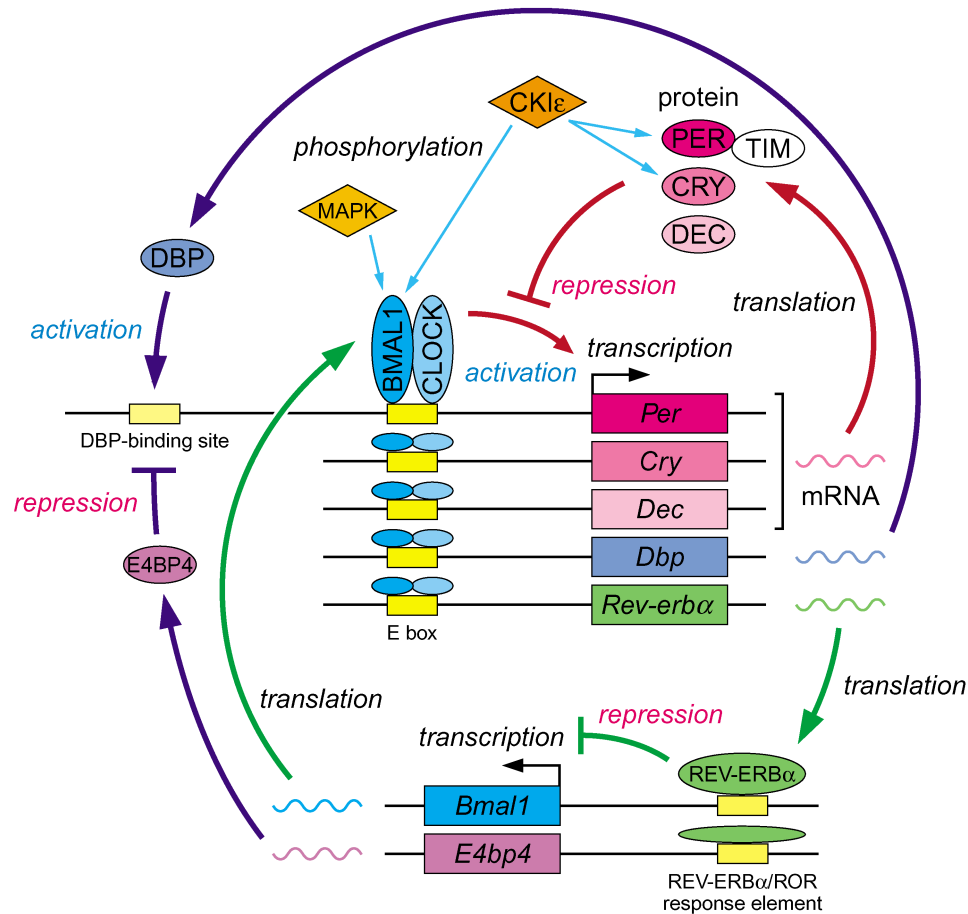


Fig. 2. A model for feedback loops of mammalian circadian clock. CKI ϵ , casein kinase I ϵ ; MAPK, mitogen-activated protein kinase.

important role of MAPK in the time-keeping mechanism, far less is known about the roles of JNK and p38 in the mammalian clock system. In the chick pineal clock, p38 exhibits a constant phosphorylation level over the day, but interestingly p38 activity has a daytime-specific phase-advancing effect on the clock (Hayashi *et al.*, 2003). On the other hand, interactions between PER and CRY proteins regulate their nucleocytoplasmic localization and ubiquitination-mediated degradation (Miyazaki *et al.*, 2001; Yagita *et al.*, 2002). Similarly, the interaction between CLOCK and BMAL1 controls their nucleocytoplasmic localization, phosphorylation, and degradation (Kondratov *et al.*, 2003). These spatiotemporal regulations appear to play key roles in generating the stable oscillation with a long period of ~24 h. For example, a defect in CKI ϵ gene causes the shortened circadian period of *tau* mutant hamster (Lowrey *et al.*, 2000). In the human, the familial advanced sleep-phase syndrome with short-period phenotype is associated with a missense mutation in *PER2* gene, in which the mutation affects phosphorylation of PER2 protein by CKI ϵ (Toh *et al.*, 2001).

RESETTING OF THE CENTRAL CLOCK BY LIGHT

The environmental light-dark cycle is the most important time cue for almost all the organisms. In mammals, the

“circadian photoreceptor” responsible for the photic resetting of the circadian clock is localized within the eye, because the resetting is abolished by bilateral enucleation. Visually blind mice lacking both rod and cone photoreceptors, however, show normal resetting by light, suggesting the presence of non-visual circadian photoreceptor (Foster and Hankins, 2002). The molecular identity of the circadian photoreceptor has been long veiled, but recent studies revealed an important role of melanopsin, a novel opsin-like protein (Berson, 2003). Melanopsin was originally identified as a putative photoreceptor expressed in *Xenopus* skin melanophores (Provencio *et al.*, 1998), and later melanopsin expression was found in a subset of retinal ganglion cells (RGCs) but not in rod and cone photoreceptor cells in the mouse (Provencio *et al.*, 2000; Provencio *et al.*, 2002). The melanopsin-containing RGCs extrude axons constituting the retinohypothalamic tract (RHT) which transmits the photic signal to the SCN (Gooley *et al.*, 2001; Hannibal *et al.*, 2002; Hattar *et al.*, 2002). Notably, these RGCs exhibit depolarizing electrical photoresponses even when isolated from the retina (Berson *et al.*, 2002). The shape of the action spectrum of the photoresponse fits with a nomogram of the absorption spectrum of a vitamin A-based photopigment, opsin, and the peak sensitivity at 484 nm estimated from the fitting (Berson *et al.*, 2002) is close to that for the resetting

of behavioral rhythms of the mouse (Takahashi *et al.*, 1984; Provencio and Foster, 1995; Yoshimura and Ebihara, 1996). These observations strongly suggest that melanopsin acts as a photoreceptor of the photosensitive RGCs resetting the SCN clock in a light-dependent manner. In melanopsin knockout mice, the intrinsic photosensitivity of the RGCs is eliminated, indicating the indispensable role of melanopsin in the cellular photoresponse (Lucas *et al.*, 2003). However, the behavioral rhythms of the knockout mice still synchronize with the environmental light-dark cycles, though they show partially impaired resetting in response to a brief light pulse (Panda *et al.*, 2002b; Ruby *et al.*, 2002). A possible contribution of rod and cone photoreceptors in the melanopsin knockout mice was tested by generating mice lacking both the functional rod-cone system and melanopsin (Hattar *et al.*, 2003; Panda *et al.*, 2003). The mutant mice exhibit complete loss of the photic resetting, indicating that the visual rod-cone photoreceptors and non-visual melanopsin serve as the circadian photoreceptors in a complementary manner, and that no additional photoreceptors are required for the process. In spite of accumulating evidence for the role of melanopsin in the circadian photoreception, it is still unclear whether melanopsin is in fact photosensitive. Recently, spectral properties of recombinant melanopsin were examined after reconstitution with 11-*cis*-retinal, and the difference absorption spectrum before and after hydroxylamine-induced bleaching showed the maximal absorbance at 424 nm (Newman *et al.*, 2003), a value that largely deviates from the peak (at 484 nm) of the action spectrum of the photosensitive RGCs (Berson *et al.*, 2002). Further experiments are required for molecular characterization of melanopsin function and its downstream phototransduction pathway.

In response to light, glutamate and PACAP are released from the RHT terminal and stimulate their receptors expressed in the SCN neuron (Reppert and Weaver, 2002) (Fig. 3). The downstream signaling causes the chromatin remodeling (Crosio *et al.*, 2000) and induces acute expression of clock genes *Per1* and *Per2* (Albrecht *et al.*, 1997; Shearman *et al.*, 1997; Shigeyoshi *et al.*, 1997) in addition to several immediate early genes (Morris *et al.*, 1998). It is noticeable that all of these genes are induced by light only during night. The light-dependent induction of *Per1* gene most probably plays an important role in the resetting of the central clock, because antisense oligonucleotides against *Per1* inhibit phase-dependent phase shifts of the clock by light, *i.e.*, phase delay in early night (Akiyama *et al.*, 1999) and phase advance in late night (Tischkau *et al.*, 2003a). Similarly, the photic induction of *Per2* gene may be involved in the phase delay (Wakamatsu *et al.*, 2001a) but not in the phase advance (Tischkau *et al.*, 2003a). Consistent with these observations, light-dependent phase-advance or delay of the clock is impaired in mice deficient in *Per1* or *Per2* gene, respectively (Albrecht *et al.*, 2001).

Photic stimuli given at night induce cAMP response element (CRE)-mediated gene expression in the SCN (Obri-

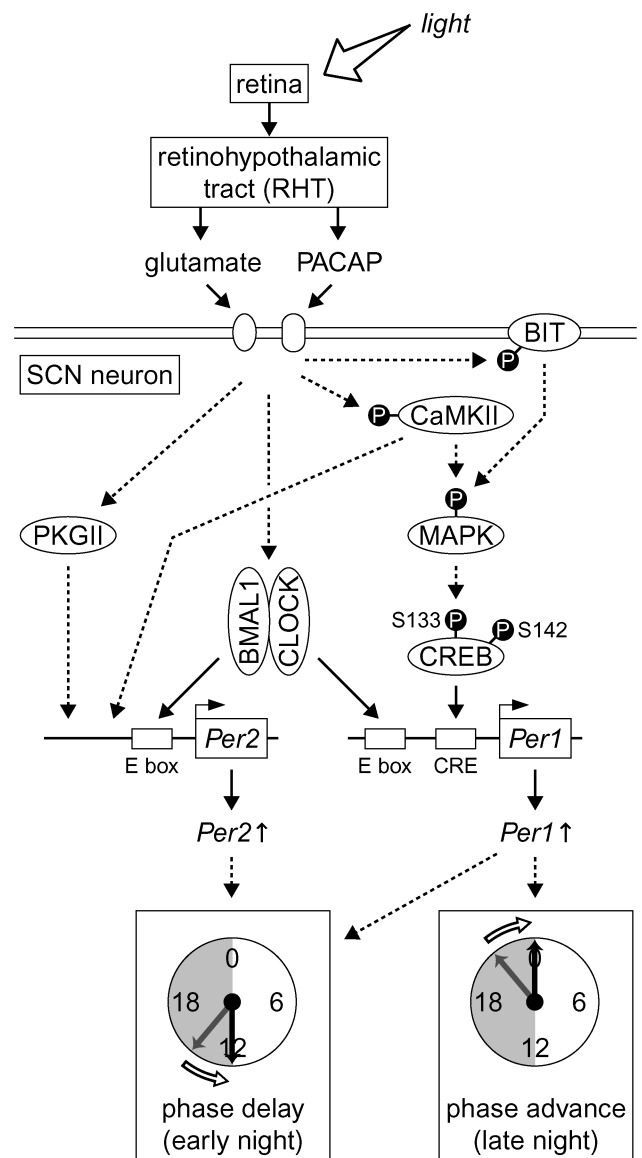


Fig. 3. Photic input signal transduction pathways in the SCN neuron. *Solid and dashed lines* indicate the direct and indirect pathways, respectively. BIT, brain immunoglobulin-like molecule with tyrosine-based activation motifs; CaMKII, calcium/calmodulin kinase II; CRE, cAMP response element; CREB, CRE-binding protein; PACAP, pituitary adenylate cyclase-activating peptide; PKGII, cGMP-dependent protein kinase II.

etan *et al.*, 1999), and this transcriptional activation is required for the induction of *Per1* gene whose promoter contains CRE (Travnickova-Bendova *et al.*, 2002; Tischkau *et al.*, 2003a) (Fig. 3). A transcription factor CREB (CRE-binding protein) is phosphorylated at Ser133 in response to light given at night (Ginty *et al.*, 1993). Phosphorylation of CREB at Ser142 is also stimulated by light at night, and the mutation of Ser142 to alanine by gene targeting in the mouse results in an attenuation of the photic induction of *Per1* but not *Per2* (Gau *et al.*, 2002). Importantly, the S142A mutation severely inhibits the light-induced phase advance and moderately reduces the phase delay. These observations

strongly suggest that the CRE-mediated induction of *Per1* gene through phosphorylation of CREB at Ser142 plays a pivotal role in photic resetting of the central clock, especially in its phase advance. Phosphorylation of CREB at Ser133 may cooperate with Ser142 phosphorylation. On the other hand, the light induction of *Per2* but not *Per1* is strongly suppressed in mice lacking cGMP-dependent protein kinase II (PKGII) (Oster *et al.*, 2003). In the mutant mice, only the light-induced phase delay is inhibited moderately, suggesting that PKGII is required for the photic induction of *Per2* that delays the phase of the clock. Pharmacological studies, however, have implicated cGMP-PKG pathway as being critical for the phase advance by light in late night (Gillette and Mitchell, 2002; Tischkau *et al.*, 2003b). This discrepancy should be resolved in future studies. Additionally, the mobilization of intracellular calcium mediated by ryanodine receptor participates not only in the circadian oscillation of cytosolic calcium concentration (Ikeda *et al.*, 2003) but also in the light-induced phase delay (Ding *et al.*, 1998). The CLOCK-BMAL1-dependent transcriptional activation also appears to be involved in the induction of *Per1* and *Per2* expression, because the mutant CLOCK protein affects this process (Shearman and Weaver, 1999; Jung *et al.*, 2003). Taken together, a wide range of signaling molecules seem to contribute to the light induction of *Per* gene expression leading to the phase-dependent phase shift of the clock (Fig. 3). However, the precise mechanism generating the phase shift in the opposite direction (delay and advance) is still unknown.

In the SCN neuron, the MAPK pathway appears to play an important role in transducing the photic input signal to the core oscillator (Fig. 3). MAPK is phosphorylated by light during night (Obrietan *et al.*, 1998), and the inhibition of MAPK phosphorylation by using MAPK kinase inhibitor attenuates the light-induced phase delay (Butcher *et al.*, 2002) and advance (Coogan and Piggins, 2003). The inhibitor also reduces stimulus-induced CREB phosphorylation at Ser133 (Obrietan *et al.*, 1998) and blocks CRE-mediated gene expression (Dziema *et al.*, 2003). It is hence possible that

light-activated MAPK resets the clock by inducing *Per1* expression via the CREB/CRE transcriptional pathway. On the other hand, calcium/calmodulin kinase (CaMK) inhibitor attenuates the photic induction of MAPK phosphorylation, implicating CaMK signaling as an upstream regulator of the MAPK pathway (Butcher *et al.*, 2002). Among CaMK family proteins, CaMKII is activated in response to light and seems to participate in the phase delay of the clock and in light-dependent induction of *Per1* and *Per2* genes (Yokota *et al.*, 2001; Nomura *et al.*, 2003). In parallel, light induces tyrosine phosphorylation of a transmembrane glycoprotein, BIT (Nakahata *et al.*, 2000). Phosphorylation of BIT activates MAPK pathway and resets the clock, suggesting that BIT contributes to the photic input pathway by regulating MAPK (Nakahata *et al.*, 2003).

The mammalian SCN is composed of anatomically and functionally distinct subregions, the ventrolateral region and the dorsomedial region, the former receiving RHT input (Moore *et al.*, 2002) (Fig. 4). The photic induction of *Per* expression and MAPK phosphorylation described above occurs only within the ventrolateral region, in which neither *Per* expression nor MAPK phosphorylation exhibits obvious rhythms in the mouse, rat, and hamster kept in constant darkness (Hamada *et al.*, 2001; Yan and Okamura, 2002; Nakaya *et al.*, 2003). A calcium-binding protein calbindin is specifically expressed in this region and regulates the phase-dependent phase shift of the clock by light (Hamada *et al.*, 2003). On the other hand, the dorsomedial region exhibits overt rhythms in *Per* expression (Hamada *et al.*, 2001; Yan and Okamura, 2002) and MAPK phosphorylation (Lee *et al.*, 2003; Nakaya *et al.*, 2003), both peaking during daytime. Notably, in the core region of the mouse SCN, MAPK shows a circadian phosphorylation pattern peaking at night, and it is dephosphorylated by light during night (Nakaya *et al.*, 2003), as are observed in the chick pineal gland (Sanada *et al.*, 2000). The eye is necessary for the circadian rhythm of MAPK phosphorylation in the core region of the hamster SCN, suggesting the influence of the ocular clock on the central clock (Lee *et al.*, 2003). Con-

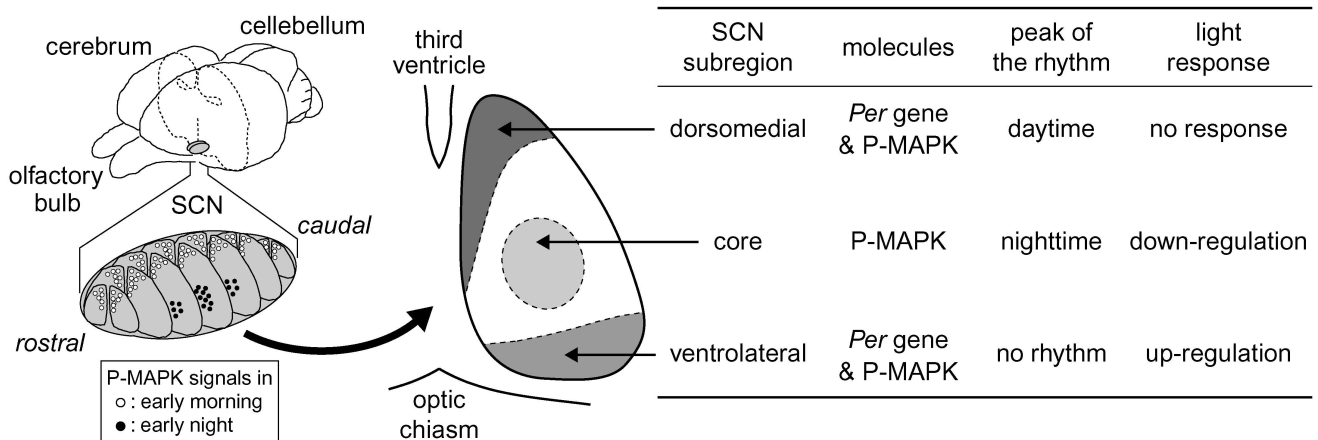


Fig. 4. Distribution of phosphorylated MAPK (P-MAPK) signals in three subregions of the mouse SCN.

sistent with the functional difference between the ventrolateral and dorsomedial regions, an abrupt shift in environmental light-dark cycle dissociates the synchronous oscillation of *Per* expression in the two SCN regions. The gene expression rhythm in the ventrolateral region (receiving RHT input) synchronizes immediately with the environmental light-dark cycle, whereas the clock phase in the dorsomedial region shifts gradually (Nagano *et al.*, 2003). Two neuropeptides, vasoactive intestinal peptide and gastrin-releasing peptide, are expressed specifically in the ventrolateral region, and they may evoke the phase shift of the dorsomedial SCN neurons during the resynchronization process (Watanabe *et al.*, 2000; Aida *et al.*, 2002; Harmar *et al.*, 2002). Sodium-dependent action potentials is also involved in the intercellular synchronization among the SCN neurons (Yamaguchi *et al.*, 2003).

RESETTING OF PERIPHERAL CLOCKS

Many of the mammalian peripheral tissues contain functional circadian clocks, and these peripheral clocks are coordinated by the central clock (Schibler and Sassone-Corsi, 2002; Schibler *et al.*, 2003) (Fig. 5). The *Per1* deficient embryonic fibroblasts show short-period phenotype in culture, but when implanted into wild-type mice, the implant exhibits a rhythmic gene expression with phase and period length that are close to those in the host peripheral tissues, indicating that the SCN can control the molecular oscillation of the peripheral clock (Pando *et al.*, 2002). However, an abrupt change in the feeding time schedule (from night to day) for several days gradually uncouples the periphery from the SCN by shifting the phase of the peripheral clocks but not the central clock in mice (Damiola *et al.*, 2000; Hara *et al.*, 2001; Stokkan *et al.*, 2001). In the absence of glucocorticoid hormone (a feeding-related hormone) or its receptor, the peripheral clocks synchronize more rapidly with the altered feeding cycle (Le Minh *et al.*, 2001). Therefore, glucocorticoid hormone signaling, which potently resets the peripheral clocks *in vivo* (Balsalobre *et al.*, 2000a), seems to act as an inhibitor of the dissociation between the central and peripheral clocks. On the other hand, another feeding-related hormone, insulin, appears to be dispensable for the feeding-dependent synchronization of the liver clock (Davidson *et al.*, 2002).

Although little is known about the molecular identities of the feeding-related signals that strongly reset the peripheral clocks, some food metabolites and body temperature rhythms are suggested to play important roles (Fig. 5, *open arrows*). The former may include retinoic acid, a derivative of vitamin A, and glucose. Retinoic acid resets the vascular clock *in vivo* through its binding to nuclear receptors, RAR α and RXR α (McNamara *et al.*, 2001). Both of the retinoic acid-bound receptors interact with CLOCK or MOP4 (a paralog of CLOCK; also termed NPAS2), and inhibit the CLOCK-BMAL1- or MOP4-BMAL1-dependent transcriptional activation, respectively. In cultured rat-1 fibroblasts, a

model system for analyzing the peripheral clock mechanism (Balsalobre *et al.*, 1998; Balsalobre *et al.*, 2000a; Balsalobre *et al.*, 2000b; Yagita and Okamura, 2000; Yagita *et al.*, 2001; Brown *et al.*, 2002), glucose-treatment elicits the circadian gene expression that starts with slow down-regulation of *Per1* and *Per2* mRNA levels (Hirota *et al.*, 2002). This unique property (signal-induced down-regulation of *Per1* and *Per2*) seems to involve glucose-induced immediate up-regulation of the genes for transcriptional regulators, TIEG1 and VDUP1, which may repress the expression of *Per* genes. In the diabetic rats lacking insulin, the phase of the circadian gene expression in the heart is advanced by about 3 h (Young *et al.*, 2002), raising the possibility that the elevation of plasma glucose levels affects the clock gene expression in the peripheral clock *in vivo* as well. In addition to such a direct resetting effect of food metabolites, the peripheral clock may be affected by feeding-dependent changes in body temperature rhythms (Damiola *et al.*, 2000). Indeed, the circadian gene expression in cultured rat-1 fibroblasts can be sustained by external temperature cycle mimicking the natural body temperature rhythms, though such temperature cycle itself is incapable of eliciting the rhythmic gene expression (Brown *et al.*, 2002).

In the forebrain that processes sensory information, circadian expression of *Per2* gene is abrogated in the mice deficient in NPAS2, and therefore the clock oscillation in the forebrain appears to depend on NPAS2 in place of CLOCK (Reick *et al.*, 2001). When the feeding time is abruptly shifted, the NPAS2 deficient mice cannot adapt their feeding behavior quickly to the change in feeding time, and as a result, they lose weight to be sick (Dudley *et al.*, 2003). Notably, the restricted feeding cycle shifts the phase of the circadian gene expression in the forebrain, such as the cerebral cortex and hippocampus (Wakamatsu *et al.*, 2001b; Dudley *et al.*, 2003). Taken together, it is possible that the change in feeding time schedule shifts the phase of the forebrain clock firstly (presumably by sensory stimuli), and then alters the time of feeding behavior to reset the peripheral clocks. Under normal *ad libitum* feeding condition, the SCN and forebrain may synchronously control the feeding behavior.

The control of the behavioral rhythm by the SCN includes neural and humoral signals (Fig. 5). Through the neural connections, the SCN transmit circadian output signals to other brain areas by the electrical activity rhythm represented by the spontaneous firing rate. This rhythm is generated by circadian modulation of calcium current which contributes to the daytime oscillations in membrane potential (Pennartz *et al.*, 2002). As the humoral signals, genes for two polypeptides, transforming growth factor- α (TGF α) and prokineticin 2 (PK2), are rhythmically expressed in the SCN with daytime peaks (Kramer *et al.*, 2001; Cheng *et al.*, 2002), and the expression of PK2 gene is regulated by E box enhancer as mentioned above. The receptor for TGF α is expressed in the hypothalamic subparaventricular zone receiving a major projection from the SCN (Kramer *et al.*,

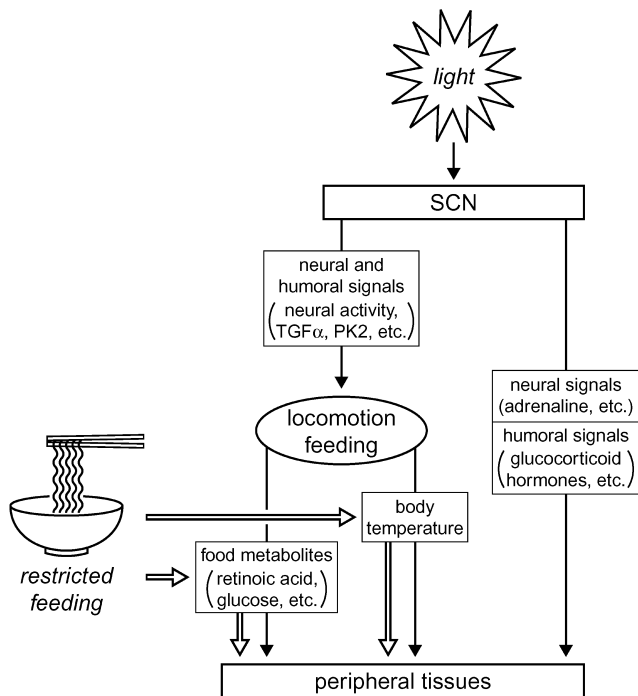


Fig. 5. Resetting signals of peripheral clocks. PK2, prokineticin 2; TGF α , transforming growth factor- α .

2001), while the receptor for PK2 is present in many primary target areas of SCN efferents, as well as in the SCN, but not in the subparaventricular zone (Cheng *et al.*, 2002). The infusion of each peptide into the hamster or rat brain ventricles inhibits the locomotor activity, suggesting that the rhythmic expression of these peptides plays an important role in regulation of the behavioral rhythm.

The SCN can also control the peripheral clocks directly (Fig. 5). Immortalized SCN cells impose the rhythmic metabolism and *Per* gene expression on co-cultured NIH-3T3 fibroblasts even when the two types of cells are separated by a semi-permeable membrane, indicating the regulation of the peripheral clock by some diffusible factors from the SCN (Allen *et al.*, 2001). On the other hand, the expression of *Per1* gene in the liver is stimulated *in vivo* by injection of adrenaline or by sympathetic nerve stimulation in the morning (Terazono *et al.*, 2003). In addition, the daily injection of adrenaline to SCN-lesioned mice restores the rhythmic gene expression in the liver. These observations suggest that the resetting of the liver clock by the SCN involves the polysynaptic autonomic neural pathways between the SCN and liver.

In sum, the SCN seems to control the oscillation of peripheral clocks directly and indirectly by virtue of multiple neural, humoral, and other signals in a cooperative manner (Fig. 5).

PERSPECTIVES

The molecular and genetic approaches with mice significantly contributed to the understanding of the mammalian

clock system in the SCN. On the other hand, similar analyses of the peripheral clock and its resetting have just started, and it should be a major issue for the future studies. In addition, it is of note that the period length of the circadian clock is far more stable to ambient temperature changes than any other biological processes (Ruby *et al.*, 1999; Tsuchiya *et al.*, 2003). However, the molecular mechanism underlying the temperature compensation is largely unknown. Because the *tau* mutation is known to affect this process (Tosini and Menaker, 1998), analyses of the clock protein phosphorylation may help to understand the stable oscillation of the circadian clock.

REFERENCES

- Aida R, Moriya T, Araki M, Akiyama M, Wada K, Wada E, Shibata S (2002) Gastrin-releasing peptide mediates photic entrainable signals to dorsal subsets of suprachiasmatic nucleus via induction of *Period* gene in mice. *Mol Pharmacol* 61: 26–34
- Akashi M, Tsuchiya Y, Yoshino T, Nishida E (2002) Control of intracellular dynamics of mammalian period proteins by casein kinase I ϵ (CKI ϵ) and CKI δ in cultured cells. *Mol Cell Biol* 22: 1693–1703
- Akhtar RA, Reddy AB, Maywood ES, Clayton JD, King VM, Smith AG, Gant TW, Hastings MH, Kyriacou CP (2002) Circadian cycling of the mouse liver transcriptome, as revealed by cDNA microarray, is driven by the suprachiasmatic nucleus. *Curr Biol* 12: 540–550
- Akiyama M, Kouzu Y, Takahashi S, Wakamatsu H, Moriya T, Maetani M, Watanabe S, Tei H, Sakaki Y, Shibata S (1999) Inhibition of light- or glutamate-induced *mPer1* expression represses the phase shifts into the mouse circadian locomotor and suprachiasmatic firing rhythms. *J Neurosci* 19: 1115–1121
- Albrecht U, Sun ZS, Eichele G, Lee CC (1997) A differential response of two putative mammalian circadian regulators, *mper1* and *mper2*, to light. *Cell* 91: 1055–1064
- Albrecht U, Zheng B, Larkin D, Sun ZS, Lee CC (2001) *mPer1* and *mPer2* are essential for normal resetting of the circadian clock. *J Biol Rhythms* 16: 100–104
- Allen G, Rappe J, Earnest DJ, Cassone VM (2001) Oscillating on borrowed time: diffusible signals from immortalized suprachiasmatic nucleus cells regulate circadian rhythmicity in cultured fibroblasts. *J Neurosci* 21: 7937–7943
- Balsalobre A, Damiola F, Schibler U (1998) A serum shock induces circadian gene expression in mammalian tissue culture cells. *Cell* 93: 929–937
- Balsalobre A, Brown SA, Marcacci L, Tronche F, Kellendonk C, Reichardt HM, Schütz G, Schibler U (2000a) Resetting of circadian time in peripheral tissues by glucocorticoid signaling. *Science* 289: 2344–2347
- Balsalobre A, Marcacci L, Schibler U (2000b) Multiple signaling pathways elicit circadian gene expression in cultured Rat-1 fibroblasts. *Curr Biol* 10: 1291–1294
- Barnes JW, Tischkau SA, Barnes JA, Mitchell JW, Burgoon PW, Hickok JR, Gillette MU (2003) Requirement of mammalian *Timeless* for circadian rhythmicity. *Science* 302: 439–442
- Berson DM, Dunn FA, Takao M (2002) Phototransduction by retinal ganglion cells that set the circadian clock. *Science* 295: 1070–1073
- Berson DM (2003) Strange vision: ganglion cells as circadian photoreceptors. *Trends Neurosci* 26: 314–320
- Brown SA, Zumbrohn G, Fleury-Olela F, Preitner N, Schibler U (2002) Rhythms of mammalian body temperature can sustain peripheral circadian clocks. *Curr Biol* 12: 1574–1583

- Butcher GQ, Dziema H, Collamore M, Burgoon PW, Obrietan K (2002) The p42/44 mitogen-activated protein kinase pathway couples photic input to circadian clock entrainment. *J Biol Chem* 277: 29519–29525
- Cheng MY, Bullock CM, Li C, Lee AG, Bermak JC, Belluzzi J, Weaver DR, Leslie FM, Zhou QY (2002) Prokineticin 2 transmits the behavioural circadian rhythm of the suprachiasmatic nucleus. *Nature* 417: 405–410
- Coogan AN, Piggins HD (2003) Circadian and photic regulation of phosphorylation of ERK1/2 and Elk-1 in the suprachiasmatic nuclei of the Syrian hamster. *J Neurosci* 23: 3085–3093
- Crosio C, Cermakian N, Allis CD, Sassone-Corsi P (2000) Light induces chromatin modification in cells of the mammalian circadian clock. *Nat Neurosci* 3: 1241–1247
- Damiola F, Le Minh N, Preitner N, Kornmann B, Fleury-Olela F, Schibler U (2000) Restricted feeding uncouples circadian oscillators in peripheral tissues from the central pacemaker in the suprachiasmatic nucleus. *Genes Dev* 14: 2950–2961
- Davidson AJ, Stokkan KA, Yamazaki S, Menaker M (2002) Food-anticipatory activity and liver *per1-luc* activity in diabetic transgenic rats. *Physiol Behav* 76: 21–26
- Ding JM, Buchanan GF, Tischkau SA, Chen D, Kuriashkina L, Faiman LE, Alster JM, McPherson PS, Campbell KP, Gillette MU (1998) A neuronal ryanodine receptor mediates light-induced phase delays of the circadian clock. *Nature* 394: 381–384
- Dudley CA, Erbel-Sieler C, Estill SJ, Reick M, Franken P, Pitts S, McKnight SL (2003) Altered patterns of sleep and behavioral adaptability in NPAS2-deficient mice. *Science* 301: 379–383
- Duffield GE, Best JD, Meurers BH, Bittner A, Loros JJ, Dunlap JC (2002) Circadian programs of transcriptional activation, signaling, and protein turnover revealed by microarray analysis of mammalian cells. *Curr Biol* 12: 551–557
- Dunlap JC (1999) Molecular bases for circadian clocks. *Cell* 96: 271–290
- Dziema H, Oatis B, Butcher GQ, Yates R, Hoyt KR, Obrietan K (2003) The ERK/MAP kinase pathway couples light to immediate-early gene expression in the suprachiasmatic nucleus. *Eur J Neurosci* 17: 1617–1627
- Eide EJ, Vielhaber EL, Hinz WA, Virshup DM (2002) The circadian regulatory proteins BMAL1 and cryptochromes are substrates of casein kinase I ϵ . *J Biol Chem* 277: 17248–17254
- Etchegaray JP, Lee C, Wade PA, Reppert SM (2003) Rhythmic histone acetylation underlies transcription in the mammalian circadian clock. *Nature* 421: 177–182
- Foster RG, Hankins MW (2002) Non-rod, non-cone photoreception in the vertebrates. *Prog Retin Eye Res* 21: 507–527
- Fu L, Pelicano H, Liu J, Huang P, Lee CC (2002) The circadian gene *Period2* plays an important role in tumor suppression and DNA damage response in vivo. *Cell* 111: 41–50
- Gau D, Lemberger T, von Gall C, Kretz O, Le Minh N, Gass P, Schmid W, Schibler U, Korf HW, Schütz G (2002) Phosphorylation of CREB Ser142 regulates light-induced phase shifts of the circadian clock. *Neuron* 34: 245–253
- Gillette MU, Mitchell JW (2002) Signaling in the suprachiasmatic nucleus: selectively responsive and integrative. *Cell Tissue Res* 309: 99–107
- Ginty DD, Kornhauser JM, Thompson MA, Bading H, Mayo KE, Takahashi JS, Greenberg ME (1993) Regulation of CREB phosphorylation in the suprachiasmatic nucleus by light and a circadian clock. *Science* 260: 238–241
- Gooley JJ, Lu J, Chou TC, Scammell TE, Saper CB (2001) Melanopsin in cells of origin of the retinohypothalamic tract. *Nat Neurosci* 4: 1165
- Gréchez-Cassiau A, Panda S, Lacoche S, Teboul M, Azmi S, Laudet V, Hogenesch JB, Taneja R, Delaunay F (2004) The transcriptional repressor STRA13 regulates a subset of peripheral circadian outputs. *J Biol Chem* 279: 1141–1150
- Grundschober C, Delaunay F, Pühlhofer A, Triqueneaux G, Laudet V, Bartfalvi T, Nef P (2001) Circadian regulation of diverse gene products revealed by mRNA expression profiling of synchronized fibroblasts. *J Biol Chem* 276: 46751–46758
- Hamada T, LeSauter J, Venuti JM, Silver R (2001) Expression of *Period* genes: rhythmic and nonrhythmic compartments of the suprachiasmatic nucleus pacemaker. *J Neurosci* 21: 7742–7750
- Hamada T, LeSauter J, Lokshin M, Romero MT, Yan L, Venuti JM, Silver R (2003) Calbindin influences response to photic input in suprachiasmatic nucleus. *J Neurosci* 23: 8820–8826
- Hannibal J, Hinderesson P, Knudsen SM, Georg B, Fahrenkrug J (2002) The photopigment melanopsin is exclusively present in pituitary adenylate cyclase-activating polypeptide-containing retinal ganglion cells of the retinohypothalamic tract. *J Neurosci* 22: RC191
- Hara R, Wan K, Wakamatsu H, Aida R, Moriya T, Akiyama M, Shibata S (2001) Restricted feeding entrains liver clock without participation of the suprachiasmatic nucleus. *Genes Cells* 6: 269–278
- Harmar AJ, Marston HM, Shen S, Spratt C, West KM, Sheward WJ, Morrison CF, Dorin JR, Piggins HD, Reubi JC, Kelly JS, Maywood ES, Hastings MH (2002) The VPAC₂ receptor is essential for circadian function in the mouse suprachiasmatic nuclei. *Cell* 109: 497–508
- Hastings MH, Reddy AB, Maywood ES (2003) A clockwork web: circadian timing in brain and periphery, in health and disease. *Nat Rev Neurosci* 4: 649–661
- Hattar S, Liao HW, Takao M, Berson DM, Yau KW (2002) Melanopsin-containing retinal ganglion cells: architecture, projections, and intrinsic photosensitivity. *Science* 295: 1065–1070
- Hattar S, Lucas RJ, Mrosovsky N, Thompson S, Douglas RH, Hankins MW, Lem J, Biel M, Hofmann F, Foster RG, Yau KW (2003) Melanopsin and rod-cone photoreceptive systems account for all major accessory visual functions in mice. *Nature* 424: 76–81
- Hayashi Y, Sanada K, Hirota T, Shimizu F, Fukada Y (2003) p38 mitogen-activated protein kinase regulates oscillation of chick pineal circadian clock. *J Biol Chem* 278: 25166–25171
- Hirota T, Okano T, Kokame K, Shirotani-Ikejima H, Miyata T, Fukada Y (2002) Glucose down-regulates *Per1* and *Per2* mRNA levels and induces circadian gene expression in cultured rat-1 fibroblasts. *J Biol Chem* 277: 44244–44251
- Honma S, Kawamoto T, Takagi Y, Fujimoto K, Sato F, Noshiro M, Kato Y, Honma K (2002) *Dec1* and *Dec2* are regulators of the mammalian molecular clock. *Nature* 419: 841–844
- Humphries A, Klein D, Baler R, Carter DA (2002) cDNA array analysis of pineal gene expression reveals circadian rhythmicity of the dominant negative helix-loop-helix protein-encoding gene, *Id-1*. *J Neuroendocrinol* 14: 101–108
- Ikeda M, Sugiyama T, Wallace CS, Gompf HS, Yoshioka T, Miyawaki A, Allen CN (2003) Circadian dynamics of cytosolic and nuclear Ca²⁺ in single suprachiasmatic nucleus neurons. *Neuron* 38: 253–263
- Jin X, Shearman LP, Weaver DR, Zylka MJ, De Vries GJ, Reppert SM (1999) A molecular mechanism regulating rhythmic output from the suprachiasmatic circadian clock. *Cell* 96: 57–68
- Jung H, Choe Y, Kim H, Park N, Son GH, Khang I, Kim K (2003) Involvement of CLOCK:BMAL1 heterodimer in serum-responsive *mPer1* induction. *Neuroreport* 14: 15–19
- Kawamoto T, Noshiro M, Sato F, Maemura K, Takeda N, Nagai R, Iwata T, Fujimoto K, Furukawa M, Miyazaki K, Honma S, Honma K, Kato Y (2004) A novel autodeedback loop of *Dec1* transcription involved in circadian rhythm regulation. *Biochem Biophys Res Commun* 313: 117–124
- Keesler GA, Camacho F, Guo Y, Virshup D, Mondadori C, Yao Z (2000) Phosphorylation and destabilization of human period 1 clock protein by human casein kinase I ϵ . *Neuroreport* 11: 951–

955

- King DP, Takahashi JS (2000) Molecular genetics of circadian rhythms in mammals. *Annu Rev Neurosci* 23: 713–742
- Kita Y, Shiozawa M, Jin W, Majewski RR, Besharse JC, Greene AS, Jacob HJ (2002) Implications of circadian gene expression in kidney, liver and the effects of fasting on pharmacogenomic studies. *Pharmacogenetics* 12: 55–65
- Klein DC, Coon SL, Roseboom PH, Weller JL, Bernard M, Gastel JA, Zatz M, Iuvone PM, Rodriguez IR, Bégay V, Falcón J, Cahill GM, Cassone VM, Baler R (1997) The melatonin rhythm-generating enzyme: molecular regulation of serotonin *N*-acetyltransferase in the pineal gland. *Recent Prog Horm Res* 52: 307–358
- Kondratov RV, Chernov MV, Kondratova AA, Gorbacheva VY, Gudkov AV, Antoch MP (2003) BMAL1-dependent circadian oscillation of nuclear CLOCK: posttranslational events induced by dimerization of transcriptional activators of the mammalian clock system. *Genes Dev* 17: 1921–1932
- Kramer A, Yang FC, Snodgrass P, Li X, Scammell TE, Davis FC, Weitz CJ (2001) Regulation of daily locomotor activity and sleep by hypothalamic EGF receptor signaling. *Science* 294: 2511–2515
- Le Minh N, Damiola F, Tronche F, Schütz G, Schibler U (2001) Glucocorticoid hormones inhibit food-induced phase-shifting of peripheral circadian oscillators. *EMBO J* 20: 7128–7136
- Lee C, Etchegaray JP, Cagampang FRA, Loudon ASI, Reppert SM (2001) Posttranslational mechanisms regulate the mammalian circadian clock. *Cell* 107: 855–867
- Lee HS, Nelms JL, Nguyen M, Silver R, Lehman MN (2003) The eye is necessary for a circadian rhythm in the suprachiasmatic nucleus. *Nat Neurosci* 6: 111–112
- Lowrey PL, Shimomura K, Antoch MP, Yamazaki S, Zemenides PD, Ralph MR, Menaker M, Takahashi JS (2000) Positional syntenic cloning and functional characterization of the mammalian circadian mutation *tau*. *Science* 288: 483–491
- Lucas RJ, Hattar S, Takao M, Berson DM, Foster RG, Yau KW (2003) Diminished pupillary light reflex at high irradiances in melanopsin-knockout mice. *Science* 299: 245–247
- Maemura K, de la Monte SM, Chin MT, Layne MD, Hsieh CM, Yet SF, Perrella MA, Lee ME (2000) CLIF, a novel cycle-like factor, regulates the circadian oscillation of plasminogen activator inhibitor-1 gene expression. *J Biol Chem* 275: 36847–36851
- Matsuo T, Yamaguchi S, Mitsui S, Emi A, Shimoda F, Okamura H (2003) Control mechanism of the circadian clock for timing of cell division in vivo. *Science* 302: 255–259
- McNamara P, Seo SB, Rudic RD, Sehgal A, Chakravarti D, Fitzgerald GA (2001) Regulation of CLOCK and MOP4 by nuclear hormone receptors in the vasculature: a humoral mechanism to reset a peripheral clock. *Cell* 105: 877–889
- Mitsui S, Yamaguchi S, Matsuo T, Ishida Y, Okamura H (2001) Antagonistic role of E4BP4 and PAR proteins in the circadian oscillatory mechanism. *Genes Dev* 15: 995–1006
- Miyazaki K, Mesaki M, Ishida N (2001) Nuclear entry mechanism of rat PER2 (rPER2): role of rPER2 in nuclear localization of CRY protein. *Mol Cell Biol* 21: 6651–6659
- Moore RY, Speh JC, Leak RK (2002) Suprachiasmatic nucleus organization. *Cell Tissue Res* 309: 89–98
- Morris ME, Viswanathan N, Kuhlman S, Davis FC, Weitz CJ (1998) A screen for genes induced in the suprachiasmatic nucleus by light. *Science* 279: 1544–1547
- Nagano M, Adachi A, Nakahama K, Nakamura T, Tamada M, Meyer-Bernstein E, Sehgal A, Shigeyoshi Y (2003) An abrupt shift in the day/night cycle causes desynchrony in the mammalian circadian center. *J Neurosci* 23: 6141–6151
- Nakahata Y, Okumura N, Shima T, Okada M, Nagai K (2000) Light-induced tyrosine phosphorylation of BIT in the rat suprachiasmatic nucleus. *J Neurochem* 74: 2436–2444
- Nakahata Y, Okumura N, Otani H, Hamada J, Numakawa T, Sano S, Nagai K (2003) Stimulation of BIT induces a circadian phase shift of locomotor activity in rats. *Brain Res* 976: 194–201
- Nakaya M, Sanada K, Fukada Y (2003) Spatial and temporal regulation of mitogen-activated protein kinase phosphorylation in the mouse suprachiasmatic nucleus. *Biochem Biophys Res Commun* 305: 494–501
- Newman LA, Walker MT, Brown RL, Cronin TW, Robinson PR (2003) Melanopsin forms a functional short-wavelength photopigment. *Biochemistry* 42: 12734–12738
- Nomura K, Takeuchi Y, Yamaguchi S, Okamura H, Fukunaga K (2003) Involvement of calcium/calmodulin-dependent protein kinase II in the induction of *mPer1*. *J Neurosci Res* 72: 384–392
- Obrietan K, Impey S, Storm DR (1998) Light and circadian rhythmicity regulate MAP kinase activation in the suprachiasmatic nuclei. *Nat Neurosci* 1: 693–700
- Obrietan K, Impey S, Smith D, Athos J, Storm DR (1999) Circadian regulation of cAMP response element-mediated gene expression in the suprachiasmatic nuclei. *J Biol Chem* 274: 17748–17756
- Oishi K, Miyazaki K, Kadota K, Kikuno R, Nagase T, Atsumi G, Ohkura N, Azama T, Mesaki M, Yukimasa S, Kobayashi H, Iitaka C, Umehara T, Horikoshi M, Kudo T, Shimizu Y, Yano M, Monden M, Machida K, Matsuda J, Horie S, Todo T, Ishida N (2003) Genome-wide expression analysis of mouse liver reveals CLOCK-regulated circadian output genes. *J Biol Chem* 278: 41519–41527
- Oster H, Werner C, Magnone MC, Maysner H, Feil R, Seeliger MW, Hofmann F, Albrecht U (2003) cGMP-dependent protein kinase II modulates *mPer1* and *mPer2* gene induction and influences phase shifts of the circadian clock. *Curr Biol* 13: 725–733
- Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M, Schultz PG, Kay SA, Takahashi JS, Hogenesch JB (2002a) Coordinated transcription of key pathways in the mouse by the circadian clock. *Cell* 109: 307–320
- Panda S, Sato TK, Castrucci AM, Rollag MD, DeGrip WJ, Hogenesch JB, Provencio I, Kay SA (2002b) Melanopsin (*Opn4*) requirement for normal light-induced circadian phase shifting. *Science* 298: 2213–2216
- Panda S, Provencio I, Tu DC, Pires SS, Rollag MD, Castrucci AM, Pletcher MT, Sato TK, Wiltshire T, Andahazy M, Kay SA, Van Gelder RN, Hogenesch JB (2003) Melanopsin is required for non-image-forming photic responses in blind mice. *Science* 301: 525–527
- Pando MP, Morse D, Cermakian N, Sassone-Corsi P (2002) Phenotypic rescue of a peripheral clock genetic defect via SCN hierarchical dominance. *Cell* 110: 107–117
- Pennartz CMA, de Jeu MTG, Bos NPA, Schaap J, Geurtsen AMS (2002) Diurnal modulation of pacemaker potentials and calcium current in the mammalian circadian clock. *Nature* 416: 286–290
- Pittendrigh CS (1993) Temporal organization: reflections of a Darwinian clock-watcher. *Annu Rev Physiol* 55: 17–54
- Pizzio GA, Hainich EC, Ferreyra GA, Coso OA, Golombek DA (2003) Circadian and photic regulation of ERK, JNK and p38 in the hamster SCN. *Neuroreport* 14: 1417–1419
- Preitner N, Damiola F, Lopez-Molina L, Zakany J, Duboule D, Albrecht U, Schibler U (2002) The orphan nuclear receptor REV-ERB α controls circadian transcription within the positive limb of the mammalian circadian oscillator. *Cell* 110: 251–260
- Provencio I, Foster RG (1995) Circadian rhythms in mice can be regulated by photoreceptors with cone-like characteristics. *Brain Res* 694: 183–190
- Provencio I, Jiang G, De Grip WJ, Hayes WP, Rollag MD (1998) Melanopsin: An opsin in melanophores, brain, and eye. *Proc Natl Acad Sci USA* 95: 340–345
- Provencio I, Rodriguez IR, Jiang G, Hayes WP, Moreira EF, Rollag MD (2000) A novel human opsin in the inner retina. *J Neurosci* 20: 600–605
- Provencio I, Rollag MD, Castrucci AM (2002) Photoreceptive net in

- the mammalian retina. *Nature* 415: 493
- Reick M, Garcia JA, Dudley C, McKnight SL (2001) NPAS2: an analog of clock operative in the mammalian forebrain. *Science* 293: 506–509
- Reppert SM, Weaver DR (2002) Coordination of circadian timing in mammals. *Nature* 418: 935–941
- Ruby NF, Burns DE, Heller HC (1999) Circadian rhythms in the suprachiasmatic nucleus are temperature-compensated and phase-shifted by heat pulses *in vitro*. *J Neurosci* 19: 8630–8636
- Ruby NF, Brennan TJ, Xie X, Cao V, Franken P, Heller HC, O'Hara BF (2002) Role of melanopsin in circadian responses to light. *Science* 298: 2211–2213
- Sanada K, Hayashi Y, Harada Y, Okano T, Fukada Y (2000) Role of circadian activation of mitogen-activated protein kinase in chick pineal clock oscillation. *J Neurosci* 20: 986–991
- Sanada K, Okano T, Fukada Y (2002) Mitogen-activated protein kinase phosphorylates and negatively regulates basic helix-loop-helix-PAS transcription factor BMAL1. *J Biol Chem* 277: 267–271
- Schibler U, Sassone-Corsi P (2002) A web of circadian pacemakers. *Cell* 111: 919–922
- Schibler U, Ripperger J, Brown SA (2003) Peripheral circadian oscillators in mammals: time and food. *J Biol Rhythms* 18: 250–260
- Shearman LP, Zylka MJ, Weaver DR, Kolakowski LF, Jr., Reppert SM (1997) Two *period* homologs: circadian expression and photic regulation in the suprachiasmatic nuclei. *Neuron* 19: 1261–1269
- Shearman LP, Weaver DR (1999) Photic induction of *Period* gene expression is reduced in *Clock* mutant mice. *Neuroreport* 10: 613–618
- Shigeyoshi Y, Taguchi K, Yamamoto S, Takekida S, Yan L, Tei H, Moriya T, Shibata S, Loros JJ, Dunlap JC, Okamura H (1997) Light-induced resetting of a mammalian circadian clock is associated with rapid induction of the *mPer1* transcript. *Cell* 91: 1043–1053
- Shimizu K, Okada M, Nagai K, Fukada Y (2003) Suprachiasmatic nucleus circadian oscillatory protein, a novel binding partner of K-Ras in the membrane rafts, negatively regulates MAPK pathway. *J Biol Chem* 278: 14920–14925
- Stokkan KA, Yamazaki S, Tei H, Sakaki Y, Menaker M (2001) Entrainment of the circadian clock in the liver by feeding. *Science* 291: 490–493
- Storch KF, Lipan O, Leykin I, Viswanathan N, Davis FC, Wong WH, Weitz CJ (2002) Extensive and divergent circadian gene expression in liver and heart. *Nature* 417: 78–83
- Takahashi JS, DeCoursey PJ, Bauman L, Menaker M (1984) Spectral sensitivity of a novel photoreceptive system mediating entrainment of mammalian circadian rhythms. *Nature* 308: 186–188
- Takano A, Shimizu K, Kani S, Buijs RM, Okada M, Nagai K (2000) Cloning and characterization of rat casein kinase 1 ϵ . *FEBS Lett* 477: 106–112
- Terazono H, Mutoh T, Yamaguchi S, Kobayashi M, Akiyama M, Udo R, Ohdo S, Okamura H, Shibata S (2003) Adrenergic regulation of clock gene expression in mouse liver. *Proc Natl Acad Sci USA* 100: 6795–6800
- Tischkau SA, Mitchell JW, Tyan SH, Buchanan GF, Gillette MU (2003a) Ca²⁺/cAMP response element-binding protein (CREB)-dependent activation of *Per1* is required for light-induced signaling in the suprachiasmatic nucleus circadian clock. *J Biol Chem* 278: 718–723
- Tischkau SA, Weber ET, Abbott SM, Mitchell JW, Gillette MU (2003b) Circadian clock-controlled regulation of cGMP-protein kinase G in the nocturnal domain. *J Neurosci* 23: 7543–7550
- Toh KL, Jones CR, He Y, Eide EJ, Hinz WA, Virshup DM, Ptáček LJ, Fu YH (2001) An h*Per2* phosphorylation site mutation in familial advanced sleep phase syndrome. *Science* 291: 1040–1043
- Tosini G, Menaker M (1998) The *tau* mutation affects temperature compensation of hamster retinal circadian oscillators. *Neuroreport* 9: 1001–1005
- Travnickova-Bendova Z, Cermakian N, Reppert SM, Sassone-Corsi P (2002) Bimodal regulation of *mPeriod* promoters by CREB-dependent signaling and CLOCK/BMAL1 activity. *Proc Natl Acad Sci USA* 99: 7728–7733
- Tsuchiya Y, Akashi M, Nishida E (2003) Temperature compensation and temperature resetting of circadian rhythms in mammalian cultured fibroblasts. *Genes Cells* 8: 713–720
- Ueda HR, Chen W, Adachi A, Wakamatsu H, Hayashi S, Takasugi T, Nagano M, Nakahama K, Suzuki Y, Sugano S, Iino M, Shigeyoshi Y, Hashimoto S (2002) A transcription factor response element for gene expression during circadian night. *Nature* 418: 534–539
- Vielhaber E, Eide E, Rivers A, Gao ZH, Virshup DM (2000) Nuclear entry of the circadian regulator mPER1 is controlled by mammalian casein kinase I ϵ . *Mol Cell Biol* 20: 4888–4899
- Wakamatsu H, Takahashi S, Moriya T, Inouye ST, Okamura H, Akiyama M, Shibata S (2001a) Additive effect of *mPer1* and *mPer2* antisense oligonucleotides on light-induced phase shift. *Neuroreport* 12: 127–131
- Wakamatsu H, Yoshinobu Y, Aida R, Moriya T, Akiyama M, Shibata S (2001b) Restricted-feeding-induced anticipatory activity rhythm is associated with a phase-shift of the expression of *mPer1* and *mPer2* mRNA in the cerebral cortex and hippocampus but not in the suprachiasmatic nucleus of mice. *Eur J Neurosci* 13: 1190–1196
- Watanabe K, Vanecek J, Yamaoka S (2000) In vitro entrainment of the circadian rhythm of vasopressin-releasing cells in suprachiasmatic nucleus by vasoactive intestinal polypeptide. *Brain Res* 877: 361–366
- Yagita K, Okamura H (2000) Forskolin induces circadian gene expression of *rPer1*, *rPer2* and *dbp* in mammalian rat-1 fibroblasts. *FEBS Lett* 465: 79–82
- Yagita K, Tamanini F, van der Horst GTJ, Okamura H (2001) Molecular mechanisms of the biological clock in cultured fibroblasts. *Science* 292: 278–281
- Yagita K, Tamanini F, Yasuda M, Hoeijmakers JH, van der Horst GTJ, Okamura H (2002) Nucleocytoplasmic shuttling and mCRY-dependent inhibition of ubiquitylation of the mPER2 clock protein. *EMBO J* 21: 1301–1314
- Yamaguchi S, Mitsui S, Yan L, Yagita K, Miyake S, Okamura H (2000) Role of DBP in the circadian oscillatory mechanism. *Mol Cell Biol* 20: 4773–4781
- Yamaguchi S, Isejima H, Matsuo T, Okura R, Yagita K, Kobayashi M, Okamura H (2003) Synchronization of cellular clocks in the suprachiasmatic nucleus. *Science* 302: 1408–1412
- Yan L, Okamura H (2002) Gradients in the circadian expression of *Per1* and *Per2* genes in the rat suprachiasmatic nucleus. *Eur J Neurosci* 15: 1153–1162
- Yokota S, Yamamoto M, Moriya T, Akiyama M, Fukunaga K, Miyamoto E, Shibata S (2001) Involvement of calcium-calmodulin protein kinase but not mitogen-activated protein kinase in light-induced phase delays and *Per* gene expression in the suprachiasmatic nucleus of the hamster. *J Neurochem* 77: 618–627
- Yoshimura T, Ebihara S (1996) Spectral sensitivity of photoreceptors mediating phase-shifts of circadian rhythms in retinally degenerate CBA/J (*rd/rd*) and normal CBA/N (*+/+*) mice. *J Comp Physiol A* 178: 797–802
- Young ME, Wilson CR, Razeghi P, Guthrie PH, Taegtmeier H (2002) Alterations of the circadian clock in the heart by streptozotocin-induced diabetes. *J Mol Cell Cardiol* 34: 223–231

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