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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 secrets 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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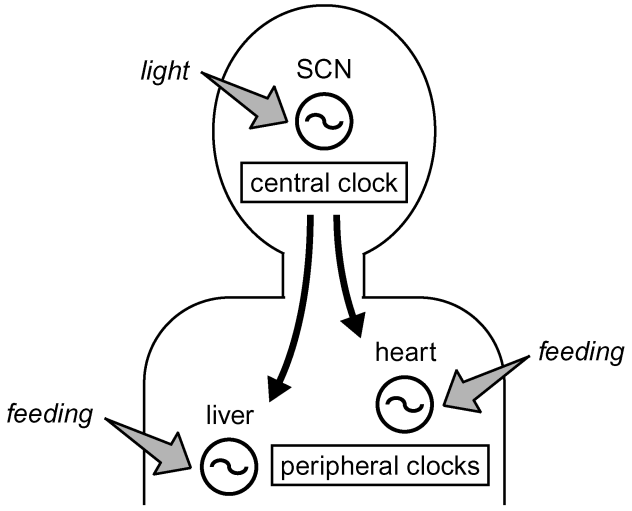


Fig. 1. Central and peripheral clocks in mammals. SCN, suprachiasmatic nucleus.

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-ERBα, 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-ERBα/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 Iε (CKIε) 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

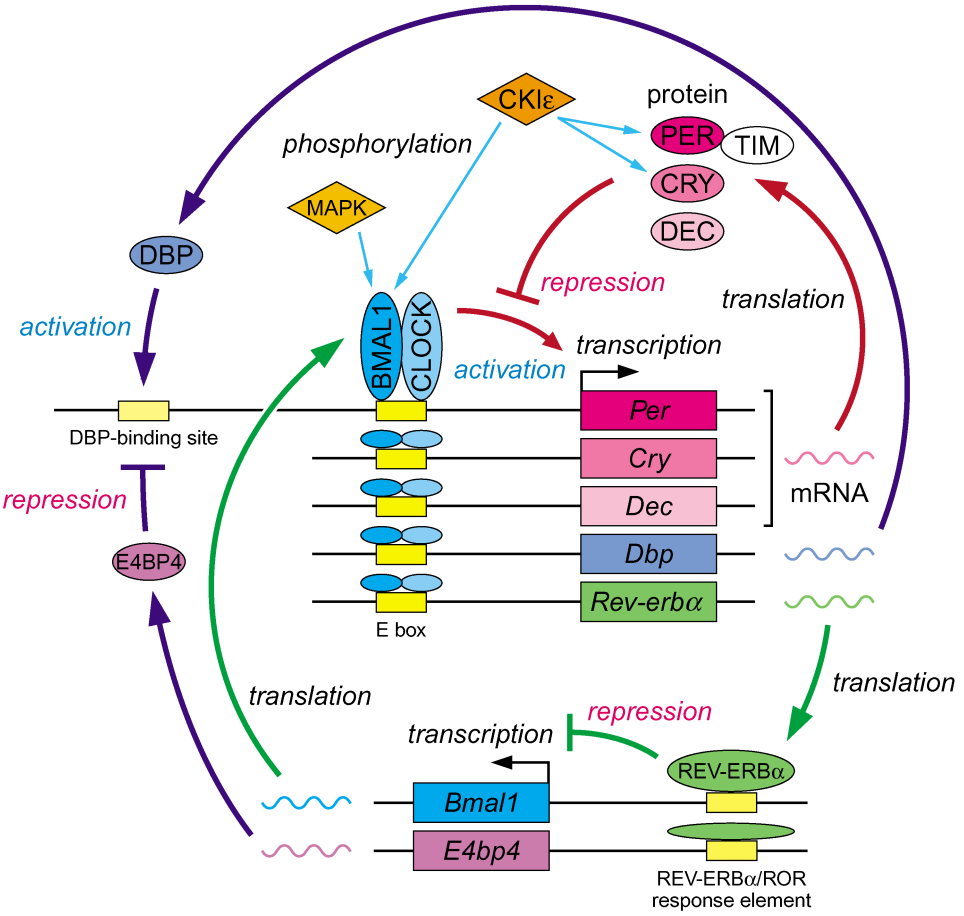


Fig. 2. A model for feedback loops of mammalian circadian clock. CKIε, casein kinase Iε; MAPK, mitogen-activated protein kinase.

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 CKIε 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 CKIε (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 (Obrietan *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

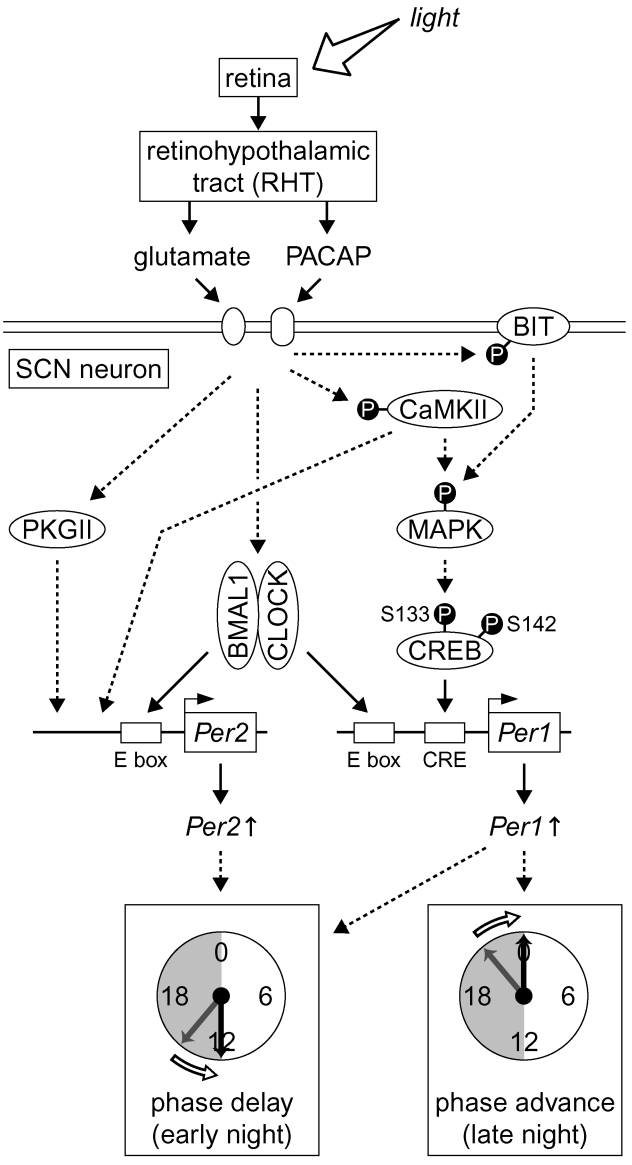
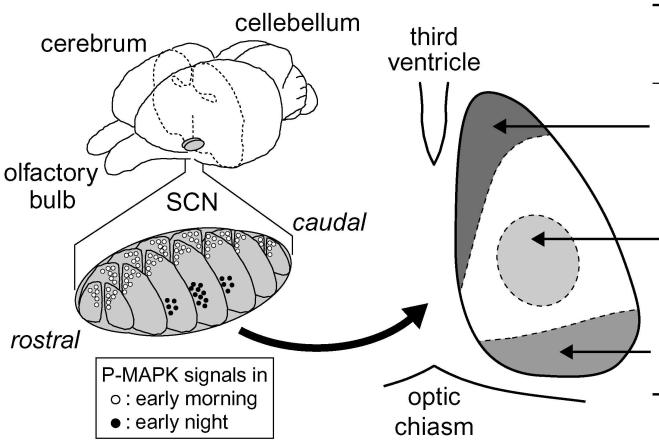


Fig. 3. Photic input signal transduction pathways in the SCN neuron. *Solid* and *dashed lines* indicate the direct and indirect pathways, respectively. BIT, brain immunoglobulin-like molecule with tyrosine-based activation motifs; CaMKII, calcium/calmodulin kinase II; CRE, cAMP response element; CREB,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

strongly suggest that the CRE-mediated induction of *Per1* gene through phopshorylation 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-



SCN subregion	molecules	peak of the rhythm	light response
dorsomedial	*Per* gene & P-MAPK	daytime	no response
core	P-MAPK	nighttime	down-regulation
ventrolateral	*Per* gene & P-MAPK	no rhythm	up-regulation

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, RARα and RXRα (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 (TGFα) 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 TGFα is expressed in the hypothalamic subparaventricular zone receiving a major projection from the SCN (Kramer *et al*.,

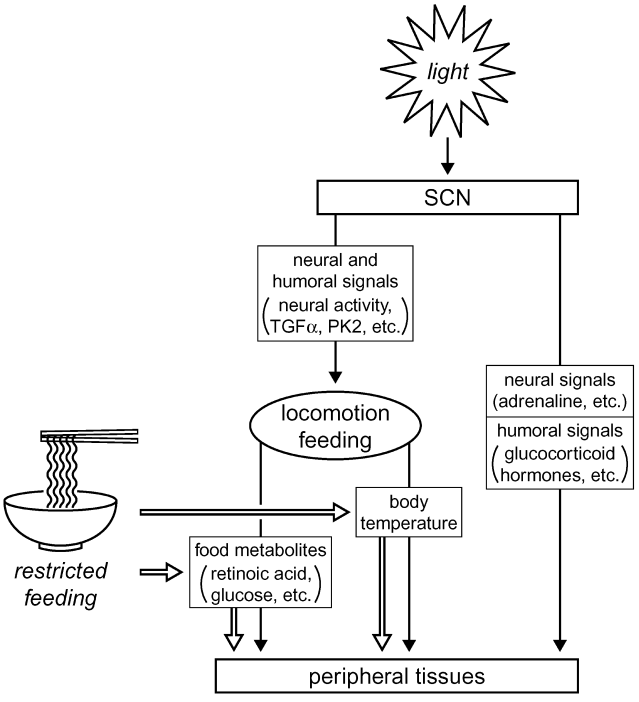


Fig. 5. Resetting signals of peripheral clocks. PK2, prokineticin 2; TGFα, transforming growth factor-α.

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.

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