

Multi-Modal Regulation by Biological Clocks

Subjects: **Biology**

Contributor: YOOL LEE

The circadian clock is a fundamental biological timing mechanism that generates nearly 24 h rhythms of physiology and behaviors, including sleep/wake cycles, hormone secretion, and metabolism. Evolutionarily, the endogenous clock is thought to confer living organisms, including humans, with survival benefits by adapting internal rhythms to the day and night cycles of the local environment. Mirroring the evolutionary fitness bestowed by the circadian clock, daily mismatches between the internal body clock and environmental cycles, such as irregular work (e.g., night shift work) and life schedules (e.g., jet lag, mistimed eating), have been recognized to increase the risk of cardiac, metabolic, and neurological diseases. Moreover, increasing numbers of studies with cellular and animal models have detected the presence of functional circadian oscillators at multiple levels, ranging from individual neurons and fibroblasts to brain and peripheral organs. These oscillators are tightly coupled to timely modulate cellular and bodily responses to physiological and metabolic cues.

circadian clock

circadian disruption

SCN

brain clocks

peripheral clocks

redox metabolism

1. Introduction

Since the formation and settlement of our solar system roughly 4.5 billion years ago, the Earth has been rotating on its axis and revolving around the Sun, bringing about continuous light and dark cycles on this planet. In accordance with these cycles, nearly all living unicellular and multicellular organisms have evolved rhythmic life processes controlled by the circadian clock (from the Latin phrase *circa diem* meaning “about a day”), which have about 24 h periods and constantly predict and adapt to daily environmental changes ^[1]. This internal timing system is believed to help organisms survive by increasing their ability to timely anticipate the cyclic changes of light and food availability as well as predation risk. At the unicellular level, the timely compartmentalization of the organism’s biochemical, metabolic, and redox processes, coordinated by the intrinsic clockwork, ensures the temporal fitness of cell physiology and functions across species ^[2]. In lower eukaryotic species, biological timers may help single-celled organisms escape the DNA-damaging effects of ionizing radiation from sunlight as well as oxidative stress during cell division ^[3]. In higher, complex organisms, including humans, common cellular oscillators constitute the brain and peripheral tissue clocks that interconnect to form a circadian network at the whole-body level. Interestingly, human or cross-species studies reveal differences in behavioral chronotype not only between species but also within and between different individuals of each species, suggesting the extent of intra- and inter-subject variability of circadian timing systems ^{[4][5][6][7][8]}. With periodic anticipation and synchronization to day–night cycles, these internal timing systems, in concert, coordinate rhythmic physiology and behaviors such as the sleep–wake

cycle, body temperature, blood pressure, hormone production, neural and immune system processes, and cell proliferation [9][10].

In contrast to the adaptive benefits of circadian rhythms, modern lifestyles result in misalignment of the working, eating, and sleeping cycles, relative to natural 24 h light/dark cycles, that historically defined human existence. Such misalignment has been found to increase our susceptibility to the onset and development of cardiometabolic, digestive, immune, and neuropsychiatric disorders, as well as cancers [11][12][13][14]. Several studies in animal models containing genetic mutations of clock genes or those exposed to forced circadian desynchrony regimens have also reinforced the causal relationship between circadian disturbances and disease pathologies [15][16][17][18][19][20]. Furthermore, increasing numbers of studies in cellular and animal models have reported that cellular and bodily rhythms are highly influenced by physiological and metabolic stimuli, such as diet, exercise, metabolites, ions, and gaseous molecules [21][22][23]. In this review, we will describe recent advances in chronobiology as well as the roles of central and peripheral clocks in physiology and diseases, with a particular focus on the dynamic interactions between biological timing systems and metabolic factors.

2. Multi-Modal Mechanisms of Circadian Physiology

The basic circadian rhythm mechanism, conserved across living species on earth, is typically characterized by a cell-autonomous autoregulatory feedback loop [3][24]. In eukaryotes, a subset of dedicated positive and negative clock regulators forms the interlocked transcriptional translational feedback loop (TTFL), which constitutes a cell-intrinsic oscillator that drives the rhythmic expression of output genes involved in metabolic, biosynthetic, and signal transduction pathways [9]. In mammals, the BMAL1 and CLOCK transcriptional activator complex cyclically drives the transcription of its own repressors, period (PER) and cryptochrome (CRY). The core oscillator is complemented by a second loop in which periodic expression of *BMAL1* is maintained by the REV-ERB α/β repressor and ROR α/β activator proteins [25] (**Figure 1**).

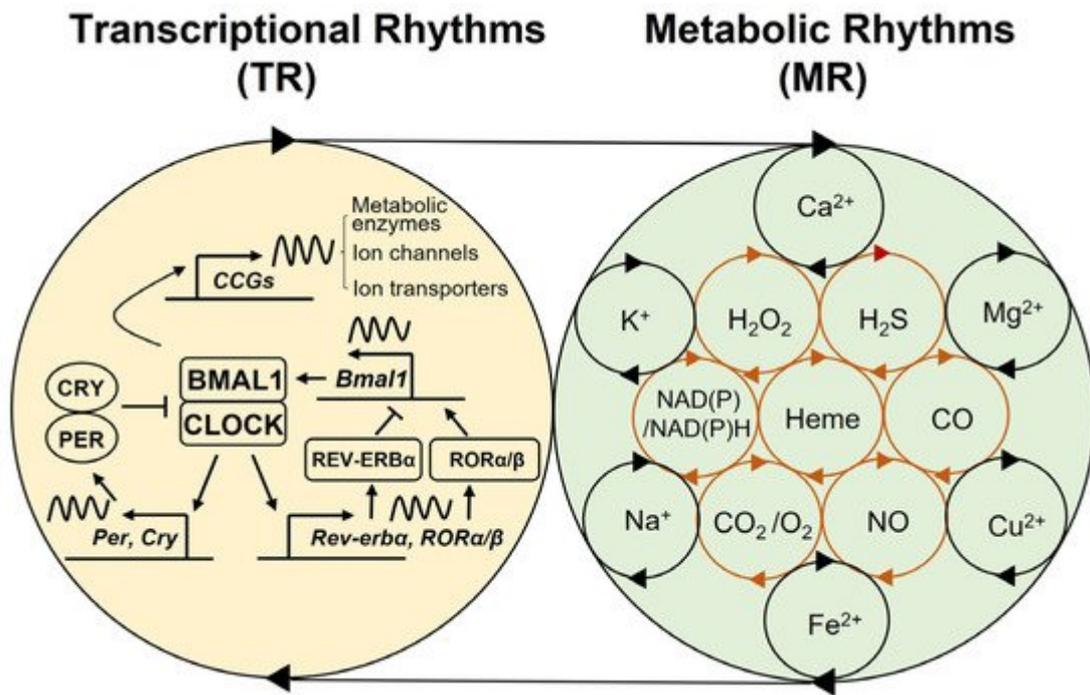


Figure 1. Coupled-cellular oscillators. Bidirectional regulation between transcriptional and metabolic rhythms. The auto-regulatory feedback cycles between the CLOCK/BMAL1 transcriptional activator complex and its transcriptional repressors (PER/CRY, REV-ERB α) and activators (ROR α/β), constituting the molecular clock oscillator. This oscillator drives the expression of multiple clock-controlled genes (CCGs), such as metabolic enzymes, ion channels, and transporters. The transcriptional rhythms (TR) mediate metabolic rhythms (MR) involving the cyclic synthesis, degradation, and transport (e.g., influx/efflux) of redox factors, gases, and ions, which, in turn, provide feedback that regulates the TR, constituting coupled-cellular oscillators.

Besides the core regulatory loops, multiple levels of epigenetic, posttranscriptional, and posttranslational regulation involving various kinases and phosphatases, ubiquitin–proteasome pathway components, nuclear–cytoplasmic transporters, non-coding RNAs, and chromatin remodelers contribute to the molecular clockwork, thus coordinating temporal programs via multiple clock–output genes involved in cellular physiology and metabolism [26][27][28][29][30][31][32][33]. Notably, recent large-scale genomic studies reveal that ~50% of mammalian genes exhibit circadian regulation in at least one tissue, although the identity of genes expressed rhythmically varies from tissue to tissue [34][35][36]. In addition, multi-scale omics studies demonstrated circadian regulation of the epigenome, the metabolome, the proteome/phosphoproteome, and the microbiome [34][35][37][38][39][40][41][42][43][44][45]. These studies reveal that proteins or metabolites display different patterns of oscillations relative to transcript rhythms in a given tissue (e.g., hippocampus, liver), and oscillations at all levels can be reprogrammed by circadian disturbances, such as sleep deprivation, jet lag, high-fat diet, and aging.

In mammalian species, the circadian clock machinery is shared across the brain and peripheral organ systems, constituting a body-wide circadian network (Figure 2).

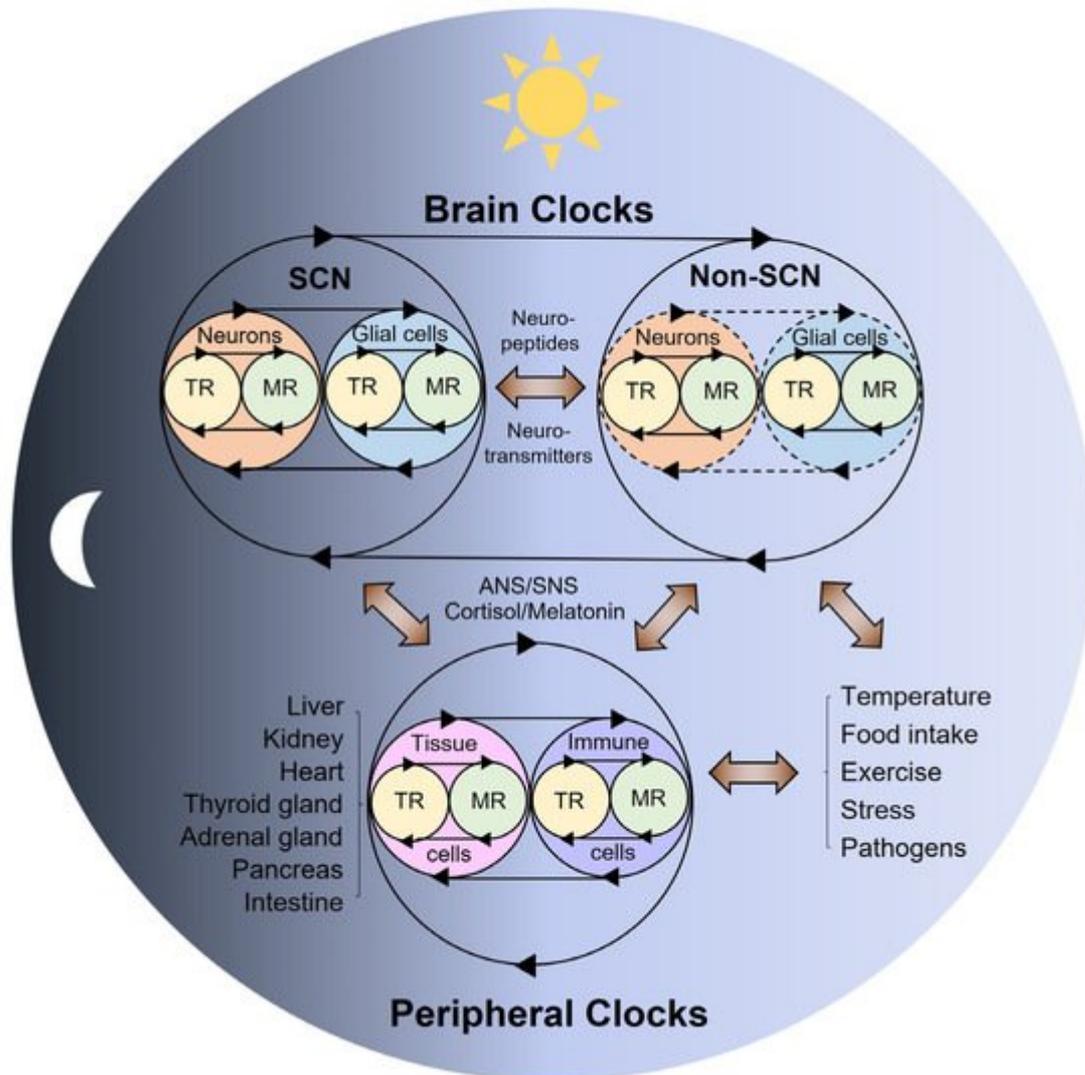


Figure 2. Coupled-tissue oscillators. Reciprocal crosstalk between the brain and peripheral clocks. The coupled TR and MR oscillators are thought to be commonly present across all body cells. Neurons and glial cells (e.g., astrocytes, microglia) interact to form the SCN central clock and non-SCN clocks in the brain. These autonomous brain clocks communicate with each other via neurotransmitters or neuropeptides, and with multiple peripheral tissue clocks via systemic innervations (ANS/SNS) or hormonal signals (e.g., cortisol, melatonin) in response to light–dark cycles. On the other hand, peripheral organs possess tissue autonomous clocks that can respond to non-photic physiological and environmental cues (e.g., temperature, food intake, exercise, stress) and provide feedback that influences the brain clocks via immune, metabolic, and endocrine signals. TR—transcriptional rhythms; MR—metabolic rhythms; ANS—autonomic nervous system; SNS—sympathetic nervous system.

The intracellular oscillators, in approximately 20,000 neurons, comprise the hypothalamic suprachiasmatic nucleus (SCN), a central clock in the rodent brain. The SCN in humans has been found to contain a total number of neurons close to 100,000, though these numbers decline with age [46][47][48]. The SCN consists of different subtypes of neurons that express the neurotransmitter c-aminobutyric acid (GABA), an inhibitory neurotransmitter in the brain, alongside a range of neuropeptides such as vasoactive intestinal peptide (VIP), arginine vasopressin (AVP), and their cognate receptors (VPAC2 and AVPR1A/B) [49][50][51][52]. These GABAergic/peptidergic SCN

neurons interact among themselves or with the other neurons in extra-SCN brain regions, constituting the main output pathway of the clock. Notably, a recent study has demonstrated that the VIP-VPAC2 neuropeptidergic axis plays a central role in mediating the endogenous pacemaking function of the SCN circadian circuit [53]. In line with this, the suprachiasmatic VIP neurons (SCN^{VIP}) have been shown to be required for normal circadian behaviors via functional connectivity between SCN^{VIP} neurons and dorsomedial hypothalamic neurons [54]. Interestingly, recent single-cell RNA sequencing (scRNASeq) studies with mouse SCN slice revealed novel neuronal phenotypes and interaction networks involved in the central clock, including the identification of five SCN neuronal subtypes, with cluster-specific marker genes of VIP, AVP, gastrin-releasing peptide (GRP), cholecystokinin (CCK), and the cell adhesion regulator C1qI3 [55][56]. Additional scRNASeq study has also identified a subgroup of cells expressing Prokineticin2 (Prok2) and its cognate receptor (ProkR2) found to be topologically and functionally distinct pacemaking element of the central clock [57]. Thus, these studies highlight diverse cellular sub-populations within the neuropeptidergic topology of the SCN, which may differently contribute to the central pacemaker function. Notably, recent studies have shown that astrocytes harbor distinct rhythmic properties, such as anti-phasic Ca²⁺ rhythms, that direct the circadian rhythmicity of SCN neurons and behavior [58][59][60]. This work suggests the importance of bipartite intercellular communication between astrocytes and neurons in modulating SCN pacemaker functions, beyond neuronal regulation of the central clock.

Along with endogenous circadian pacemaking activity, the SCN central clock also mediates the periodic synchronization of internal body rhythms with external day and night cycles by communicating retinal light information received from the retinohypothalamic tract (RHT) to peripheral clock systems [26]. In a hierarchical organization model, the SCN master clock coordinates the circadian phases of individual subordinate clocks in other brain regions via rhythmic release of neurotransmitters and neuropeptides as well as in peripheral tissues via systemic hormonal secretion and neural innervations, thus generating rhythmic output physiology and behaviors that are in keeping with the daily changes in environment and needs [61][62][63][64]. For example, the SCN coordinates the rhythmic anti-phasic secretion of the night sleep hormone melatonin in the pineal gland and the morning stress hormone glucocorticoid in the adrenal glands via the sympathetic nervous system, ensuring daily rhythms in sleep/wake, as well as neural, metabolic, and immune functions [65][66][67]. In addition, the brain master clock controls peripheral clock functions in the heart, kidney, pancreas, lung, intestine, and thyroid glands by circadian regulation of the autonomic nervous system [68][69][70][71][72][73].

Besides SCN-driven clock entrainment, a growing number of studies have reported that non-SCN brain regions and peripheral tissues possess their own autonomous, entrainable oscillators that influence not only circadian functions in the SCN and neighboring local clocks, but also whole body rhythms via neural, hormonal, and metabolic feedback mechanisms [13][74][75][76][77][78][79][80]. The SCN receives a myriad of nonphotic input, arousal, feeding behavior, locomotor activity, immune function, blood pressure, and melatonin, which are all able to adjust and synchronize the SCN [81][82][83][84]. The SCN can receive this feedback through its large array of reciprocal neuronal connections with different hypothalamic regions, such as the arcuate nucleus (ARC), intergeniculate leaflet (IGL), nucleus tractus solitarius (NTS), dorsal raphe, and dorsomedial hypothalamus, allowing these nuclei to convey nonphotic feedback to the SCN and thus adjusting circadian rhythmicity [85][86][87][88][89].

Beyond photic entrainment, multiple physiological and environmental cues (e.g., food intake, gut microbial products, redox cofactors, metal ions, metabolic gases) control non-SCN and peripheral clock functions, which, in turn, impact the entire host clock system via neural and immune–metabolic circuits [12][22][72][90][91][92][93][94][95]. These findings suggest that systemic circadian rhythms are achieved through multi-modal regulation of tightly coupled body clocks according to daily changes that occur in the internal and external environments.

3. Conclusions

In recent decades, extensive chronobiological research has expanded our understanding of the functional roles and mechanisms of the circadian clockwork in human health and diseases. Thus, research trends in chronobiology have undergone a paradigm shift in many ways, particularly changing from hierarchical models to more integrated ones for understanding the circadian clock mechanism. In this regard, the overall evidence points to bidirectional crosstalk between transcriptional and metabolic rhythms, neuronal and glial clocks, SCN and non-SCN clocks, as well as brain and peripheral clocks (**Figure 1, Figure 2**). Our growing knowledge of the interactive nature of clock regulatory systems is expected to not only diversify our understanding of circadian physiology and pathophysiology but also increase our capacity to harness chronobiological knowledge to improve the prevention and treatment of multiple circadian-related disorders.

References

1. Dunlap, J.C. Molecular bases for circadian clocks. *Cell* 1999, 96, 271–290.
2. Bass, J.; Lazar, M.A. Circadian time signatures of fitness and disease. *Science* 2016, 354, 994–999.
3. Chaix, A.; Zarrinpar, A.; Panda, S. The circadian coordination of cell biology. *J. Cell Biol.* 2016, 215, 15–25.
4. Kalmbach, D.A.; Schneider, L.D.; Cheung, J.; Bertrand, S.J.; Kariharan, T.; Pack, A.I.; Gehrman, P.R. Genetic Basis of Chronotype in Humans: Insights From Three Landmark GWAS. *Sleep* 2017, 40, zsw048.
5. Refinetti, R.; Wassmer, T.; Basu, P.; Cherukalady, R.; Pandey, V.K.; Singaravel, M.; Giannetto, C.; Piccione, G. Variability of behavioral chronotypes of 16 mammalian species under controlled conditions. *Physiol. Behav.* 2016, 161, 53–59.
6. Bloch, G.; Barnes, B.M.; Gerkema, M.P.; Helm, B. Animal activity around the clock with no overt circadian rhythms: Patterns, mechanisms and adaptive value. *Proc. Biol. Sci.* 2013, 280, 20130019.
7. Dominoni, D.M.; Borniger, J.C.; Nelson, R.J. Light at night, clocks and health: From humans to wild organisms. *Biol. Lett.* 2016, 12, 20160015.

8. Cederroth, C.R.; Albrecht, U.; Bass, J.; Brown, S.A.; Dyhrfeld-Johnsen, J.; Gachon, F.; Green, C.B.; Hastings, M.H.; Helfrich-Förster, C.; Hogenesch, J.B.; et al. Medicine in the Fourth Dimension. *Cell Metab.* 2019, 30, 238–250.
9. Patke, A.; Young, M.W.; Axelrod, S. Molecular mechanisms and physiological importance of circadian rhythms. *Nat. Rev. Mol. Cell. Biol.* 2020, 21, 67–84.
10. Lee, Y.; Field, J.M.; Sehgal, A. Circadian Rhythms, Disease and Chronotherapy. *J. Biol. Rhythms* 2021, 7487304211044301.
11. Logan, R.W.; McClung, C.A. Rhythms of life: Circadian disruption and brain disorders across the lifespan. *Nat. Rev. Neurosci.* 2019, 20, 49–65.
12. Scheiermann, C.; Gibbs, J.; Ince, L.; Loudon, A. Clocking in to immunity. *Nat. Rev. Immunol.* 2018, 18, 423–437.
13. Segers, A.; Depoortere, I. Circadian clocks in the digestive system. *Nat. Rev. Gastroenterol. Hepatol.* 2021, 18, 239–251.
14. Masri, S.; Sassone-Corsi, P. The emerging link between cancer, metabolism, and circadian rhythms. *Nat. Med.* 2018, 24, 1795–1803.
15. Aiello, I.; Fedele, M.L.M.; Roman, F.; Marpegan, L.; Caldart, C.; Chiesa, J.J.; Golombek, D.A.; Finkielstein, C.V.; Paladino, N. Circadian disruption promotes tumor-immune microenvironment remodeling favoring tumor cell proliferation. *Sci. Adv.* 2020, 6, eaaz4530.
16. Hadadi, E.; Taylor, W.; Li, X.M.; Aslan, Y.; Villote, M.; Riviere, J.; Duvallet, G.; Auriau, C.; Dulong, S.; Raymond-Letron, I.; et al. Chronic circadian disruption modulates breast cancer stemness and immune microenvironment to drive metastasis in mice. *Nat. Commun.* 2020, 11, 3193.
17. Mattis, J.; Sehgal, A. Circadian Rhythms, Sleep, and Disorders of Aging. *Trends Endocrinol. Metab.* 2016, 27, 192–203.
18. Shafi, A.A.; McNair, C.M.; McCann, J.J.; Alshalalfa, M.; Shostak, A.; Severson, T.M.; Zhu, Y.; Bergman, A.; Gordon, N.; Mandigo, A.C.; et al. The circadian cryptochrome, CRY1, is a pro-tumorigenic factor that rhythmically modulates DNA repair. *Nat. Commun.* 2021, 12, 401.
19. Lee, Y.; Lahens, N.F.; Zhang, S.; Bedont, J.; Field, J.M.; Sehgal, A. G1/S cell cycle regulators mediate effects of circadian dysregulation on tumor growth and provide targets for timed anticancer treatment. *PLoS Biol.* 2019, 17, e3000228.
20. Lee, Y.; Fong, S.Y.; Shon, J.; Zhang, S.L.; Brooks, R.; Lahens, N.F.; Chen, D.; Dang, C.V.; Field, J.M.; Sehgal, A. Time-of-day specificity of anticancer drugs may be mediated by circadian regulation of the cell cycle. *Sci. Adv.* 2021, 7, eabd2645.
21. Diallo, A.B.; Coiffard, B.; Leone, M.; Mezouar, S.; Mege, J.L. For Whom the Clock Ticks: Clinical Chronobiology for Infectious Diseases. *Front. Immunol.* 2020, 11, 1457.

22. Gabriel, B.M.; Zierath, J.R. Circadian rhythms and exercise—Re-setting the clock in metabolic disease. *Nat. Rev. Endocrinol.* 2019, 15, 197–206.
23. Lewis, P.; Oster, H.; Korf, H.W.; Foster, R.G.; Erren, T.C. Food as a circadian time cue—Evidence from human studies. *Nat. Rev. Endocrinol.* 2020, 16, 213–223.
24. Johnson, C.H.; Zhao, C.; Xu, Y.; Mori, T. Timing the day: What makes bacterial clocks tick? *Nat. Rev. Microbiol.* 2017, 15, 232–242.
25. Takahashi, J.S. Transcriptional architecture of the mammalian circadian clock. *Nat. Rev. Genet.* 2017, 18, 164–179.
26. Koronowski, K.B.; Sassone-Corsi, P. Communicating clocks shape circadian homeostasis. *Science* 2021, 371, eabd0951.
27. Anafi, R.C.; Lee, Y.; Sato, T.K.; Venkataraman, A.; Ramanathan, C.; Kavakli, I.H.; Hughes, M.E.; Baggs, J.E.; Growe, J.; Liu, A.C.; et al. Machine learning helps identify CHRONO as a circadian clock component. *PLoS Biol.* 2014, 12, e1001840.
28. Lee, Y.; Lee, J.; Kwon, I.; Nakajima, Y.; Ohmiya, Y.; Son, G.H.; Lee, K.H.; Kim, K. Coactivation of the CLOCK-BMAL1 complex by CBP mediates resetting of the circadian clock. *J. Cell Sci.* 2010, 123, 3547–3557.
29. Lee, J.; Lee, Y.; Lee, M.J.; Park, E.; Kang, S.H.; Chung, C.H.; Lee, K.H.; Kim, K. Dual modification of BMAL1 by SUMO2/3 and ubiquitin promotes circadian activation of the CLOCK/BMAL1 complex. *Mol. Cell. Biol.* 2008, 28, 6056–6065.
30. Lee, Y.; Shen, Y.; Francey, L.J.; Ramanathan, C.; Sehgal, A.; Liu, A.C.; Hogenesch, J.B. The NRON complex controls circadian clock function through regulated PER and CRY nuclear translocation. *Sci. Rep.* 2019, 9, 11883.
31. Lee, Y.; Jang, A.R.; Francey, L.J.; Sehgal, A.; Hogenesch, J.B. KPNB1 mediates PER/CRY nuclear translocation and circadian clock function. *eLife* 2015, 4, e08647.
32. Lee, Y.; Chun, S.K.; Kim, K. Sumoylation controls CLOCK-BMAL1-mediated clock resetting via CBP recruitment in nuclear transcriptional foci. *Biochim. Biophys. Acta* 2015, 1853, 2697–2708.
33. Korge, S.; Maier, B.; Bruning, F.; Ehrhardt, L.; Korte, T.; Mann, M.; Herrmann, A.; Robles, M.S.; Kramer, A. The non-classical nuclear import carrier Transportin 1 modulates circadian rhythms through its effect on PER1 nuclear localization. *PLoS Genet.* 2018, 14, e1007189.
34. Zhang, R.; Lahens, N.F.; Ballance, H.I.; Hughes, M.E.; Hogenesch, J.B. A circadian gene expression atlas in mammals: Implications for biology and medicine. *Proc. Natl. Acad. Sci. USA* 2014, 111, 16219–16224.
35. Mure, L.S.; Le, H.D.; Benegiamo, G.; Chang, M.W.; Rios, L.; Jillani, N.; Ngotho, M.; Kariuki, T.; Dkhissi-Benyahya, O.; Cooper, H.M.; et al. Diurnal transcriptome atlas of a primate across major

- neural and peripheral tissues. *Science* 2018, 359, eaao0318.
36. Ruben, M.D.; Wu, G.; Smith, D.F.; Schmidt, R.E.; Francey, L.J.; Lee, Y.Y.; Anafi, R.C.; Hogenesch, J.B. A database of tissue-specific rhythmically expressed human genes has potential applications in circadian medicine. *Sci. Transl. Med.* 2018, 10, eaat8806.
 37. Thaiss, C.A.; Zeevi, D.; Levy, M.; Zilberman-Schapira, G.; Suez, J.; Tengeler, A.C.; Abramson, L.; Katz, M.N.; Korem, T.; Zmora, N.; et al. Transkingdom control of microbiota diurnal oscillations promotes metabolic homeostasis. *Cell* 2014, 159, 514–529.
 38. Dyar, K.A.; Lutter, D.; Artati, A.; Ceglia, N.J.; Liu, Y.; Armenta, D.; Jastroch, M.; Schneider, S.; de Mateo, S.; Cervantes, M.; et al. Atlas of Circadian Metabolism Reveals System-wide Coordination and Communication between Clocks. *Cell* 2018, 174, 1571–1585.e11.
 39. Solanas, G.; Peixoto, F.O.; Perdiguero, E.; Jardi, M.; Ruiz-Bonilla, V.; Datta, D.; Symeonidi, A.; Castellanos, A.; Welz, P.S.; Caballero, J.M.; et al. Aged Stem Cells Reprogram Their Daily Rhythmic Functions to Adapt to Stress. *Cell* 2017, 170, 678–692.e20.
 40. Wang, J.; Mauvoisin, D.; Martin, E.; Atger, F.; Galindo, A.N.; Dayon, L.; Sizzano, F.; Palini, A.; Kussmann, M.; Waridel, P.; et al. Nuclear Proteomics Uncovers Diurnal Regulatory Landscapes in Mouse Liver. *Cell Metab.* 2017, 25, 102–117.
 41. Wang, Y.; Song, L.; Liu, M.; Ge, R.; Zhou, Q.; Liu, W.; Li, R.; Qie, J.; Zhen, B.; Wang, Y.; et al. A proteomics landscape of circadian clock in mouse liver. *Nat. Commun.* 2018, 9, 1553.
 42. Robles, M.S.; Humphrey, S.J.; Mann, M. Phosphorylation Is a Central Mechanism for Circadian Control of Metabolism and Physiology. *Cell Metab.* 2017, 25, 118–127.
 43. Chiang, C.K.; Xu, B.; Mehta, N.; Mayne, J.; Sun, W.Y.; Cheng, K.; Ning, Z.; Dong, J.; Zou, H.; Cheng, H.M.; et al. Phosphoproteome Profiling Reveals Circadian Clock Regulation of Posttranslational Modifications in the Murine Hippocampus. *Front. Neurol.* 2017, 8, 110.
 44. Noya, S.B.; Colameo, D.; Bruning, F.; Spinnler, A.; Mircsof, D.; Opitz, L.; Mann, M.; Tyagarajan, S.K.; Robles, M.S.; Brown, S.A. The forebrain synaptic transcriptome is organized by clocks but its proteome is driven by sleep. *Science* 2019, 366, eaav2642.
 45. Malik, D.M.; Paschos, G.K.; Sehgal, A.; Weljie, A.M. Circadian and Sleep Metabolomics Across Species. *J. Mol. Biol.* 2020, 432, 3578–3610.
 46. Hofman, M.A.; Fliers, E.; Goudsmit, E.; Swaab, D.F. Morphometric analysis of the suprachiasmatic and paraventricular nuclei in the human brain: Sex differences and age-dependent changes. *J. Anat.* 1988, 160, 127–143.
 47. Hofman, M.A.; Swaab, D.F. A brain for all seasons: Cellular and molecular mechanisms of photoperiodic plasticity. *Prog. Brain Res.* 2002, 138, 255–280.

48. Hofman, M.A.; Swaab, D.F. Living by the clock: The circadian pacemaker in older people. *Ageing Res. Rev.* 2006, 5, 33–51.
49. Harmar, A.J.; Marston, H.M.; Shen, S.; Spratt, C.; West, K.M.; Sheward, W.J.; Morrison, C.F.; Dorin, J.R.; Piggins, H.D.; Reubi, J.C.; et al. The VPAC(2) receptor is essential for circadian function in the mouse suprachiasmatic nuclei. *Cell* 2002, 109, 497–508.
50. Brown, T.M.; Colwell, C.S.; Waschek, J.A.; Piggins, H.D. Disrupted neuronal activity rhythms in the suprachiasmatic nuclei of vasoactive intestinal polypeptide-deficient mice. *J. Neurophysiol.* 2007, 97, 2553–2558.
51. Yamaguchi, Y.; Suzuki, T.; Mizoro, Y.; Kori, H.; Okada, K.; Chen, Y.; Fustin, J.M.; Yamazaki, F.; Mizuguchi, N.; Zhang, J.; et al. Mice genetically deficient in vasopressin V1a and V1b receptors are resistant to jet lag. *Science* 2013, 342, 85–90.
52. Mieda, M.; Ono, D.; Hasegawa, E.; Okamoto, H.; Honma, K.; Honma, S.; Sakurai, T. Cellular clocks in AVP neurons of the SCN are critical for interneuronal coupling regulating circadian behavior rhythm. *Neuron* 2015, 85, 1103–1116.
53. Patton, A.P.; Edwards, M.D.; Smyllie, N.J.; Hamnett, R.; Chesham, J.E.; Brancaccio, M.; Maywood, E.S.; Hastings, M.H. The VIP-VPAC2 neuropeptidergic axis is a cellular pacemaking hub of the suprachiasmatic nucleus circadian circuit. *Nat. Commun.* 2020, 11, 3394.
54. Todd, W.D.; Venner, A.; Anaclet, C.; Broadhurst, R.Y.; De Luca, R.; Bandaru, S.S.; Issokson, L.; Hablitz, L.M.; Cravetchi, O.; Arrigoni, E.; et al. Suprachiasmatic VIP neurons are required for normal circadian rhythmicity and comprised of molecularly distinct subpopulations. *Nat. Commun.* 2020, 11, 4410.
55. Wen, S.; Ma, D.; Zhao, M.; Xie, L.; Wu, Q.; Gou, L.; Zhu, C.; Fan, Y.; Wang, H.; Yan, J. Spatiotemporal single-cell analysis of gene expression in the mouse suprachiasmatic nucleus. *Nat. Neurosci.* 2020, 23, 456–467.
56. Park, J.; Zhu, H.; O'Sullivan, S.; Ogunnaike, B.A.; Weaver, D.R.; Schwaber, J.S.; Vadigepalli, R. Single-Cell Transcriptional Analysis Reveals Novel Neuronal Phenotypes and Interaction Networks Involved in the Central Circadian Clock. *Front. Neurosci.* 2016, 10, 481.
57. Morris, E.L.; Patton, A.P.; Chesham, J.E.; Crisp, A.; Adamson, A.; Hastings, M.H. Single-cell transcriptomics of suprachiasmatic nuclei reveal a Prokineticin-driven circadian network. *EMBO J.* 2021, 40, e108614.
58. Brancaccio, M.; Patton, A.P.; Chesham, J.E.; Maywood, E.S.; Hastings, M.H. Astrocytes Control Circadian Timekeeping in the Suprachiasmatic Nucleus via Glutamatergic Signaling. *Neuron* 2017, 93, 1420–1435.e5.
59. Tso, C.F.; Simon, T.; Greenlaw, A.C.; Puri, T.; Mieda, M.; Herzog, E.D. Astrocytes Regulate Daily Rhythms in the Suprachiasmatic Nucleus and Behavior. *Curr. Biol.* 2017, 27, 1055–1061.

60. Brancaccio, M.; Edwards, M.D.; Patton, A.P.; Smyllie, N.J.; Chesham, J.E.; Maywood, E.S.; Hastings, M.H. Cell-autonomous clock of astrocytes drives circadian behavior in mammals. *Science* 2019, 363, 187–192.
61. Buijs, R.M.; Guzman Ruiz, M.A.; Mendez Hernandez, R.; Rodriguez Cortes, B. The suprachiasmatic nucleus; a responsive clock regulating homeostasis by daily changing the setpoints of physiological parameters. *Auton. Neurosci.* 2019, 218, 43–50.
62. Gizowski, C.; Zaelzer, C.; Bourque, C.W. Clock-driven vasopressin neurotransmission mediates anticipatory thirst prior to sleep. *Nature* 2016, 537, 685–688.
63. Paul, S.; Hanna, L.; Harding, C.; Hayter, E.A.; Walmsley, L.; Bechtold, D.A.; Brown, T.M. Output from VIP cells of the mammalian central clock regulates daily physiological rhythms. *Nat. Commun.* 2020, 11, 1453.
64. Collins, B.; Pierre-Ferrer, S.; Muheim, C.; Lukacsovich, D.; Cai, Y.; Spinnler, A.; Herrera, C.G.; Wen, S.; Winterer, J.; Belle, M.D.C.; et al. Circadian VIPergic Neurons of the Suprachiasmatic Nuclei Sculpt the Sleep-Wake Cycle. *Neuron* 2020, 108, 486–499.e5.
65. Ishida, A.; Mutoh, T.; Ueyama, T.; Bando, H.; Masubuchi, S.; Nakahara, D.; Tsujimoto, G.; Okamura, H. Light activates the adrenal gland: Timing of gene expression and glucocorticoid release. *Cell Metab.* 2005, 2, 297–307.
66. Buijs, R.M.; Kalsbeek, A. Hypothalamic integration of central and peripheral clocks. *Nat. Rev. Neurosci.* 2001, 2, 521–526.
67. Russell, G.; Lightman, S. The human stress response. *Nat. Rev. Endocrinol.* 2019, 15, 525–534.
68. Buijs, F.N.; León-Mercado, L.; Guzmán-Ruiz, M.; Guerrero-Vargas, N.N.; Romo-Nava, F.; Buijs, R.M. The Circadian System: A Regulatory Feedback Network of Periphery and Brain. *Physiology* 2016, 31, 170–181.
69. Firsov, D.; Bonny, O. Circadian rhythms and the kidney. *Nat. Rev. Nephrol.* 2018, 14, 626–635.
70. Ikegami, K.; Refetoff, S.; Van Cauter, E.; Yoshimura, T. Interconnection between circadian clocks and thyroid function. *Nat. Rev. Endocrinol.* 2019, 15, 590–600.
71. Stenvers, D.J.; Scheer, F.; Schrauwen, P.; la Fleur, S.E.; Kalsbeek, A. Circadian clocks and insulin resistance. *Nat. Rev. Endocrinol.* 2019, 15, 75–89.
72. Challet, E. The circadian regulation of food intake. *Nat. Rev. Endocrinol.* 2019, 15, 393–405.
73. Tahara, Y.; Shibata, S. Circadian rhythms of liver physiology and disease: Experimental and clinical evidence. *Nat. Rev. Gastroenterol. Hepatol.* 2016, 13, 217–226.
74. Hasegawa, S.; Fukushima, H.; Hosoda, H.; Serita, T.; Ishikawa, R.; Rokukawa, T.; Kawahara-Miki, R.; Zhang, Y.; Ohta, M.; Okada, S.; et al. Hippocampal clock regulates memory retrieval via

- Dopamine and PKA-induced GluA1 phosphorylation. *Nat. Commun.* 2019, 10, 5766.
75. Myung, J.; Schmal, C.; Hong, S.; Tsukizawa, Y.; Rose, P.; Zhang, Y.; Holtzman, M.J.; De Schutter, E.; Herzel, H.; Bordyugov, G.; et al. The choroid plexus is an important circadian clock component. *Nat. Commun.* 2018, 9, 1062.
76. Son, G.H.; Chung, S.; Choe, H.K.; Kim, H.D.; Baik, S.M.; Lee, H.; Lee, H.W.; Choi, S.; Sun, W.; Kim, H.; et al. Adrenal peripheral clock controls the autonomous circadian rhythm of glucocorticoid by causing rhythmic steroid production. *Proc. Natl. Acad. Sci. USA* 2008, 105, 20970–20975.
77. Myung, J.; Wu, M.Y.; Lee, C.Y.; Rahim, A.R.; Truong, V.H.; Wu, D.; Piggins, H.D.; Wu, M.S. The Kidney Clock Contributes to Timekeeping by the Master Circadian Clock. *Int. J. Mol. Sci.* 2019, 20, 2765.
78. Sinturel, F.; Gos, P.; Petrenko, V.; Hagedorn, C.; Kreppel, F.; Storch, K.F.; Knutti, D.; Liani, A.; Weitz, C.; Emmenegger, Y.; et al. Circadian hepatocyte clocks keep synchrony in the absence of a master pacemaker in the suprachiasmatic nucleus or other extrahepatic clocks. *Genes Dev.* 2021, 35, 329–334.
79. Bano-Otalora, B.; Piggins, H.D. Contributions of the lateral habenula to circadian timekeeping. *Pharmacol. Biochem. Behav.* 2017, 162, 46–54.
80. Van Drunen, R.; Eckel-Mahan, K. Circadian Rhythms of the Hypothalamus: From Function to Physiology. *Clocks Sleep* 2021, 3, 189–226.
81. Antle, M.C.; Mistlberger, R.E. Circadian clock resetting by sleep deprivation without exercise in the Syrian hamster. *J. Neurosci.* 2000, 20, 9326–9332.
82. Mendoza, J. Circadian clocks: Setting time by food. *J. Neuroendocrinol.* 2007, 19, 127–137.
83. Marchant, E.G.; Mistlberger, R.E. Morphine phase-shifts circadian rhythms in mice: Role of behavioural activation. *Neuroreport* 1995, 7, 209–212.
84. Guerrero-Vargas, N.N.; Salgado-Delgado, R.; Basualdo, M.e.C.; García, J.; Guzmán-Ruiz, M.; Carrero, J.C.; Escobar, C.; Buijs, R.M. Reciprocal interaction between the suprachiasmatic nucleus and the immune system tunes down the inflammatory response to lipopolysaccharide. *J. Neuroimmunol.* 2014, 273, 22–30.
85. Saderi, N.; Salgado-Delgado, R.; Avendaño-Pradel, R.; Basualdo, M.e.C.; Ferri, G.L.; Chávez-Macías, L.; Roblera, J.E.; Escobar, C.; Buijs, R.M. NPY and VGF immunoreactivity increased in the arcuate nucleus, but decreased in the nucleus of the Tractus Solitarius, of type-II diabetic patients. *PLoS ONE* 2012, 7, e40070.
86. Buijs, F.N.; Cazarez, F.; Basualdo, M.C.; Scheer, F.A.; Perusquía, M.; Centurion, D.; Buijs, R.M. The suprachiasmatic nucleus is part of a neural feedback circuit adapting blood pressure response. *Neuroscience* 2014, 266, 197–207.

87. Shioiri, T.; Takahashi, K.; Yamada, N.; Takahashi, S. Motor activity correlates negatively with free-running period, while positively with serotonin contents in SCN in free-running rats. *Physiol. Behav.* 1991, 49, 779–786.
88. Yi, C.X.; van der Vliet, J.; Dai, J.; Yin, G.; Ru, L.; Buijs, R.M. Ventromedial arcuate nucleus communicates peripheral metabolic information to the suprachiasmatic nucleus. *Endocrinology* 2006, 147, 283–294.
89. Acosta-Galvan, G.; Yi, C.X.; van der Vliet, J.; Jhamandas, J.H.; Panula, P.; Angeles-Castellanos, M.; Del Carmen Basualdo, M.; Escobar, C.; Buijs, R.M. Interaction between hypothalamic dorsomedial nucleus and the suprachiasmatic nucleus determines intensity of food anticipatory behavior. *Proc. Natl. Acad. Sci. USA* 2011, 108, 5813–5818.
90. Thaiss, C.A.; Levy, M.; Korem, T.; Dohnalova, L.; Shapiro, H.; Jaitin, D.A.; David, E.; Winter, D.R.; Gury-BenAri, M.; Tatrovsky, E.; et al. Microbiota Diurnal Rhythmicity Programs Host Transcriptome Oscillations. *Cell* 2016, 167, 1495–1510.e12.
91. Buhr, E.D.; Yoo, S.H.; Takahashi, J.S. Temperature as a universal resetting cue for mammalian circadian oscillators. *Science* 2010, 330, 379–385.
92. Reinke, H.; Asher, G. Crosstalk between metabolism and circadian clocks. *Nat. Rev. Mol. Cell Biol.* 2019, 20, 227–241.
93. Parmalee, N.L.; Aschner, M. Metals and Circadian Rhythms. *Adv. Neurotoxicol.* 2017, 1, 119–130.
94. Rey, G.; Valekunja, U.K.; Feeney, K.A.; Wulund, L.; Milev, N.B.; Stangherlin, A.; Ansel-Bollepalli, L.; Velagapudi, V.; O'Neill, J.S.; Reddy, A.B. The Pentose Phosphate Pathway Regulates the Circadian Clock. *Cell Metab.* 2016, 24, 462–473.
95. Ch, R.; Rey, G.; Ray, S.; Jha, P.K.; Driscoll, P.C.; Dos Santos, M.S.; Malik, D.M.; Lach, R.; Weljie, A.M.; MacRae, J.I.; et al. Rhythmic glucose metabolism regulates the redox circadian clockwork in human red blood cells. *Nat. Commun.* 2021, 12, 377.

Retrieved from <https://encyclopedia.pub/entry/history/show/42806>