International Journal of Current Research and Review
DOI: https://doi.org/10.31782/IJCRR.2021.131827

Review Article

Pineal Gland Rhythm and Circadian Physiology

Chetri Ranju

Department of Zoology, North-Eastern Hill university, Shillong-793022, India.

IJCRR
Section: Healthcare
ISI Impact Factor (2019-20): 1.628
IC Value (2019): 90.81
SJIF (2020) = 7.893

ABSTRACT

An unpaired neuroendocrine and highly vascularized organ, the pineal gland is located in the middle of the brain nearly in all vertebrates. Its main function is to synthesize the melatonin hormone (N-acetyl-5-methoxytryptamine) in the pinealocytes, which converts light and dark information to complete body physiology. Light inhibits melatonin production whereas darkness stimulates it. Melatonin is synthesized from amino acid tryptophan. Dietary amino acid tryptophan is converted into melatonin in four consecutive biochemical steps.This conversion process includes: conversion of amino acid tryptophan to 5-hydroxytryptophan (5-HTP) by tryptophan hydroxylase 1 (TPH1); synthesis of 5-hydroxytryptamine (5-HT or serotonin) by aromatic amino acid decarboxylase; formation of N-acetylserotonin (NAS) by arylalkylamine N-acetyltransferase (AANAT), and production of melatonin by hydroxyindole-O-methyltransferase (HIOMT) (also termed N-acetylserotonin methyltransferase or ASMT).The pineal gland in rat exhibits circadian rhythms of release for all four tryptophan enzymatic derivatives, with larger levels at night. 5-HTP and serotonin are both released at quite high levels during the day and increase much more at night, in contrast to NAS and melatonin, which are hardly detectable during the day.

Keywords: Pineal, Melatonin, Rhythm, Serotonin, Cycle, Hormone

INTRODUCTION

Humans have a tiny (100–150 mg), highly vascularized gland called the pineal gland that secretes neuroendocrine hormones. It is situated in the middle of the brain, outside of the blood-brain barrier, and has a small stalk that connects it to the roof of the third ventricle. The superior cervical ganglia are the source of the sympathetic main innervation.[1] Both the anterior and posterior circulations deliver blood to the pineal gland's arterial vascularization, with the posterior circulation's lateral pineal artery serving as the primary blood vessel.[2] Pinealocytes (95%) and scattered glial cells (astrocytic and phagocytic subtypes) are the two primary cell types in mammals present in the pineal gland.[3] Melatonin is produced by pinealocytes.The primary role of the pineal gland is to collect and transmit information from the environment about the present light-dark cycle through the cyclical production and release of melatonin at night (dark period).[4] Although the pineal gland is photosensitive in cold-blooded vertebrates (lower-vertebrate species), higher vertebrates lack this ability. In higher vertebrates, the inner retina (retinal ganglion cells) detects light and transmits neural impulses to the brain's optic regions. A small number of retinal ganglion cells do, however, contain melanopsin and have an intrinsic photoreceptor capability that allows them to transmit neurological signals via intricate neuronal connections to regions of the brain that do not participate in image formation, such as the pineal gland. The suprachiasmatic nucleus (SCN), the main rhythm-generating mechanism or "clock" in mammals, receives the photic information from the retina and transmits it to other hypothalamic regions. Gamma-amino butyric acid, secreted by the SCN when the light signal is positive inhibits the neurons that synapses in the paraventricular nucleus (PVN) of the hypothalamus and it also interrupts the signal to the pineal gland and prevents the synthesis of melatonin. In contrast, the SCN secretes glutamate in the absence of light (darkness), which helps the PVN to transmit the signal to the pineal gland. It's crucial to remember, though, that the SCN, which serves as an endogenous oscillator (master pacemaker or clock), continues to produce rhythmic output in the absence of light suppression. The rhythm deviates

Corresponding Author:
Chetri Ranju, Department of Zoology, North-Eastern Hill university, Shillong-793022, India
Email: ranjuchetri8@gmail.com

ISSN: 2231-2196 (Print) **ISSN:** 0975-5241 (Online)

Received: 27.02.2021 **Revised:** 18.05.2021 **Accepted:** 28.07.2021 **Published:** 26.09.2021

from 24 hours and "free-runs" when the crucial cue of light time is absent. Cycles of light and dark help to synchronise the rhythm to 24 hours. Prior to transmitting information to the pineal gland via sympathetic postsynaptic fibres and the release of norepinephrine (NE) , the superior cervical ganglion gets input from the PVN nucleus and higher thoracic segments of the spinal column. Fibres and the release of norepinephrine (NE). By stimulating the transcription of the mRNA encoding the enzyme arylalkylamine N-acetyltransferase (AA-NAT), the first molecular step for melatonin production, NE causes the pinealocytes to produce melatonin.[79]

Enzymatic production of melatonin in the pinealocyte

An increase in the activity of the enzyme serotonin-N-acetyltransferase (also known as arylalkylamine N-acetyltransferase, or AA-NAT), which converts 5-hydroxytryptamine (5HT, or serotonin) into N-acetylserotonin (NAS), stimulates the production of melatonin (N-acetyl-5-methoxytryptamine). This process generally occurs during the dark phase of a 24h day. Finally, N-acetylserotonin is converted to melatonin by acetylserotonin O-methyltransferase (Fig. 1). 5HT is a monoamine neurotransmitter having physiological function.[81] Many drugs that affect the 5HT receptor can treat a wide range of diseases by altering the central serotogenic activity.[81] The generation of melatonin is constrained by both AA-NAT and serotonin availability. The pineal gland, retina, and, to a lesser extent, the pituitary and testis, are the principal locations where AA-NAT mRNA is expressed. The activation of β1 and α1b adrenergic receptors by NE results in AA-NAT activation.[80] NE is the major transmitter via β-1 adrenoceptors with potentiation by α-1 stimulation. The availability of NE and serotonin both stimulate the production of melatonin. Melatonin's rhythmic synthesis and the light-dark regulation of its production are both eliminated by pathological, surgical, or traumatic sympathetic denervation of the pineal gland or by the use of adrenergic antagonists.

Adrenergic innervation of the pineal gland triggers a series of circadian events that cause serotonin to be converted to melatonin each night. In the absence of melatonin production, serotonin is present in the pineal gland at high levels throughout the day and increases even more at night.[9] Moreover, 5-HTP and serotonin present in the rat pineal gland is lower than its daytime levels due to the consumption of these substances during melatonin synthesis. [5,6,7,8,9] Lower than its daytime levels due to the consumption of these substances during melatonin synthesis (Sun et al., 2002). TPH1, the rate-limiting enzyme of serotonin synthesis, possesses enhanced enzyme activity and protein levels, drives the increased night time synthesis of serotonin. The TPH1 protein is stabilised after translation by the phosphorylation of serine-58, which results in increased in serotonin synthesis at night.[10,11,12,13]

Serotonin secretion exhibits biphasic patterns at night, with an early peak in amplitude and a continuous fall in concentration throughout the balance of the night.[14] Release of serotonin increases in the early hours of the night and occurs before the beginning of melatonin secretion in both rats and hamsters. AANAT activation is transcriptionally controlled in both these species.[14,15] Syrian hamsters have a 4 h delay between serotonin surge and melatonin induction, in contrast to the rat pineal gland where serotonin release spikes 1 h before melatonin onset.[15] These findings are in line with study done by other researchers.[16,17] These researches shows that rats and hamsters have different pathways of transcriptional activation of melatonin synthesis downstream of adrenergic stimulation in the pineal. However, the nocturnal surge of serotonin release has not been found in the degu pineal gland, where AANAT activation is post-transcriptionally controlled.[18] These findings imply that nightly adrenergic signalling stimulation causes a delayed transcriptional stimulation of AANAT and an immediate posttranscriptional activation of TPH1, which results in a surge in serotonin and melatonin secretion.[9,13,15] The lag in serotonin and melatonin release time is eliminated in degus when both TPH1 and AANAT are stimulated post-transcriptionally.[18,19]

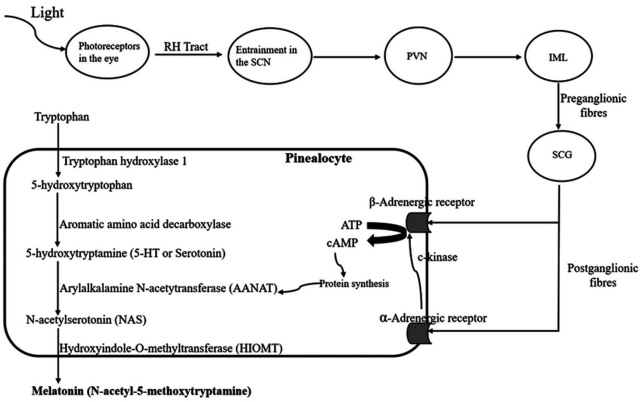

Figure 1: Schematic diagram showing neurocircuitry involved in melatonin synthesis (Redrawn as per Arendt, 1998)[78].

Melatonin synthesis in the pinealocyte from serotonin requires activities of both AANAT and HIOMT. Since the discovery of AANAT's strong diurnal patterns in enzyme activity, the enzyme has traditionally been thought of as the rate-limiting enzyme of the production of melatonin.[20,21] Due to AANAT's reduced enzyme activity during the day, it is obvious that it restricts melatonin generation. Yet, AANAT does not restrict the amplitudes of melatonin synthesis over the majority of the night.[22] The following recent evidences point to the view: (1) In the night pineal, a strain of rats with the H28Y mutation in the AANAT sequence exhibits low levels of AANAT protein and activity.[23] Even so, according to Liu and Borjigin's study, melatonin levels are the same as those of control rats with normal AANAT;[22](2) Rat pineal

glands and human circulation both exhibit molar excesses of NAS, the enzymatic result of AANAT, at night;[19,22,24] (3) Hours after melatonin production peaked, the levels of AANAT protein keeps rising in the second half of the night[22] and (4) A change in NAS concentration does not cause a commensurate change in melatonin concentration within the same individual animal.[22].

Regulation of melatonin synthesis

The pineal gland and the suprachiasmatic nucleus (SCN) of the hypothalamus which contains the central rhythm generator are linked by a number of synaptic pathways.[25] The SCN sends circadian signals to the paraventricular nuclei (PVN), intermediolateral nucleus of the spinal cord (IML), superior cervical ganglion (SCG) and then to the pineal gland.[26]

Circadian signals from the SCN in that order (Borjigin et al., 1999). The parasympathetic system also innervates the pineal, albeit its function and control are currently unknown.[27]

Neurotransmitters and the circuit

Diurnal rhythms of melatonin secretion are controlled by a complex cascade of neurotransmission that originates in the SCN.SCN may suppress the glutamatergic inputs from PVN during the daytime via a synaptic input from GABAergic SCN terminals to autonomic PVN neurons.[28,29] Melatonin production during the day is suppressed as a result of the effect on the preganglionic sympathetic neurons in the IML.[25,30] Nevertheless, as melatonin is not one of the outputs examined in the study along with heart rate, arterial pressure, and renal sympathetic activity, the experimental evidence for the glutamatergic transmission from PVN to IML to modulate melatonin output is indirect.[30] Glutamatergic SCN output innervating PVN promotes melatonin production in the pineal during the night.[31,32] The release of norepinephrine from the SCG during the night triggers the synthesis of melatonin within the pineal gland.[33,34] By causing the release of glutamate in the SCN from the nerve endings of the retinohypothalamic (RH) tract, which is the bundles of axons of the melanopsin-containing retinal ganglion cells, light can effectively limit the release of norepinephrine.[34,35]

One of the best-understood neuronal circuits in the brain is the SCN-pineal circuit, which has well-defined core components and a straightforward, reliable, and consistent readout of circuit activity (melatonin). Also, a simple light switch can turn off the neural activity that stimulates the physiological output (melatonin production) of the target organ (pineal gland).The pineal gland is a good system for comprehending activity dependent neural plasticity because of these benefits. Additionally, because the pineal is bilaterally innervated by two SCGs, it is possible to conduct an examination into the functional recovery from partial nerve lesions by performing a partial injury to the circuit.[36] According to research from the Zigmond laboratory, the pineal gland fully recovers in just two days after losing 50% of its adrenergic input.[36,37] The spontaneous and quick functional recovery of the pineal gland after partial circuit injury is interestingly only reproducible after partial denervation of the pineal gland; no recovery is seen after a partial decentralisation of the pineal by denervating one of the two SCGs.[38,39] To elucidate this crucial process further, a thorough research of neuroplasticity in the SCN-pineal circuit is necessary.

Genes involved in the pineal rhythmicity

After bilateral SCN lesions, circadian cycles of melatonin production and secretion are eliminated, proving that the SCN is the source of generation of the melatonin rhythm.[25] Via a series The SCN Produces circadian rhythms through positive and negative feedback loops involving transcription and translation.[40,41]

The PAS domain helix-loop-helix proteins CLOCK and BMAL1, which form dimers to stimulate the transcription of two Cryptochrome (Cry1-2) and three Period (Per1-3) genes via the E-Box sequences in their promoters, are involved in rhythm generation. PER-Cry dimers adversely affect the CLOCK/BMAL1-dependent transcription by translocating into the nucleus.[42]

*CLOCK:*It has been shown that CLOCK protein mutation eliminates behavioural cycles.[43] Unexpectedly, CLOCK-null mice nevertheless exhibit strong circadian activity rhythms.[44] A study shows that the function of CLOCK in melatonin rhythm generation by mating melatonin-deficient CLOCK mutant mice with melatonin-sufficient ones.[45] The fact that the resulting CLOCK mutant mice have regular melatonin rhythms suggests that the SCN has a functional CLOCK homolog. An intriguing study by shows that melatonin directly inhibits the SCN to decrease the behavioural phenotype of the CLOCK mutant.[46] This discovery points to melatonin's significant feedback role in circadian timing.

Cry1/2: Cry 1 and Cry 2 double-deficient mice (Cry1/2 null) held in constant darkness, exhibit arrhythmic behaviour.[47] When exposed to typical light and dark conditions, Cry1/2 null animals from melatonin-proficient backgrounds do not exhibit circadian rhythms of melatonin production, but they do exhibit extremely weak rhythms when exposed to constant darkness.[47] Per1: AANAT gene expression and nocturnal melatonin secretion are considerably higher in Per1 null mice than in wild type mice, suggesting that PER1 ordinarily suppresses melatonin production.[48,49]

Most cell types are thought to have the basic clock mechanism, and tissues isolated on Petri dishes can exhibit dramatic oscillations in the expression of clock genes, including per1.[41] No exception can be made for the pineal gland [50,51]. Pineal rhythms are eliminated in vivo when sympathetic input is not present, indicating that the pineal melatonin rhythm cannot be produced by the local clock mechanism

alone. One cannot, however, rule out the possibility that one or more of these local clock elements, in addition to the SCN's central input, are necessary for the regular oscillation of pineal rhythms. It is yet unknown how the pineal gland's clock genes affect SCN-regulated pineal rhythmicity.

Effect of light on pineal

The clock-driven melatonin production endures in constant dark conditions and is entrained to the solar environment by the light:dark cycle.[52] Rods, cones, and melanopsin-expressing retina ganglion cells are stimulated by light entering the eyes, and these photoreceptors translate light impulses into electric signals in the ganglion cells.[53]The retinohypothalamic pathways transmit the circadian light signal from the melanopsin-positive ganglion cells to the SCN.[53]Under entrained conditions, the same person's melatonin secretion is stable from day to day with the same timings of onset and offset.[15,52,54]The quick termination of norepinephrine secretion from the SCG that occurs when the nighttime lighting schedule is interrupted by a light pulse has a significant impact on the pineal rhythm. This results into the decrease in the generation of melatonin.[34]

The light-stimulated release of neurotransmitters mediates the light effect. These neurotransmitters are glutamate and pituitary adenylate cyclase-activating polypeptide (PACAP).[55,56] These are co-stored in the presynaptic terminals in the SCN. Previous research in hamsters demonstrates that MK801, a non-competitive NMDA receptor inhibitor, does not prevent light-mediated suppression of melatonin at night.[57]According to research done on rats, MK801 prevents the reduction of melatonin at night caused by red light, but not by white light.[58,59]

Physiological function of the pineal rhythmicity

A daily secretion of NAS and melatonin occurs from the pineal gland. In both rats and humans, NAS levels are higher than melatonin in the circulation at night.[19,60] More and more research is pointing to NAS's potential role as an antioxidant that outperforms melatonin.[61] In retinal samples, NAS was demonstrated to protect against 6-hydroxydopamine-induced neurotoxicity and glutamine-induced lipid peroxidation.[62] More recently, it was shown that NAS activates the receptor TrkB, a brain-derived neurotrophic factor (BDNF), causing behaviour similar to that of an antidepressant.[63] These findings imply that endogenous NAS generated by the pineal gland may have physiological uses in addition to its function as a precursor to melatonin.

Type 1 and type 2 melatonin receptors, which are found in numerous tissues and cell types, including the SCN, enable melatonin to exert its central and peripheral effects.[64] Melatonin is a well-known seasonal information transducer in the periphery that determines the length of the night.[26,65] Melatonin acts on the pars tuberalis of the pituitary, which is home to a higher expression of melatonin receptors, and plays an important role in the cycles of seasonal animals' reproduction.[66,67] Melatonin is an efficient antioxidant and free radical scavenger, much like NAS.[68] Melatonin receptors have recently been identified in pancreatic islets, indicating a potential direct function for melatonin in the control of insulin secretion.[69] Melatonin receptor allele variants have been linked to hyperglycemia and reduced insulin secretion in human genetic investigations.[69,70] The relationship between melatonin signalling and insulin production is further strengthened by increased insulin secretion in isolated islets from mice lacking melatonin receptors.[71]Melatonin directly affects the SCN in the brain, modulating how the clock works.[67,72] Neuronal firing rate rhythms are phase-dependently shifted when low concentrations of melatonin are applied to SCN slices in vitro.[73] The fact that melatonin directly affects SCN activity supports its usefulness in humans as the model chronobiotic, a family of medications that affects the circadian clock.[74] Melatonin was timed administered to blind people who had no circadian light perceptions for the purpose of entrainment.[75,76,77] Melatonin has also been frequently used in healthy individuals to reduce the effect of jet lag.[74] It has been found that melatonin suppresses the Clock mutant's phenotype and interacts with clock to affect circadian systems in mice.[46]

CONCLUSION

Melatonin, a hormone released by the pineal gland, has a distinct circadian cycle. During the dark phase of the day, melatonin production is at its highest. The length of the secretion of this hormone corresponds to the length of the night. A completely new pharmacology of chronobiotic medicines has been sparked by melatonin. Moreover, it is promoted as a potent immunostimulant, anti-aging agent, and powerful antioxidant.

ACNOWLEDGEMENT

I am grateful to all those authors/editors/publishers of all those articles, journals and books from where the literature for this article has been reviewed and discussed.

Conflict of interest: There is no conflict of interest.

Source of Funding: The work has not been supported by any fund.

REFERENCES

1. Kappers J.A. Innervation of the Vertebrate Pineal Organ. In: Axelrod J, Fraschini,F., Velo, G.P. (eds).1983.
2. Kahilogullari G, Ugur H.C., Comert A., Brohi R.A., Ozgural O, Ozdemir M. Arterial vascularization of the pineal gland. Childs Nerv Syst.2013. 29(10):1835-1841.

3. Moller, M., Baeres F.M. The anatomy and innervation of the mammalian pineal gland. Cell.Tissue. Res. 2002. 309(1):139-150.
4. Goldman B.D.Mammalian photoperiodic system: formal properties and neuroendocrine mechanisms of photoperiodic time measurement. J Biol Rhythms. 2001;16(4):283-301.
5. Bach, A.G., Muhlbauer, E., Peschke, E., Adrenoceptor expression and diurnal rhythms of melatonin and its precursors in the pineal gland of type 2 diabetic goto kakizaki rats. Endocrinol.2010. 151, 2483-2493.
6. Champney, T.H., Holtorf, A.P., Steger, R.W., Reiter, R.J., Concurrent determination of enzymatic activities and substrate concentrations in the melatonin synthetic pathway within the same rat pineal gland. J. Neurosci. Res. 1984. 11, 59-66.
7. Snyder, S.H., Axelrod, J., Circadian rhythm in pineal serotonin: effect of monoamine oxidase inhibition and reserpine. Science. 1965. 149, 542–544.
8. Snyder, S.H., Zweig, M., Axelrod, J., Fischer, J.E.,Control of the circadian rhythm in serotonin content of the rat pineal gland. Proc. Natl. Acad. Sci. USA 1965. 53, 301–305.
9. Sun, X., Deng, J., Liu, T., Borjigin, J.,Circadian 5-HT production regulated by adrenergic signaling. Proc. Natl. Acad. Sci. USA. 2002. 99, 4686–4691.
10. Ehret, M., Pevet, P., Maitre, M., Tryptophan hydroxylase synthesis is induced by 30, 50-cyclic adenosine monophosphate during circadian rhythm in the rat pineal gland. J. Neurochem.1991. 57, 1516-1521.
11. Shibuya, H., Toru, M., Watanabe, S., A circadian rhythm of tryptophan hydroxylase in rat pineals. Brain Res.1977. 138, 364-368.
12. Sitaram, B.R., Lees, G.J., Diurnal rhythm and turnover of tryptophan hydroxylase in the pineal gland of the rat. J. Neurochem.1978. 31, 1021-1026.
13. Huang, Z., Liu, T., Chattoraj, A., Ahmed, S., Wang, M.M., Deng, J., Sun, X., Borjigin, J., Posttranslational regulation of TPH1 is responsible for the nightly surge of 5 HT output in the rat pineal gland. J. Pineal Res.2008. 45, 506-514.
14. Borjigin, J., Zhang, L.S., Calinescu, A. Circadian regulation of the pineal gland rhythmicity. Mol. Cell. Endocrinol. 2012. 349, 13-19.
15. Liu, T., Borjigin, J., Relationship between nocturnal serotonin surge and melatonin onset in rodent pineal gland. J. Circadian Rhythms.2006. 4, 12.
16. Simonneaux, V., Ribelayga, C., Generation of the melatonin endocrine message in mammals: a review of the complex regulation of melatonin synthesis by norepinephrine, peptides, and other pineal transmitters. Pharmacol. Rev.2003. 55, 325-395.
17. Simonneaux, V., Sinitskaya, N., Salingre, A., Garidou, M.L., Pevet, P., Rat and Syrian hamster: two models for the regulation of AANAT gene expression. Chronobiol. Int. 2006. 23, 351-359.
18. Lee, S.J., Liu, T., Chattoraj, A., Zhang, S.L., Wang, L., Lee, T.M., Wang, M.M., Borjigin, J., Posttranscriptional regulation of pineal melatonin synthesis in Octodon degus. J. Pineal Res.2009. 47, 75-81.
19. Chattoraj, A., Liu, T., Zhang, L.S., Huang, Z., Borjigin, J., Melatonin formation in mammals: in vivo perspectives. Rev. Endocr. Metab. Disord. 2009. 10, 237-243.
20. Klein, D.C., Weller, J.L., Indole metabolism in the pineal gland: a circadian rhythm in N-acetyltransferase. Science1970. 169, 1093-1095.
21. Klein, D.C., Arylalkylamine N-acetyltransferase: "the Timezyme". J. Biol. Chem.2007. 282, 4233-4237.
22. Liu, T., Borjigin, J., N-acetyltransferase is not the rate-limiting enzyme of melatonin synthesis at night. J. Pineal Res. 2005.39, 91-96.
23. Huang, Z., Deng, J., Borjigin, J., A novel H28Y mutation in LEC rats leads to decreased NAT protein stability in vivo and in vitro. J. Pineal Res. 2005. 39, 84-90.
24. Sun, X., Liu, T., Deng, J., Borjigin, J., Long-term in vivo pineal microdialysis. J. Pineal Res.2003. 35, 118-124.
25. Kalsbeek, A., Garidou, M.L., Palm, I.F., Van Der Vliet, J., Simonneaux, V., Pevet, P., Buijs RM (2000) Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. Eur J Neurosci 12: 3146–3154.
26. Borjigin, J., Li, X., Snyder, S.H., The pineal gland and melatonin: molecular and pharmacologic regulation. Annu. Rev. Pharmacol. Toxicol.1999. 39, 53-65.
27. Larsen, P.J.,Tracing autonomic innervation of the rat pineal gland using viral transneuronal tracing. Microsc. Res. Tech. 1999. 46, 296-304.
28. Buijs, R.M., Melatonin sees the light: blocking GABA-ergic transmission in the paraventricular nucleus induces daytime secretion of melatonin. Eur. J. Neurosci. 2000. 12, 3146-3154.
29. Buijs, R.M., van Eden, C.G., Goncharuk, V.D., Kalsbeek, A., The biological clock tunes the organs of the body: timing by hormones and the autonomic nervous system. J. Endocrinol. 2003. 177, 17-26.
30. Teclemariam-Mesbah, R., Ter Horst, G.J., Postema, F., Wortel, J., Buijs, R.M., Anatomical demonstration of the suprachiasmatic nucleus-pineal pathway. J. Comp. Neurol.1999. 406, 171-182.
31. Kannan, H., Hayashida, Y., Yamashita, H., Increase in sympathetic outflow by paraventricular nucleus stimulation in awake rats. Am. J. Physiol. 1989. 256, R1325–-1330.
32. Hermes, M.L., Coderre, E.M., Buijs, R.M., Renaud, L.P., GABA and glutamate mediate rapid neurotransmission from suprachiasmatic nucleus to hypothalamic paraventricular nucleus in rat. J. Physiol. 1996. 496 (3), 749-757.
33. Perreau-Lenz, S., Kalsbeek, A., Pevet, P., Buijs, R.M., Glutamatergic clock output stimulates melatonin synthesis at night. Eur. J. Neurosci. 2004. 19, 318-324.
34. Drijfhout, W.J., van der Linde, A.G., Kooi, S.E., Grol, C.J., Westerink, B.H., Norepinephrine release in the rat pineal gland: the input from the biological clock measured by in vivo microdialysis. J. Neurochem.1996. 66, 748-755.
35. Drijfhout, W.J., van der Linde, A.G., de Vries, J.B., Grol, C.J., Westerink, B.H., Microdialysis reveals dynamics of coupling between noradrenaline release and melatonin secretion in conscious rats. Neurosci. Lett.1996. 202, 185-188.
36. Guler, A.D., Ecker, J.L., Lall, G.S., Haq, S., Altimus, C.M., Liao, H.W., Barnard, A.R., Cahill, H., Badea, T.C., Zhao, H., Hankins, M.W., Berson, D.M., Lucas, R.J., Yau, K.W., Hattar, S., Melanopsin cells are the principal conduits for rod-cone input to non-image forming vision. Nature. 2008.453, 102–105.
37. Zigmond, R.E., Baldwin, C., Bowers, C.W., Rapid recovery of function after partial denervation of the rat pineal gland suggests a novel mechanism for neural plasticity. Proc. Natl. Acad. Sci. USA.1981. 78, 3959-3963.
38. Kuchel, G.A., Zigmond, R.E., Functional recovery and collateral neuronal sprouting examined in young and aged rats following a partial neural lesion. Brain Res.1991. 540, 195-203.
39. Dornay, M., Gilad, V.H., Gilad, G.M., Compensatory changes in contralateral sympathetic neurons of the superior cervical ganglion and in their terminals in the pineal gland following unilateral ganglionectomy. J. Neurosci.1985. 5, 1522-1526.
40. Zigmond, R.E., Baldwin, C., Bowers, C.W., Rapid recovery of pineal function after partial denervation: a possible role for heteroneuronal uptake of transmitter in modulating synaptic efficacy. J. Neurosci.1985. 5, 142-150.

41. Mendoza, J., Challet, E., Brain clocks: from the suprachiasmatic nuclei to a cerebral network. Neuroscientist.2009. 15, 477-488.
42. Welsh, D.K., Takahashi, J.S., Kay, S.A., Suprachiasmatic nucleus: cell autonomy and network properties. Annu. Rev. Physiol.2010. 72, 551-577.
43. Reppert, S.M., Weaver, D.R., Coordination of circadian timing in mammals. Nature2002. 418, 935-941.
44. Vitaterna, M.H., King, D.P., Chang, A.M., Kornhauser, J.M., Lowrey, P.L., McDonald, J.D., Dove, W.F., Pinto, L.H., Turek, F.W., Takahashi, J.S., Mutagenesis and mapping of a mouse gene, clock, essential for circadian behavior. Science.1994. 264, 719-725.
45. Debruyne, J.P., Noton, E., Lambert, C.M., Maywood, E.S., Weaver, D.R., Reppert, S.M., A clock shock: mouse CLOCK is not required for circadian oscillator function. Neuron.2006. 50, 465-477.
46. Kennaway, D.J., Owens, J.A., Voultsios, A., Varcoe, T.J., Functional central rhythmicity and light entrainment, but not liver and muscle rhythmicity, are clock independent. Am. J. Physiol. Regul. Integr. Comp. Physiol.2006. 291, R1172–-1180.
47. Shimomura, K., Lowrey, P.L., Vitaterna, M.H., Buhr, E.D., Kumar, V., Hanna, P., Omura, C., Izumo, M., Low, S.S., Barrett, R.K., LaRue, S.I., Green, C.B., Takahashi, J.S., Genetic suppression of the circadian clock mutation by the melatonin biosynthesis pathway. Proc. Natl. Acad. Sci. USA.2010. 107, 8399-8403.
48. van der Horst, G.T., Muijtjens, M., Kobayashi, K., Takano, R., Kanno, S., Takao, M., de Wit, J., Verkerk, A., Eker, A.P., van Leenen, D., Buijs, R., Bootsma, D., Hoeijmakers, J.H., Yasui, A., Mammalian Cry1 and Cry2 are essential for maintenance of circadian rhythms. Nature 1999. 398, 627-630.
49. Bae, K., Jin, X., Maywood, E.S., Hastings, M.H., Reppert, S.M., Weaver, D.R., Differential functions of mPer1, mPer2, and mPer3 in the SCN circadian clock. Neuron.2001. 30, 525-536.
50. Christ, E., Pfeffer, M., Korf, H.W., von Gall, C., Pineal melatonin synthesis is altered in Period1 deficient mice. Neuroscience2010. 171, 398-406.
51. Maronde, E., Stehle, J.H., The mammalian pineal gland: known facts, unknown facets. Trends Endocrinol. Metab. 2007. 18, 142-149.
52. Yoshikawa, T., Yamazaki, S., Menaker, M., Effects of preparation time on phase of cultured tissues reveal complexity of circadian organization. J. Biol. Rhythms.2005. 20, 500-512.
53. Liu, T., Borjigin, J., Free-running rhythms of pineal circadian output. J. Biol. Rhythms. 2005. 20, 430-440.
54. Do, M.T., Yau, K.W., Intrinsically photosensitive retinal ganglion cells. Physiol. Rev. 2010. 90, 1547-1581.
55. Liu, T., Borjigin, J., Reentrainment of the circadian pacemaker through three distinct stages. J. Biol. Rhythms 2005.20, 441-450.
56. Ebling, F.J., The role of glutamate in the photic regulation of the suprachiasmatic nucleus. Prog. Neurobiol. 1996. 50, 109-132.
57. Hannibal, J., Neurotransmitters of the retino-hypothalamic tract. Cell Tissue Res.2002. 309, 73-88.
58. Vuillez, P., Jacob, N., Teclemariam-Mesbah, R., Van Rossum, A., Vivien-Roels, B., Pevet, P., Effect of NMDA receptor antagonist MK-801 on light-induced Fos expression in the suprachiasmatic nuclei and on melatonin production in the Syrian hamster. J. Neuroendocrinol.1998. 10, 671-677.
59. Poeggeler, B.H., Barlow-Walden, L.R., Reiter, R.J., Saarela, S., Menendez-Pelaez, A., Yaga, K., Manchester, L.C., Chen, L.D., Tan, D.X., Red-light-induced suppression of melatonin synthesis is mediated by N-methyl-D-aspartate receptor activation in retinally normal and retinally degenerate rats. J. Neurobiol. 1995. 28, 1-8.
60. Rowe, S.A., Kennaway, D.J., Effect of NMDA receptor blockade on melatonin and activity rhythm responses to a light pulse in rats. Brain Res. Bull.1996. 41, 351– 358.
61. Attanasio, A., Rager, K., Gupta, D., Ontogeny of circadian rhythmicity for melatonin, serotonin, and N-acetylserotonin in humans. J. Pineal Res. 1986.3, 251-256.
62. Oxenkrug, G., Antioxidant effects of N-acetylserotonin: possible mechanisms and clinical implications. Ann. NY Acad. Sci.2005. 1053, 334–347.
63. Tang, Q., Hu, Y., Cao, Y., Neuroprotective effect of melatonin on retinal ganglion cells in rats. J. Huazhong Univ. Sci. Technolog. Med. Sci. 2006. 26, 235-237. Teclemariam-Mesbah, R., Ter Horst, G.J., Postema, F., Wortel, J., Buijs, R.M., 1999.
64. Jang, S.W., Liu, X., Pradoldej, S., Tosini, G., Chang, Q., Iuvone, P.M., Ye, K., N- acetylserotonin activates TrkB receptor in a circadian rhythm. Proc. Natl. Acad. Sci. USA. 2010. 107, 3876-3881.
65. Dubocovich, M.L., Melatonin receptors: role on sleep and circadian rhythm regulation. Sleep Med.2007. 8(3), 34-42.
66. Reiter, R.J., The melatonin rhythm: both a clock and a calendar. Experientia. 1993. 49, 654-664.
67. Hazlerigg, D.G., Morgan, P.J., Messager, S., Decoding photoperiodic time and melatonin in mammals: what can we learn from the pars tuberalis? J. Biol. Rhythms.2001. 16, 326-335.
68. Pevet, P., Agez, L., Bothorel, B., Saboureau, M., Gauer, F., Laurent, V., Masson-Pevet, M., Melatonin in the multi-oscillatory mammalian circadian world. Chronobiol. Int. 2006.23, 39-51.
69. Reiter, R.J., Tan, D.X., Fuentes-Broto, L., Melatonin: a multitasking molecule. Prog. Brain Res.2010. 181, 127–151.
70. Bouatia-Naji, N., A variant near MTNR1B is associated with increased fasting plasma glucose levels and type 2 diabetes risk. Nat. Genet.2009. 41, 89–94.
71. Lyssenko, V., Common variant in MTNR1B associated with increased risk of type 2 diabetes and impaired early insulin secretion. Nat. Genet. 2009. 41, 82–-88.
72. Muhlbauer, E., Gross, E., Labucay, K., Wolgast, S., Peschke, E., Loss of melatonin signalling and its impact on circadian rhythms in mouse organs regulating blood glucose. Eur. J. Pharmacol. 2009. 606, 61-71.
73. Challet, E., Minireview: entrainment of the suprachiasmatic clockwork in diurnal and nocturnal mammals. Endocrinol.2007. 148, 5648-5655.
74. McArthur, A.J., Gillette, M.U., Prosser, R.A., Melatonin directly resets the rat suprachiasmatic circadian clock in vitro. Brain Res.1991. 565, 158–161.
75. Brown, G.M., Pandi-Perumal, S.R., Trakht, I., Cardinali, D.P., Melatonin and its relevance to jet lag. Travel Med. Infect. Dis. 2009. 7, 69-81.
76. Arendt, J., Broadway, J., Light and melatonin as zeitgebers in man. Chronobiol. Int. 1987. 4, 273-282.
77. Lockley, S.W., Evans, E.E., Scheer, F.A., Brainard, G.C., Czeisler, C.A., Aeschbach, D., Short-wavelength sensitivity for the direct effects of light on alertness, vigilance, and the waking electroencephalogram in humans. Sleep. 2006. 29, 161-168.
78. Sack, R.L., Lewy, A.J., Blood, M.L., Stevenson, J., Keith, L.D., Melatonin administration to blind people: phase advances and entrainment. J. Biol. Rhythms.1991. 6, 249-261.
79. Arendt, J. Melatonin and the pineal gland: influence on mammalian seasonal and circadian physiology. Rev. Reprod. 1998. 3, 13-22.
80. Cipolla-Neto J, Amaral F.G.D. Melatonin as a Hormone: New Physiological and Clinical Insights. Endocr Rev. 2018. 39(6), 990-1028.

81. Gastel, J.A., Roseboom, P.H., Rinaldi, P.A., Weller, J.L., Klein, D.C. Melatonin production: proteasomal proteolysis in serotonin N-acetyltransferase regulation. Science (New York, NY). 1998. 279(5355),1358-60.

82. Venkatesh, P., Venkhat Balaji B.R., Venu Gopal K., Vinodhini S., Vinodhini T., Vinodhini C., Chitra K. A Review on Lorcaserin - A Selective 5-HT Serotonin Receptor Agonist in Obesity Management. Int. J. Curr. Res. Rev. 2017. 9(17),37-40.