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Suprachiasmatic nucleus: center of mammalian biological clock

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ABSTRACT

Revolutions of the earth around the sun and its polar axis give rise to the unfailing seasonal procession, and movements of the moon in relation to the earth and the sun give rise to the lunar month and to the tidal cycles. Given the occurrence of all these cycles, it is not surprising to find that most organisms show rhythmic modulations in their bodily processes and behaviour as predictive and adaptive mechanisms. Biological rhythms are the natural cycle of change in our body's chemicals or functions. These rhythms display an endogenous, entrainable oscillation of a definite period and driven by a circadian clock, widely observed in plants, animals, fungi, and cyanobacteria. Anatomically circadian system consists of an oscillatory machine, including a central pacemaker, the Suprachiasmatic nucleus (SCN) in the hypothalamus, peripheral oscillators located in most tissues, various input tract and output tracts. The retina of the eye contains "classical" photoreceptors (rods and cones), which are used for conventional vision. But the retina also contains specialized ganglion cells which are directly photosensitive, and project directly to the SCN where they help in the entrainment of this master circadian clock. These cells contain the photo pigment melanopsin and their signals follow a pathway called the retino-hypothalamic tract, leading to the SCN. Non photic information can also be send by other tract like geniculo-hypothalamic tract. The SCN takes the information on the lengths of the day and night from the retina and other tract, interprets it, and passes it on to the other neural center and to the pineal gland, to synchronize the various body activities in rhythmic manner. Use of time as Chronotherapy can help to reduce adverse drug reactions and optimize drug efficacy by timing drug administration in accordance with the body's circadian rhythms. Time management can increase the performance efficiency of animal by using management of time with different physiological and biochemical reactions of body. So, Timing is everything, and optimal circadian timing in animal bodily tissues is a key aspect of well-adapted physiology and behaviour.

Keywords: *circadian clock, circadian rhythm, chronotherapy, eye, peripheral circadian oscillator, retina and suprachiasmatic nucleus.*

Introduction

Clock can be defined as a device that measure time or a device that produce synchronized pulse at regular interval. Likewise biological clock is an inherent clock mechanism of a living system that leads to periodicity of physiological and behavioral activity. Owing to the movement of the earth on its axis, around sun and the complete movement of moon around the earth result in to rhythmic seasons, day light lunar month and tidal cycles so the presence of rhythm in living organism is not unreliable. These rhythms are biological rhythm, defined as natural cycle of changes in biochemical and functional status of an organism (14). These rhythm can be classified as in the different categories on the basis of their length of time as ultradian occurs in less than 24 hrs, circadian rhythm with in 24 hrs and infradian occurs in more than 24 hrs time interval (such as circatidal, circalunar or circannual). Among all these rhythm circadian rhythm is the most important rhythm as it helps to anticipate the environmental changes as well as reduce the energetic cost of different biochemical reaction of body (18). Circadian clock is also important because mostly biological cells are daily clock and tick tock at 24 hrs time interval and are supposed to evolve to prevent DNA replication from ultraviolet radiation of sunlight, as replication was relegate to the dark. Although circadian rhythm is inert function of the body, it gets affected by the external clues (Zeitgebers) as well. Biological time keeping at the circadian cycle ensures that physiological and behavioural activity should takes place at the particular time of the day and also helps to anticipate predictable environmental changes (9). To characterize rhythm as a circadian rhythm, it has to be repeat once in a day at particular time, endogenous in nature, entrainable by external clues and compensate with temperature. The formal study of biological clock is known as chronobiology. Now a day chronobiology get attention due to its clinical significance and a proper understanding of phenomenon of chronobiology required detailed awareness about the circadian system of the body. Looking in to the importance of circadian rhythm and system in this review we address about the anatomy and physiology of the circadian system in special reference to suprachiasmatic nucleus as the central clock.

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Chronology of chronobiology

It was started in 1729 when Jeans Jacques d. ortous De Mairan performed an experiment on the tree of heliotrope in a cupboard and he saw that leaves were closed during night and open during day light so, he proposed that there should be a presence of intrinsic time keeper which respond to the light and dark cycle of environment. Later on flower clock was formed by Linneaus by observing opening and closing of leaves of different flowers in result of light and dark cycle changes. Mile stone regarding research of mammalian circadian rhythm was established by Kleitman and Richardson in 1937 in a mammoth cave to switch sleep and wake cycle for 28 hrs, however result was non significant due to small sample size.

Sir J.C. Bose was the first Indian who performed experiment on plant regarding biological rhythm. In 1972 I. Jucker and Moor identify the role of SCN in circadian rhythm. In 2002 Hatter et al. identify the connection between intrinsic photoreceptor ganglionic cells and suprachaismatic nucleus and define how environmental light entrain the brain. Milestone was recognized in 2017 when a Nobel Prize was given to Jeffery C. Hall, Michael Rosbash and Michael W. Young for their discoveries of molecular mechanisms that control circadian rhythms (7).

Anatomy of the circadian system:

Anatomically circadian system consists of an oscillatory machine, including a central pacemaker, the SCN in the hypothalamus, peripheral oscillators located in most tissues, various input tract and output tracts (Fig.1) (16).

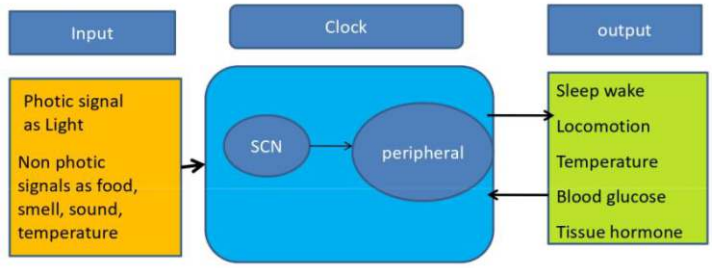

Fig.1: Schematic Presentation of Circadian system

Input tract to central clock: input formation is either in the form of light or other than the light. Light information passes through the retino-hypothalamic tract while non light information passes through the geniculo-hypothalamic tract and neurons from mid brain raphae. Photic information also passes to the suprachiasmatic nucleus through the indirect manner as some fibers of optic nerve also passes to the geniculo-hypothalamic tract center of coordination between photic and non photic information.

Photic input tract/Retino-hypothalamic tract

The most important Zeitgeber for the mammalian circadian clock is the light and dark cycle, which is detected by retinal photoreceptor and these light input signals are transmitted to the SCN via the retino hypothalamic tract where they act as phase setting signals for the master circadian clock (25). The Retino-hypothalamic tract certainly, the best characterized projection to the SCN. Both from an anatomical and functional standpoint arise from the retina. The axons of the intrinsically photosensitive Retinal Ganglionic Cells (ipRGCs) belonging to the retino-hypothalamic tract project directly, mono synaptically to the suprachiasmatic nucleus via the optic nerve and the optic chiasm.

The retina is the inner most layer of the eyeball. It is composed of a sensory portion, also referred to as the pars optica retinae, and a non sensory portion, which begins at the ora serrata and covers the ciliary body as pars ciliaris retinae, and the iris as pars iridis retinae. Sensory portion of retina can further be divided broadly in two layers, that is outer pigmented layer and inner neural layer, or in ten layers mentioned here(3):-

1. Pigment epithelium
2. Layers of rods and cones
3. External limiting membrane
4. Outer nuclear layer
5. Outer plexiform layer
6. Inner nuclear layer (Neural Layer)
7. Inner plexiform layer
8. Ganglion cell layer
9. Optic nerve fiber layer
10. Internal limiting membrane

The pigmented epithelial layer is one cell thick layer of melanin containing epithelial cells and store vitamin A. Neural layer of retina is multilayered and consists of three cell type that are photoreceptor cells (rod and cone), bipolar cells and ganglion cells. Out of all these, layers of rods and cones and ganglion cell layer have photo receptors activity (1). Photoreception involves the conversion of light energy focused on the retina to an electrical signal carried by the optic nerve to the various nuclei of the hypothalamus.

1. Rod and Cone Cells: - Rod and cone cells (20 ± 1.2 µm) consist of an outer segment, which is a photosensitive part, and an inner segment, which includes the nucleus and cytoplasm. The rod cells are long, slender, highly specialized cells and comprise an outer and inner segment. The peripheral part of the rod cells is situated between the outer limiting membrane and the pigmented epithelium, while the inner end of the rod cells extends through the outer limiting membrane into the outer nuclear layer. The rod nuclei represent the majority of the nuclei of the outer nuclear layer. Rhodopsin is the photopigment expressed within the rod outer segment and has a peak sensitivity (λmax) around 505 nm (blue-green). Rods are very sensitive to light and mediate colour less vision in very dim light (scotopic) conditions.

The cone cells also consist of an outer and inner segment. The cone outer segment is a long conical structure, considerably wider than a rod at its base and tapering down to a blunt, rounded tip. Proximal to the outer limiting membrane, the inner cone segment is found, containing the nucleus that is larger and paler than the rod nucleus. The nuclei of the cones, in contrast to those of the rods, are arranged in a single row immediately beneath the outer limiting membrane. Color vision is achieved by a multimodal integration of signals from three types of cone photoreceptors. S-cones are a minority (5–10%ofallcones) and contain short-wavelength-sensitive (λmax~430nm, blue) pigments; M-cones and L-cones contain, respectively middle wavelength (λmax~530nm,green) and long-wavelength sensitive (λmax~560 nm, yellow) pigments. The presence of these three types of cones in there retina makes color vision"trichromatic."

2. Ganglion cell: - The ganglion cell layer (12 ± 0.6 µm) includes the nuclei and cell bodies of the retinal ganglion cells of varying sizes, arranged in one or several layers. The ganglion cell bodies are very large and have round, eccentric nuclei and abundant cytoplasm.

The dendritic synapses with the bipolar cells lie in the inner plexiform layer. The non mylinated axons of the ganglion cells are arranged parallel to the surface of the retina, forming the optic nerve fiber layer. It is a thick layer(25±1.4µm).The inner most layer of this nerve fiber layer is composed of the end feet of the supporting glial (Müller's) cells. The photopigment melanopsin presents in subset of retinal ganglion cells (RGC) was first identified in melanophores, brain and eyes of the African clawed frog (*Xenopus laevis*). Remarkably, in 2002, Berson and coworkers demonstrated that RGC expressing melanopsin could directly respond to light independent of any input from rods or cones. Given the irinnate ability to respond to light, these RGC have been called intrinsically photosensitive RGC (ipRGC). Peak sensitivity of melanopsin and subsequently ipRGCs is around 480 nm (blue/indigo) in rodents, primates and humans. In addition to the intrinsic sensitivity to light, that generates a sluggish yet long lasting response at high irradiances, ipRGCs synapse with bipolar and amacrine cells and receive synaptic input from rods and cones(extrinsic light input). The rods and cones generate a fast and short response to light at low and high irradiances, respectively. Therefore, an integration of nervous signals incoming from rods,cones,and melanopsin takes place at the level of the ipRGC before being conveyed to nonimage forming(NIF)brain structures, such as the SCN for circadian photo-entrainment. To date, five subtypes of ipRGCs (M1, M2, M3, M4, and M5) have been identified. These subtypes differ by dendritic morphology, intra retinal dendritic ramification and signaling, and axonal projections (17).

- M1: These cells stratify in the inner plexiform layer (IPL) of retina, structurally having less complex dendritic arbors than the M2 and M3. Functionally, these cells are very sensitive and have the largest intrinsic light-evoked responses. Widest action potentials and spike at lower frequencies, increased intrinsicphoto-sensitivityinM1cells.
- M2: These cells stratify in the ON center sub lamina of the IPL. M2 and M3cells are closely similar with larger and more complex dendritic arbors and somas.
- M3: These cells are variable, stratifying in the ON and OFF center sublamina of the IPL.
- M4: These cells stratify in the ON center sublamina of the IPL, M4 cells have the largest somas and dendritic arbors of all subtypes.
- M5: These cells stratify in the ON center sublamina of the IPL,M5 have small and bushy dendritic arbors. (22)

M2-M5 cells innervate the core, and superior colliculus, and are involved in rudimentary,low-acuity visual function or brightness discrimination in mice and humans. These subtypes also project throughout the brain, directly influencing activity, sleep/wake states, nociception, and anxiety (18) the information received by this photoreceptor send to the ventral part of the SCN through the retino-hypothalamic projections.

(B) Non photic input:
The daily cycle of light and darkness is the principal zeitgeber for the circadian system, but non-photic cues such as cycles of feeding, temperature, social interactions, behavioral activity, or arousal and sleep deprivation interact and often antagonize in a phase-dependent manner the effect of light on the circadian rhythm, and vice versa. The two major neuronal pathways involved in non-photic regulation of the circadian system are:
(1) The serotoninergic projections- Originate in the midbrain raphe nuclei (i.e., the median and the dorsal raphe).
(2) The geniculo-hypothalamic tract (GHT)-Originates from the Inter geniculate leaflet (IGL). The GHT in all mammalian species contains Neuropeptide Y (NPY) and Gamma amino butyric acid (GABA) (12).

(3) Other afferents from different parts of brain

(1) Serotoninergic Afferents:- Serotoninergic afferents passes to the SCN through the median raphae nuclei. The median raphe nuclei are traditionally considered to be the medial portion of the reticular formation, and appear as a ridge of cells in the center and most medial portion of the brain stem. In order from caudal to rostral, the raphe nuclei are known as the nucleus raphe obscurus, the nucleus raphe pallidus, the nucleus raphe magnus, the nucleus raphe pontis, the median raphe nucleus, the dorsal raphe nucleus, caudal linear nucleus. These different raphe nuclei give rise to each projection, with the median raphe innervating the SCN and the dorsal raphe projecting to the inter geniculate leaflet (IGL).

(2) The Geniculo-hypothalamic Tract:-Medial and lateral geniculate bodies along with pulvinar constitute the posterior group of nuclei of the thalamus. A projection from the lateral geniculate complex to the SCN was apparent in the early developmental studies of geniculate efferent and subsequently shown to arise from a distinct lamina of neurons interposed between the dorsolateral and ventrolateral geniculate nuclei known as the inter geniculate leaflet (IGL). The intergeniculate leaflet is a nucleus in the lateral thalamic complex bordered dorsally along most of its length by the dorsal lateral geniculate nucleus and ventrally by the ventral lateral geniculate nucleus. The lateral border is the optic tract and medial border, the super thalamic radiation. Toward the caudal end, the intergeniculate leaflet is bordered medially by the medialgeniculate nucleus and lateral part of the zona incerta and ventrally it is bordered by the lateral terminal and subgeniculate nuclei (1). IGL gives rise to a dense neuropeptide Y (NPY)-containing projection that terminates densely and bilaterally within the ventro lateral Suprachiasmatic Nuclei (vlSCN). A Portion of the retinal afferents that innervate the IGL is collaterals offibers and also innervates the SCN. These optic afferents form complex synaptic glomeruli in the IGL that are analogous to those demonstrated in the SCN and are known to synapse upon the NPY neurons that give rise to the GHT. Thus, photic influences of the retina act upon the SCN not only via direct projections through the RHT but also in a multi-synaptic fashion through the IGL. In this way, the IGL acts to integrate photic information with other non-photic information to exert a regulatory influence upon the SCN (Fig.2).

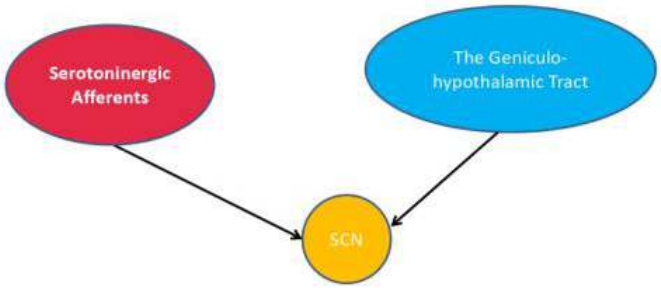

Fig.2: Schematic presentation of two main non photic input pathways to SCN

(3) Other Afferents: Although the afore mentioned afferents constitute the best characterized projections to the SCN, a number of other regions of the neuraxis project upon this nucleus have been identified, including the preoptic, arcuate, ventromedial, and dorso-medial nuclei; the bed nucleus of the stria terminalis; lateral hypothalamic area; and caudal hypothalamus (posterior hypothalamic area and tubero mammillary nuclei). Additional extra hypothalamic projections from the zona incerta, paraventricular thalamic nuclei, the lateral septal nucleus, pretectum, ventral subiculum,and infralimbic cortex have also been demonstrated.

SUPRACHIASMATIC NUCLEUS (SCN)

Suprachiasmatic nucleus is the part of the hypothalamus. Hypothalamus is found ventral to the thalamus and forms the infero- lateral walls of the third ventricle. Hypothalamus plays an important role in the control of homeostasis and reproduction. It can be divided into three major are as: anterior, middle and posterior.

- Anterior region(preoptic region)-Contains Suprachiasmatic nuclei, anterior hypothalamic nuclei, lateral and medial preoptic nuclei
- Middle region-Contains ventro-medial, paraventricular, supraoptic and arcuate nuclei
- Posterior region-Contains Mammilary bodies, Tubero mammillary nucleus and Posterior hypothalamic region

Position of SCN: The suprachiasmatic nucleus (SCN) is the primary circadian oscillator in the brain ,and is located in the ventral periventricular zone of the hypothalamus. It is situated dorsal to the optic chiasm that's why it named as Suprachiasmatic. It is medial to the anterior hypothalamic area and lateral to the ventral aspect of the third ventricle. Each of the paired suprachiasmatic nuclei is composed of a heterogeneous group of ≈10,000 interconnected small neurons that express circadian rhythms in both gene expression and in the rate of action potential firing. Its function specified after the demonstration of a retinal projection terminating in the SCN, the retino-hypothalamic tract (RHT)(22). Suprachiasmatic nuclei are distinguishable from other hypothalamic nuclei by several factors:

- Tight packing density of its small neurons, which are among the smallest in the brain.
- Frequent long perikaryal appositions.

Subdivisions of SCN: Heterogenous population of SCN can be subdivided into two groups as:
Dorso-medial group
Ventro-lateral group

- **Dorso-medial group**: It is also known as shell. It is characterized by smaller tightly packed neurons and astroglia.
- **Ventro-lateral group**: it is the core of the SCN. It is characterized by the presence of neurons with invaginated nuclei. Majority of neurons form input tract such as retina and ventral lateral geniculate nuclei terminate on this less densely packed neurons of ventro-lateral SCN.

Neurons of SCN: - The cells or neurons of SCN are smaller in size than the area of other brain region. The shape and size of dendritic appendages of neurons are variable. The neurons of SCN can be divided in different groups on the basis of dendritic arborisation as (26):

1. Simple bipolar : Characterized by a fusiform shape with two fairly straight dendrite sex tending in opposite directions.
2. Curly bipolar: Dendrites of these cells show a greater tendency to bifurcate and to curve away from the initial trajectory.
3. Monopolar cells: These cells present with a single large branching dendrite
4. Spiny neurons: These neurons are present with many large dendritic appendages.
5. Radial multipolar: These neurons have three to five primary dendrites radiating out from the cell body.

All cell types have axons both on perikarya and emanating from proximal dendrites. Dendrites of medial and ventral SCN cells tend to remain within the nucleus, however, some lateral and dorsal cells send dendrites laterally into the adjoining anterior hypothalamus, dorsally into the periventricular region, into optic chiasm and tractus infundibularis. Since, SCN dendrites receive synaptic contact outside the nucleus itself, so its neurons may be influenced by axon and neurotransmitters not found within the SCN boundaries. Most cells in SCN do communicate with one another through numerous local axon as well as dendro-dendritic, dendro-somatic, somatic-somatic and somato-dendritic synapses. Between two nucleuses commissural connection exists and SCNneurons can be defined by the synaptic targets.

Glial Cells

Other than the neurons, neuroglial cells are also present in the SCN. Astroglia are commonly found glial cells interspersed with the neurons predominantly in the dorso-medial part of SCN. Astrocytes often have a richer organelle population than do nearby neurons. These cells appear to be well-equipped for synthetic activity. Long processes of astroglia reach from cell bodies deep in the optic chiasm and branch within the SCN in the area innervated by retinal axons. Furthermore, as in other areas of the brain, gap junctions exist between astroglia ; gap junctions may serve to couple cells electrically ,to couple cells metabolically, or to allow for intercellular passage of substances from one cell to another. Glial cells help to differentially regulation of signaling to AVP and VIP neurons.

Functional Organization of the SCN

The earliest immune histochemical studies of neurons in the SCN provide dmSCN and vl SCN subdivisions and also help to probe the functional activity of the nuclei (fig.3). On the basis of secretion of different chemicals neurons can be classified as:

- Vasopressin(VP) or AVP containing Neurons:-It is the principal neurotransmitter of the neurons of the dorso-medial region. The circadian fluctuation of VP is independent of photic input and exhibits highest levels during the light phase of photoperiod. Its deficiency may cause lower amplitude rhythms of sleep, melatonin release and corticosteroids release.(6) also reported a rhythmic expression pattern of AVP in soay sheep.
- Somatostatin containing neurons: - A small group of somatostatin- containing neurons is also present in the dmSCN. They are preferentially concentrated at the border of the dm-and vl SCN. Somatostatin and its mRNA exhibit a circadian fluctuation that peaks during the subjective day.
- Vasoactive intestinal polypeptide (VIP) containing neurons:- VIP was the first peptide to be localized exclusively within the vlSCN. These neurons fill the vlSCN, extend into the underlying optic chiasm.

The levels of VIP vary across the circadian cycle, with the highest levels occurring during the dark phase of the photoperiod, however, unlike VP, the fluctuation of VIP is dependent upon photic input.

- Corticotropin-releasing hormone (CRH) containing neurons:- These neurons have also been reported in vlSCN.
- Gastrin releasing peptide (GRP) containing neurons: A substantial number of these neurons are present in the vlSCN. Gastrin releasing peptide mRNA is known to localize with VIP, and co-injection of these peptides into the region of the SCN alters the functional activity of SCNneurons.
- GABA containing neurons:- GABA (Gama aminobutyric acid) is the principal small molecule neurotransmitter in the SCN. Analyses have shown that GABA is present in essentially all SCN neurons. Terminal levels of GABA fluctuate through out the circadian cycle. It regulates SCNNeuronal activities, modulates the photic input and serve as an output signals to downstream tissues. GABA signaling is also involved in the transfer of resetting information from the SCN core to SCN shell (8).

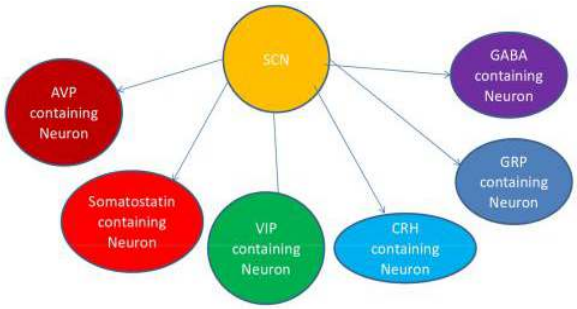

Fig.3: Schematic presentation of different chemical neurons of SCN

SCN Efferents: After receiving photic or non photic input, information processed in SCN and efferent signal send to different region of brain to further communicate the information to peripheral oscillators. Among the common principles of efferent communication that have emerged are that (1) the nuclei project to a restricted set of structures, primarily in the surrounding hypothalamus, (2) some areas receive a particularly dense innervations and may serve as "relays" for the distribution of temporal information arising in the SCN, and (3) with the exception of SCN commissural connections, the efferent of each nucleus are largely ipsilateral. SCN efferent communications can be subdivided in to 6 different groups as:

1. To preoptic area
2. To Supraventricular zone(SPZ) and periventricular nucleus
3. To dorso-medial hypothalamus nuclei
4. Commissural connection
5. To Inter geniculate leaflet nuclei

Among of these efferent communications SPZ is an important relay that plays an integral role in the maintenance of circadian rhythm.

1. Preoptic Area: This area of hypothalamus contains prominent cell groups involve in the regulations of sleep, reproduction, fluid homeostasis and thermoregulation. This area may receive direct or indirect input from SCN.

2. Supraventricular zone and paraventricular nucleus : From dorsomedial and ventrolateral subdivision of SCN projections are send to the SPZ.

Two aspects of this projection have particularly important implications as first extent to which SCN innervate the PVN and result in to release of melatonin because melatonin release involve multisynaptic projection involving the PVN. Second is control of circadian function by SPZ. SPZ acts to integrate and amplify the temporal information arising from SCN.

3. Dorso-medial hypothalamus nuclei (DMHN/DMN): Projections of SCN reaches to DMN augmented to brain stem, telencephalon and intra hypothalamic area. This pathway mediates the effect of SCN upon the plasma corticosteroidal rhythm. This area receives a dense plexus of neurons of VP fibers.

4. Commisural connections:- commissural connection present between two SCN nuclei. This connection provides an important substrate for integrated activity of SCN in control of circadian functions. Local circuit connections between nuclei and within nuclei provide dynamic regulatory capacity.

5. IGL: minor projections are sending to this area.
Other than these efferent projections some projections also send to the ventro-medial and arcuate nuclei, zona incerta and posterior hypothalamic area.

Different Functions under the control of SCN

(I) Locomotor Activity: The most apparent output of the circadian clock in animals is locomotor activity, which has also been used to define the temporal niche of an animal (diurnal, nocturnal or crepuscular). As such, locomotor activity is the most widely used tool to assess clock functioning in non human animals. The regulation of circadian locomotor rhythms involves relays in the ventral sub paraventricular zone (vSPZ) and DMH(1). Study performed (21) found that intensity of light plays a crucial role in regulating the activity rhythms of dogs. Dogs in brighter, natural light conditions showed fewer age-related differences in their activity patterns compared to those in standard indoor lighting.

(ii) Heart Rate: Resting heart rate follows a circadian pattern, being high at phases corresponding to the active part of the daily cycle. This circadian modulation of heart rate is due to a multi synaptic autonomic connection between SCN neurons and the heart with a relay at the autonomic part of the PVN. Light can also directly impact on heart rate such that light in the middle of the night and particularly in the early morning, when heart rate is low, induces an increase in heart rate, while light during the day has little or no effect. This acute effect of light on heart rate requires an intact SCN and is modulated by melatonin (18).

(iii) Temperature: Homeothermic creatures maintain a stable internal core body temperature (CBT) regardless of external thermal fluctuations. In such animals, endogenous body temperature follows regular24-h variation and is under both homeostatic and circadian regulations.CBT clearly shows an endogenous circadian profile as a minimum core temperature approximately 2 h before habitual wake time and a maximum at the end of the normal day. The SCN rhythmically regulates CBT via the dSPZ neurons and the MPO.

(iv) The Corticosteroid System: The endogenous circadian rhythm is integral to the release of cortisol from the adrenal glands, as evidenced by lesion studies that demonstrated the

lack of rhythmic secretion of these hormones after lesions of the SCN. The cortisol peak proceeds the activity period in both diurnal and nocturnal animals. Such a secretion pattern is thought to prepare the organism for awakening and the active period that follows. The circadian control of the cortisol rhythm appears to involve SCN connections to both neuroendocrine and autonomic systems. The SCN controls the activity of the hypothalamo-pituitary-adrenal (HPA) axis by affecting the release of cortisol via projections to the corticotrophin-releasing hormone (CRH) producing neurons of the medial parvocellular part of the PVH, and by adjusting the sensitivity of the adrenal cortex to adreno-corticotropic hormone (ACTH) via SCN projections to the autonomic neurons of the PVH. The cortisol rhythm cannot be fully maintained by the direct SCN pathways to the PVH, and mainly depends on indirect pathways via the vSPZ and the DMH. Cortisol levels are mainly affected by different stress stimuli. In addition, light has an acute impact on corticosteroid levels.When applied at the beginning of the active period, light increases cortisol levels in diurnal humans, and decreases levels in nocturnal rats. As the cortisol peak is thought to prepare an organism for the active period and as light is the signal for the active period in diurnal animals, and the signal for the inactive period in nocturnal animals, the acute response of light on cortisol levels in both nocturnal and diurnal animals is adaptively and evolutionary significant. The fast and acute light-induced change in plasma cortisol requires an intact SCN and appears to depend on the circadian phase, thus suggesting an active involvement of the SCN in the transmission of the light signal.

(v) Melatonin Secretion: Characterized and isolated for the first time from bovine pineal tissue by Aaron Lernerin1958, melatonin (*N*-acetyl-5-methoxytryptamine) is the main hormone synthesized by the pineal gland. Pineal gland is the part of epithalamus located just below the splenium of the corpus callosum on the body side of the blood-brain barrier. The pineal gland consists of a capsule and the parenchyma. The parenchymal cells include: pinealocytes, peptidergic neuron-like cells, pineal neurones and neuroglia which include the astrocytes, perivascular phagocyte, interstitial cells and vascular endothelium. The pinealocytes or chief cells account for about 95% of the cell population and classified as light and dark type. Each cell has a polyhedral body and 4 to 6 long processes. They are highly modified neurons arranged as cords and clusters. About 5 to 10% pinealocytes have a selective group of retinal proteins. The cell processes, 4 to 6 in number are long with expanded terminal buds. The buds end on the wall of the capillaries and on the ventricular ependyma of the pineal recess. Besides other organelles the terminal buds also contain polypeptide hormones, the monoamines and gama-amino butyric acid(GABA) which is a neurotransmitter .The major function of the pinealocytes is synthesis and secretion of the melatonin. Minute blood vessels enter the pineal gland through the trabeculae and form a network of fenestrated capillaries. They are closely related to the terminal buttons of the cell processes of pinealocytes. Various secretions of pinealocytes are discharged in the blood stream and also various amino acids and other substances required for the synthesis of pineal hormones are taken up by the pinealocytes through this route(20)

Melatonin's secretion by the pineal gland is under direct control of the SCN via projections to the autonomic division of the PVN that reach the pineal gland through a multi synaptic pathway involving relays in the inter medio-lateral column of the thoracic spinal cord and the superior cervical ganglion. This cerebrospinal pathway is the main reason why individuals with neurologically complete damage to their cervical spinal cord have been demonstrated to produce little to no melatonin. There are no blood-brain-barriers in the pineal gland. The pineal gland is the locus of one of the circumventricular organs; the ependyma of the pineal recess is lined by modified ependymal cells, the tanycytes (tall, columnar ciliated cells),for to and fro transport of neurochemicals. Transneuronal tract tracing from the pineal gland has demonstrated that the majority of the SCN neurons involved in this pathway are located in the dorso-medial portion of the SCN. Melatonin secretion may be used by the SCN to distribute rhythmic information across an organism and control other physiological functions (e.g., sleep-wake cycle, immune functions);secreted melatonin can also feed back at the level of the SCN and alter SCN function via specific melatonin receptors. The duration of the nocturnal melatonin secretory episode increases with the duration of nocturnal darkness, thereby providing a measure of day length that can be used to regulate seasonal cycles in reproduction and other functions in photoperiodic species(18).

(vi) Production performance: Environmental variables such as photoperiod, heat, stress, nutrition and other external factors have profound effects on quality and quantity of production of animals. For example, in dairy cows, it is clear that changes in photoperiod during the dry period and/or during lactation influences milk production (19). The mammary circadian clock may not only respond to systemic cues, but may also be regulated by local signals. Serotonin (5-HT), which acts as both a neurotransmitter and hormone that entrains circadian clocks, has been proposed to be a feedback inhibitor of lactation. Plasma concentrations of metabolic hormones including insulin, somatotropin, cortisol, melatonin, and triiodothyronine show diurnal patterns of secretion circadian oscillation in plasma glucose. Study performed on rumen of sheep found that the digestibility of nutrients in the rumen of sheep varies significantly between day and night. Specifically, the digestibility of dry matter (DM), crude protein (CP), and ether extract (EE) was higher during the day time compared to night time. For example, the average rumen digestibility of DM was 35.28% during the day versus 30.70% at night, indicating that the time of day directly affects nutrient digestibility in the rumen.

The activities of key digestive enzymes in the rumen, such as amylase, lipase, and cellulase, were also measured. These enzymes were found to be more active during the day, with amylase activity being 4.17% higher, lipase 3.75% higher, and cellulase 31.07% higher compared to nighttime levels. This suggests that the digestive processes in the rumen are more efficient during the day (27).

(vii) Seasonal Breeding:-In seasonal mammals, a key environmental signal responsible for the timing of reproductive transitions is day length or photoperiod. In female sheep, the short day lengths of fall and winter are stimulatory to the reproductive neuro-endocrine axis leading to ovulatory cycles and fertility; by contrast, the long day lengths of spring and summer, are inhibitory to the reproductive axis and produce an an ovulatory state. Reverse is true for long day breeder. Photoperiodic information is conveyed to the reproductive neuro-endocrine system by way of a neuro-hormonal pathway

that starts withretinal projections to the suprachiasmatic nucleus (SCN), and thence by way of a multi-synaptic circuit that includes neurons in the paraventricular nucleus, inter medio-lateral spinal cord and superior cervical ganglion, terminating in the innervations of the pineal gland. In sheep,the duration of the night time elevation in melatonin serves as an internal code of the external photoperiod , with long duration melatonin coding for short(stimulatory) day lengths, and short duration melatonin coding long (inhibitory) day lengths. Other than this hormonal mechanism neural mechanism responsible for negative feed back effect of estrogen. Two primary are as involve in this mechanism are ventro-medial preoptic (vmPOA) and retro chiasmatic area(24).

PERIPHERAL CIRCADIAN OSCILLATOR

Over the past decade it has become clear that the SCN is not the only circadian oscillator in mammalian systems. Several regions of the brain outside the SCN have the capacity to generate circadian oscillations in neural activity and virtually all organs of the body contain autonomous circadian oscillators. The oscillators outside the SCN utilize the same core clock genes that generate circadian oscillations in the SCN, and 5-10% of the transcriptome in peripheral tissues display circadian rhythms(i.e.,upto≈10%of the genes are clock-driven genes), although the subset of rhythmic transcripts is distinct among the various tissues, reflecting their specific functions. The most significant difference between the SCN oscillator and the vast majority of peripheral oscillators is that the latter depend on SCN-derived signals to maintain sustained rhythms due to the lack of strong coupling between cells in peripheral tissues compared to the tightly coupled neural network of the SCN.

In addition, while photic cues entrain the SCN and contribute to coupling among SCN neurons, peripheral tissues have no direct access to signals from there tina and thus are dependent on the SCN both for entrainment to the day/night cycle and for maintaining intercellular coupling. Lastly, a crucially important temporal signal that helps maintain synchrony among peripheral (and central) oscillators is the SCN-regulated daily rhythm in glucocorticoids (cortisol in humans and corticosterone in rodents). Glucocorticoids are potent transcriptional regulators. The robust corticosterone rhythm is critically important in synchronizing subordinate circadian. oscillators in the periphery. This is accomplished through the action of glucocorticoid receptors(GRs)on glucocorticoid-responsive elements within the promoter and enhancer sequences of the*Per1*and*Per2*genes.

MOLECULAR MECHANISM OF CIRCADIAN RHYTHM:

The core clock mechanism which underpins these rhythmic changes, is a cell autonomous intracellular transcriptional–translational feedback loop (TTFL) which oscillates with a period of approximately 24 h. The TTFL itself comprises a number of 'clock genes' [including period 1 and 2 (Per1-2), cryptochrome 1 and 2(Cry1-2), Circadian locomotor output cycles kaput (Clock), and Brain and muscle ARNTL like 1{Bmal1 (Bmal1 or Arntl)} and the transcription of various downstream genes is controlled either via transcriptional action of core clock genes or via clock output genes such as Dbp (D site of albumin promoter binding protein)(6). Measure the gene expression in sheep that were first acclimated to a short photoperiod (8 hours of light) and then transferred to a long photoperiod (16 hours of light) after an 8-hour delay in lights off.

The expression levels of key clock genes, specifically Per1, Per2, and Fbxl21, significantly increased following the transition to a long photoperiod. This suggests that these genes play a crucial role in the sheep's ability to synchronize their biological rhythms with the changing environment.

The time and tissue specificity of these down stream'clock-controlled' genes regulates the peripheral clocks found throughout the body. It is also notable that many clock-controlled genes are themselves transcription factors which will drive secondary transcriptional rhythms within cells, allowing the generation of rhythms not directly regulated by the core clock genes. Expression analysis has demonstrated that the rhythms generated by different transcription factors have different properties. Additionally, post-translational mechanisms such as RNA interference and protein Ubiquitination can further regulate the cycling of the core clock genes, the clock-controlled genes, and their corresponding outputs. These multiple levels of regulation allow for great complexity and flexibility in both the core and peripheral clocks found throughout the body.

(11) studied the expression patterns of six clock genes (Clock, BMAL1, Per1, Per2, Cry1, and Cry2) in Small-tailed Han (STH) sheep during two phases of the estrous cycle: the follicular phase and the luteal phase and found that all six clock genes were found to be expressed in various tissues, including the brain, cerebellum, hypothalamus, pituitary, ovary, uterus, and oviduct, during both the follicular and luteal phases.

The core clock genes constitute a transcriptional feedback loop which maintains a period of approximately 24 h. Note that CLOCK and BMAL1 regulate the expression of two Per genes (Per1 and Per2) and two Cry genes (Cry1 and Cry2). In the absence of external cues, these clocks will maintain rhythmicity with a period(tau,τ)of around24h.However,as a key function of the circadian clock is to predict changes in the environment, the core clock needs to synchronize with (or become entrained to)external time cues/zeitgebers (4).

Significance of circadian rhythm:

a.Chrono-management:- Circadian clocks have an impact on many aspects of animal physiology as it help to regulate sleep patterns, feeding behaviour, hormone release, blood pressure and body temperature. Molecular clocks also play critical roles locally in many tissues. Ablation of clock genes in animal models results in arrhythmic production of hormones, such as corticosterone and insulin. Clock genes also exert a profound influence on metabolism through the control of gluconeogenesis, insulin sensitivity, and systemic oscillation of blood glucose**.** By understanding how chronobiology works, scientists and doctors can apply its principles to bettering life. So, this discipline can be use as chrono-management of animals, that is the management of animals with time to increase the productivity as well as performance of animals. Chronobiologists can develop light therapy for improve the production performance of animals. Understanding the seasonal rhythms through chronobiology can help to treat other disorders, such as seasonal affective disorder. Managing diet with a chronobiological application is one of the newest areas of sub-study in the field. Chrono- diets optimize cycles of hormones in the bloodstream (like insulin, glucagon and thyroid hormones) to plan eating when food will be most efficiently digested and utilized for nutrition.

b. Chronotherapy:- Use of time as Chronotherapy can help to reduce adverse drug reactions and optimise drug efficacy by timing drug administration in accordance with the body's circadian rhythms. The principle is very simple and derives from practical observations showing that patients treated at different times but with the same drug experience differential levels of toxicityor improvements in drug efficacy. With regard to the latter, if the expression of a drug target fluctuates periodically, then said drug will be more efficient if administered when the target is expressed at its highest level. Beyond chronotherapy, strengthening the link between the circadian clock and medicine may lead to additional innovations. Indeed, although still in a primordial phase of development, drugs targeting circadian clock regulators may provide new therapeutic strategies against various diseases. Recently, for instance, observations showing that pharmacological modulation of REV-ERBα and REV-ERBβ (two crucial circadian regulators)is selectively lethal in cancer cells in culture and in glioblastoma animal models and it seems to have a wide therapeutic window with limited toxic effects (23). Such observations shedding light on a new therapeutic paradigm could put the circadian clock machinery at the centre of the next pharmacological revolution. In the future, many disorders may benefit from the development of drugs targeting circadian clocks such as metabolic, mood disorders, production performance and others. It's time for a new era of medicine.

Conclusion

The precise regulation of circadian timing, whether driven or merely coordinated by the central circadian pacemaker in the SCN, is crucial to the sustenance of both physical and mental health. Much work remains to be done to uncover the full range of the mechanisms through which this regulation is effected, but each discovery yields new opportunities to help restore the temporal balance that is required to live in harmony with the ineluctable cyclicity of the earth's rotation. Information regarding the anatomy and neurochemistry of the SCN can act as a window into understanding the ways in which the brain clock regulates physiology and behavior on a daily basis. The story to date shows how an apparently simple functions—namely, adjustment to daily changes in light-dark cycles—is orchestrated by a small bilateral hypothalamic nucleus comprised of about 20,000 neurons and about one third as many astrocytes. The implications of circadian rhythms point to an optimal time for many biological processes. Good alignment of various circadian rhythms in bodies is necessary for optimal health. Disruptions in circadian rhythm are associated with suboptimal function and poor health. Also, it has been documented that many of the most useful drugs available have targets in the circadian system. In most organs, oscillating genes peaked around dawn and dusk. Importantly, themajority of drugs directly target the products of rhythmic genes, many of which have short half-lives and might benefit from timed dosage. Infact, an entire field of chronotherapeutics is devoted to optimal timing for the administration of various drugs. Timing is everything, and optimal circadian timing in animal bodily tissues is a key aspect of well-adapted physiology and behaviour.

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REFERENCES

1. Akers RM, Denbow DM, 2008. Anatomy and Physiology of Domestic Animals, 1st Edn., Blackwell Publishing, Iowa, USA, pp227-289.

2. Albrecht U, 2012. Timing to perfection: the biology of central and peripheral circadian clocks. Neuron74:246-260. doi: 10.1016/j.neuron.2012.04

3. AlyK,2003.Glyco histochemichal, immune histochemical and electron microscopic examination of the bovine eyeball. Ph.D thesis(VeterinaryMedicine)Ludwig-Maximilians-University Munich ,pp 74-78.

4. Banks G, Nolan PM, Peirson SN, 2016. Reciprocal interactions between circadian clocks and aging. Mammlian Genome27:332–340.https://doi.org/10.1007/s00335-016-9639-6

5. Berson DM, Dunn FA, Takao M, 2002. Photo transduction by retinal ganglion cells that set the circadian clock. Science 295(5557):1070-1073. doi: 10.1126/science.1067262.

6. Dardente, H., Dardente, H., Wyse, C. A., Lincoln, G. A., Wagner, G., Wagner, G., Hazlerigg, D. G., & Hazlerigg, D. G. (2016). Effects of Photoperiod Extension on Clock Gene and Neuropeptide RNA Expression in the SCN of the Soay Sheep. PLOS ONE 11(7). https://doi.org/10.1371/JOURNAL.PONE.0159201

7. Erren TC, 2018. Achronology of chronobiology. Physiology News 113**:** 32-35.https://doi.org/10.36866/pn.113.32

8. Evans JA, 2016.Collective time keeping among cells of the master circadian clock.Journal of Endocrinology230: 27-49.https://doi.org/10.1530/joe-16-0054

9. Evans JA, Gorman MR, 2016. In synch but not in step: circadian clock circuits regulating plasticity in daily rhythms. Neuroscience 320: 259 280. https://doi.org/10.1016/j.neuroscience.2016.01.072

10. Foster RG, Provencio I, Hudson D, Fiske S, DeGrip W, Menaker M, 1991. Circadian photo reception in the retinally degenerate mouse(rd/rd).Journal of Comparative Physiology169:39–50.https://doi.org/10.1007/bf00198171

11. Han, Q., He, X., Di, R., & Chu, M.-X. (2021). Comparison of expression patterns of six canonical clock genes of follicular phase and luteal phase in Small-tailed Han sheep. Archives Animal Breeding 64(2): 457–466. https://doi.org/10.5194/AAB-64-457-2021

12. Hannibal J, Fahrenkrug J, 2006. Neuronal input pathways to the brain's biological clock and their functional significance. Advances in Anatomy, Embryology and Cell Biolology182:1-71. PMID: 1656643

13. Hattar S, Liao HW, Takao M, Berson DM, Yau K W,2002.Melanopsin–containing retinal ganglion cells: architecture, projections and intrinsic photosensitivity. Science295(5557):1065-1070.https://doi.org/10.1126/science.1069609

14. Kuhlman SJ, CraigL M, Duffy JF, 2018. Introduction to chronobiology. Cold Spring Harbor Perspectives in Biology10:1-11.https://doi.org/10.1101/cshperspect.a033613

15. Lerner AB, Case JD, Takahashi Y, Lee TH, Mori W, 1958.Isolation of melatonin, the pineal gland factor that lightens melanocytes. Journal of American Chemical Society 80(10): 2587.https://doi.org/10.1021/ja01543a060

16. Lopes RS, Resende NM, Honorio-França AC, França EL, 2013. Application of bioinformatics in chronobiology research. The Scientific World Journal10:1- 8 .https://doi.org/10.1155/2013/153839

17. Mc MahonDG, LuvonePM, Tosini G,2013. Circadian organization of the mammalian retina: from gene regulation to physiology and diseases. Progress in Retinal and Eye Research1:58–76.https://doi.org/10.1016/j.preteyeres.2013.12.001

18. NajjarRP, ZeitzerJM, 2017. Anatomy and Physiology of the Circadian System. *In*: :Miglis, M.G.(ed.)Sleep and Neurologic Disease,1st Edn.,Academic Press,Cambridge,United Kingdom , pp 29-53.

19. Plaut K, Casey T, 2012. Does the circadian system regulate lactation? Animal 6(3):394–402.https://doi.org/10.1017/s1751731111002187.

20. Sahai A, Sahai RK, 2013. Pineal gland: A structural and functional enigma. Journal of Anatomical Society of India 62:170-177.http://dx.doi.org/10.1016/j.jasi.2014.01.001

21. Siwak, C. T., Tapp, P. D., Zicker, S. C., Murphey, H. L., Muggenburg, B. A., Head, E., Cotman, C. W., & Milgram, N. W. (2003). Locomotor activity rhythms in dogs vary with age and cognitive status. Behavioral Neuroscience 117(4): 813–824. https://doi.org/10.1037/0735-7044.117.4.813

22. Sollars PJ,Pickard GE, 2015. The neurobiology of circadian rhythms. Psychiatric Clinic of North America38 (4):645–665.https://doi.org/10.1016/j.psc.2015.07.003

23. Sulli G, 2018. Time for a medical revolution. Physiology News113:10.https://doi.org/10.36866/pn.113.10

24. Weems PW, Goodman RL, Lehman MN, 2015. Neural mechanisms controlling seasonal reproduction: principles derived from the sheep model and its comparison with a msters.Frontiers in Neuroendocrinology 37:43–51. https://doi.org/10.1016/j.yfrne.2014.12.002

25. Welsh DK,TakahashiJS,KaySA,2010.Suprachiasmatic nucleus:cell autonomy and network properties. ––Annual Revision of Physiology72:551577.https://doi.org/10.1146/annurev-physiol-021909-135919

26. Vandenpol AN,1980.The hypothalamic suprachiasmatic nucleus of rat:intrinsic anatomy.Journal of ComparativeNeurology191:661-702. https://doi.org/10.1002/cne.901910410

27. Zhang, C., Tu, Y., Ma, T., and Diao, Q. (2022). Connection between Circadian Rhythm and Rumen Digestibility of Concentrate and Roughage in Sheep. Agriculture 12(12): 2152. https://doi.org/10.3390/agriculture12122152