

A STUDY ON THE IMPACT OF CIRCADIAN RHYTHM IN HUMAN LIFE

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ABSTRACT

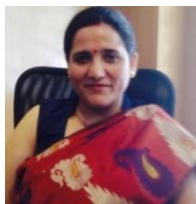
The series of Circadian rhythms (CR) are of endogenic independent oscillator's causes by the molecular in circadian clock which acts on synchronize internal time with the outside environment on daily basis. The process of circadian clock is a big organizational factor for about all emotional and mental actions and its variations has intense outcomes on health of human. Therefore, the circadian rhythm set off a system having self-control on body of human to adjust our activities, habits and functions of body. Regarding to this, daily functions should have trouble over food, physical activities of surroundings comprised lightings, exercises, work habits, sleeping and various activities. All contemplation and essentially, a mind clock should be set with daily function for a healthy lifestyle.

Keywords: circadian rhythm, mind clock, human, self-control, sleeping

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INTRODUCTION

Actual working and body and mind of a person rely on how the person sustains a healthy circadian rhythm. Circadian rhythm is normally a biological clock that is developed in our brain and function on day and night both. The circadian rhythm of human body is a system of self-controlling to maintain our eating habits, function of body and actions like getting hungry and digestion, passing urine and sustaining blood pressure, waking up process and body temperature. Therefore, our eating style, food and time, life disciplinary procedure, lights and our body experience and other day to day manner of living elements are the essential factors that design everyone's circadian rhythm.

As per the explanation of [8] that disturbance of the circadian rhythm can be directly lead to grow potential disease and emerging as the main source for the seriousness of probable diseases within human body. They also recognize studies to clearly hold out that disturbance of circadian rhythm can lead to more concern than its value. Hence, it is very essential for everyone to sustain a better circadian rhythm to surpass some unwanted circumstances in our daily life.

CIRCADIAN RHYTHM SYNCHRONIZERS

Cell- autonomous circadian clock exist in about every eukaryotic. It also reveals 24 hr physiologic oscillations and can also be affecting by outer signal. These all outer signals are called "synchronizers", "zeitgeber" or "entraining agents" can restart the circadian clock of body and put all the cells in the same stage of circadian oscillation, a procedure called circadian rhythm synchronization. As per the explanation of Li et al., (2017), "ZT" is utilized to depict outer prompts that synchronize CR, for example, LD cycles or temperature cycles, and "CT" is used to portray timing without outside signs. In the field of chronobiology research, regardless of whether in vivo or in vitro, specialists utilize these entraining operators to synchronize CR of the trial creatures or cells. An assortment of elements which go about as synchronizers are summed up in Figure below:

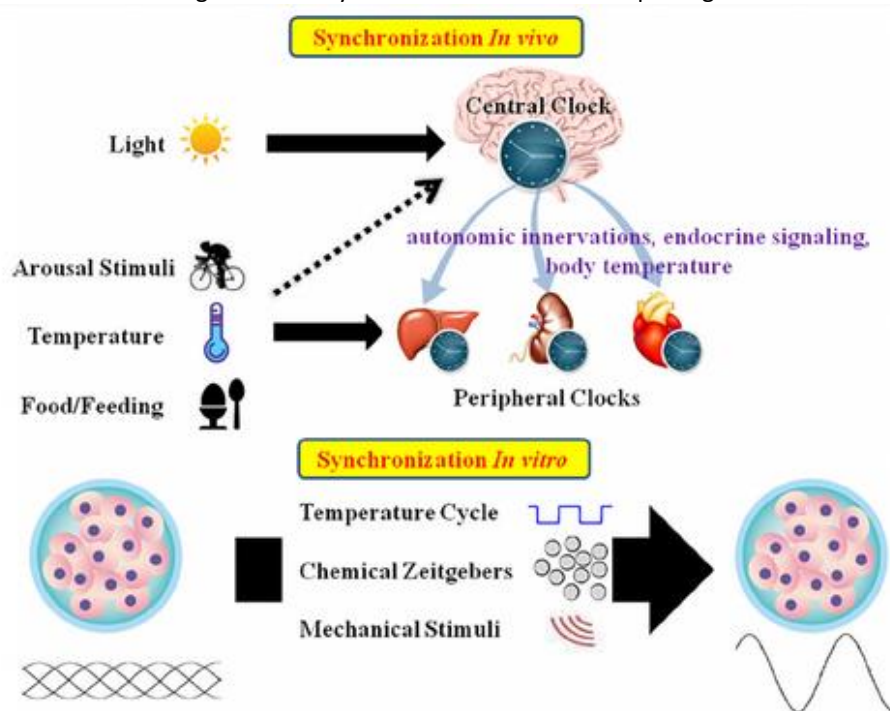


Figure 1: Schematic summary of in vivo and in vitro circadian synchronization. In vivo, the photic zeitgeber mainly entrains the central clock, which regulates the peripheral clocks through the internal timing cues including autonomic innervations, endocrine signaling and body temperature; the non-photoc zeitgebers including arousal stimuli, temperature and food mainly entrain the peripheral clocks. In vitro, the circadian oscillations of cells or explants can be synchronized by temperature cycles, chemical factors (such as Dex, Fsk, or horse serum) and mechanical stimuli.

- **Light**

Different organisms need the time information regarding the change in the light intensity through the day in order to reset their own clock which is basically states as "photic entrainment" by Foster and Roenneberg (1997). In chronobiology experiments, light is basically known as a stimulus to induce the responses from the circadian clock. The light basically determining the cascade which is fairly complex. In the case of vivo, PRGCs basically are able to receive light information, which is basically transferred to the SCN basically through the

RHT in direct manner. As per the explanation of [35] [37] [40] van Diepen *et al.*, (2015); [57] Mouland *et al.*, (2017); Astizet *et al.*, (2019), The regulation of the peripheral clocks by the SCN via secreting certain neurohumoral factors (Mohawk *et al.*, 2012). The light sensitive photo pigment melanopsin is basically expressed in the pRGCs which basically respond through the series of responses to light [31][21] Schmidt *et al.*, 2011). Provoking of melanopsin basically cause the activation of the G protein linked with the signalling of the cascades and PLC pathway which basically lead to the opening of the TRPCs such as TRPC6 and TRPC7, Ca²⁺ influx, and cellular depolarization. The input of the SCN basically depends on the monosynaptic RHT. One of the major primary transmitters in the RHTs are glutamate, PACAP, SP and aspartate [24] [15]; [32][28] [26]. Glutamate, which basically stated regarding the glutamatergic anode such as NMDA or AMPA anodes which are basically known to be the main signal for the photic entrainment (Mikkelsen *et al.*; (1993), Golombek and Ralph, (1996); [12] Peytevi *et al.*, 2000; Michel and Colwell, (2001); Paul *et al.* *et al.* (2005) and which states increase in the intracellular CA²⁺ concentrations (Kim *et al.*, (2005) PACAP, which basically helps in the activation of the PAC1 receptor which is basically also known for mediating synchronization to light [33] 2008; Shen *et al.*, (2000), [18] [34]. The influx of CA²⁺ basically activates range of kinases which include PKA, MAPK, CaMK, PKCA and PKG [46]. The kinases are basically included in the phosphorylation of CREB which basically combines to cAMP response elements in the promoters, which basically lead to in transcription of the clock genes such as PER1 and PER2. Apart from this there are different transcription factors such as c-FOS [74] and EGR1 [62] which also indulge in the regulation of the SCN clock through the method of the optical signals.

The things which are based on the RHT innervations and the neurochemical nature of the cells, where the SCN is basically divided into two main subdivisions which are the VL area which is known to be the core area and the DM area which is known to be the shell area (Moore *et al.* (2002). The VL-SCN basically consist of VIP and gastrin releasing peptide which is basically located above the optic chiasm, and basically receive like most of its photic input from RHT innervations. In contrast to this the DM-SCN region is basically that region which consists of AVP and Arginine, which basically receive large number of the neural signals from the hypothalamus, limbic areas and the VL-SCN. The VL-SCN basically respond to the photic stimuli during the subject night and have interaction with the DM-SCN neurons through different kind of neurotransmitters such as VIP, GRP and SP (Best *et al.*, (1999); Berson *et al.*, (2002), which basically results in the synchronization of the DM-SCN to the expression of these kind of proteins. Therefore it can be stated that DM-SCN neurons basically depend on neuropeptide which are basically released from the VL-SCN, as they basically show strong changes [48] [46] [4]

- **Arousal Stimuli**

Other stimuli can completely synchronize CR, that basically result in the “non-photoc entrainment.” Arousal stimuli basically are the non-photoc kind of entrainments which basically constitute of the social interactions, exercise, depression, stress and caffeine included arousal [47]. There are different kinds of the species which respond in different manner to the arousal stimuli. For example, in the day, gentle handling or wheel running basically cause a robust phase advance in locomotor activity rhythms of Syrian hamsters, whereas these stimuli do not arise in same phase of advance in the behavioural rhythms of rats or mice [3] Mistlberg *et al.*, 2002). The phase advance in the peripheral clocks such as liver and kidney can be instigated by restraining stress or running wheel exercise during the intervening of the light phase in mice (Thara *et al.*, (2015), Sasaki *et al.*, (2016). The above given studies basically states that under LD cycles, the peripheral tissues usually respond to the behavioural entrainment without impacting the SCN. However in the darkness which is basically projected in daytime, different behavioural rhythms of the mice is basically observed under several hour daily wheel stimulation which basically results that the master clock mice is influenced by the light rather than arousal stimuli.

One of the reviews of the study made by [28] stated that the arousal stimuli can be transferred to the SCN by two major paths. The GHT from the thalamic IGL employs NPY, GABA, and endorphins as neurotransmitters and plays a major role of importance in enabling of the Y2 receptor/PKC pathway. One of the other is the serotonergic median raphe nucleus projection to the SCN, where the serotonergic effects are arbitrated by 5-HT_{1A/7} receptors and PK activation. This mechanism and scenario is basically applicable for behavioural entrainment of the peripheral clocks which basically include physiological factors such as glucocorticoids, sympathetic nerves, oxidative stress, hypoxia, PH, cytokines and temperature (Tahara and Shibata, 2018)

- **Food/Feeding**

Animals CR is basically identified by light and the central clock for light response, the SCN basically considers a light-entrainable oscillator. Food is basically known to be a non-photoc stimulus which can basically reset the circadian rhythm. There have been different studies made in order to confirm the existence of a FEO, but there different anatomical location and molecular time keeping mechanisms of the FEO have been not stated in a clear manner. In the case of the mammalian research, food is provided to the mammal and is consumed within

couple of hours which the situation is basically termed as time-restricted feeding or temporal food restriction, and is major used is basically to study FAA [11]. FAA basically refers to the production of the FEO, which is done under time restricted feeding but disappears under ad libitum access and reoccurs during the fasting [56]. The mice basically are allowed to a certain limited dieted libitum typically ingest 60-80% of the daily food consumption during the night time.

The circadian clock is basically reset during the fast feeding signals in the peripheral tissues which basically cause the periodic availability of different circulation of the micronutrients [78]. For example, ingestion basically cause the release of the insulin into the blood and ingest the clock gene expression in insulin sensitive tissues in the liver, adipose and muscle [53]. Feeding basically also helps in improving the blood glucose levels and high glucose concentrations basically help in reducing the expression of PER1 and PER2 in the fibroblasts and in indirect manner help in regulating AMPK, which basically help in maintaining the firmness of CRYs [43]. There are different proofs which state that liver is basically a communication centre of the FAA synchronization signal. In the case of time restricted feeding, the liver increased β OHB production through the regulation of Cpt land Hmgcs 2by Per 2, which was basically used as a signal to cause animals predict feeding time [14]. In addition, food restriction basically may bring change in the anabolic/catabolic cycles of tissues which can basically affect the cellular redox state and basically further promote the circadian feedback loop (Mendoza, 2007). For instance, NADH and NADPH, the classical co factors in the case of the redox actions which basically helps in the promotion of the combination of the CLOCK/BMAL1 and NPAS2/BMAL1 dimers to DNA, while their oxidized forms, NAD (P) +. Basically promote this binding [64][65] [67]. The restricted kind of feeding basically promote the body temperature cycle which have been confirmed to entrain peripheral clocks. [19] [71] stated that the oscillators which are in centre are basically not affected by any kind of temporal food restriction during the light phase of the day. SCN derived physiological rhythms such as locomotor activity and the temperature of the body can be entrained by caloric restriction which is also known as the hypocaloric diet, which basically is characterized by the caloric intake reduction to 60% of the animal's total daily food intake under LD cycles or the time restricted feeding in a constant darkness. The process through which the SCN clock is basically affected by the caloric restriction which has not been characterized, there have been different studies made in the past which stated the condition of the receptors of the metabolism related hormones such as insulin, leptin and ghrelin which basically which basically exist in the SCN cells and which include the process of the synchronization of the SCN. The feeding basically helps in regulating the brain structures which goes in straight manner to the SCN such as the DM hypothalamus and the arcuate nucleus through orexin and ghrelin [2] Mieda et al., (2004) [44] [49] [1]. The glucose which is present basically helps in promoting the neural activity phase in the vitro SCN slices [30]. The researchers are basically helping in order to promote certain kind of factors which influence SCN.

• Temperature

Temperature basically can be known as the non-photic synchronizer with a weakness synchronization effect of the light. Robero Refinetti founded that like about a percentage between 60 to 80 mice can be adapt by the normal temperature cycles, and stable entrainment which takes longer in response to the temperature cycles that LD cycles as stated by Refinetti, (2010). Through the implementation of certain kind of physiological process it can be stated that these process depend on the ambient temperature, the CR system basically plays a major role of importance which is known as the temperature compensation, in which the circadian oscillation remain impenetrable to the temperature changes which basically results in the period length still maintaining approximately 24 hours despite the ambient temperature changes [38] [50]. In addition, the SCN clock basically does not react to the temperature stimuli, whereas the cells and the tissues which are outside of the SCN can be synchronized by the fluctuations in the temperature. [9] [10][52]. There is one of the major reason that the SCN is resistant to the changes in the temperature which is basically due to the circadian clocks in the SCN cells which have robust couplings and after the case of the uncoupling of the SCN cells by the use of the tetrodotoxin or nimodipine, the temperature sensitivity was detected due to the reason that temperature is weak synchronizer and is not used as zeitgeber in experiments of the animal.

In one of the study the phase shift of the clock in response to the simulate body temperature changes has been stated in vitro [9] [10] [66] [23] and the amplitude of the circadian gene expression was basically promoted by the temperature cycles [20] [70] [23]. In the case of the mammals the cell sense basically fluctuations in the temperature basically through the series of the temperature stimulated TRP channel sub family members which are called thermo-TRPs, and in this the each of them are basically activated in the narrow thermal range [58]. The inherent scenario of the temperature basically affects the CR which can be arbitrated by HSF1 and CIRBPs (Kiet et al., 2015). HSF1 can be basically known as circadian transcription factor which combines the heat shock element sequence thereby causing circadian activation of the downstream

promoters such as Per2 [41] [61] [72]. The CIRBP-mediated post-transcriptional regulation allows high-amplitude clock genes express which include core clock gene CLOCK.

- **Chemical Factors**

In vitro experiments lack the humoral and neuronal factors that can act as entrainments in vivo. As such, cultured cells or explants are desynchronized and circadian oscillations are absent. Thus, to observe endogenous oscillations of cells or explants in vitro, chemical factors with similar effects to in vivo entrainments are required.

Many chemical factors can function as synchronizers. It has been reported that glucocorticoid, a kind of anti-inflammatory hormones released by the adrenal cortex, serves as a vigorous synchronizer of peripheral tissues [7], [80] [68] [16]. Dex, an artificial glucocorticoid, exposure for 1h can be used to restart the oscillations of circadian clock genes [7][78]. Glucocorticoids activate GRs, which bind to the GREs on the promoters of core clock genes such as Per1, Per2, and E4bp4, thereby directly activating the core clock cycle, or by activating the transcription factor HNF4 α , which targets downstream rhythmic genes without GRE elements [59] [16]. Dex cannot be used for SCN synchronization, because the SCN does not express GRs.

A study performed in 1998 indicated that serum shock could induce the rhythmic expression of Perl, Per2, Revb- α , Dip, and Tefin cultured rat fibroblasts [6]. Thereafter, serum shock was used to synchronize the circadian oscillations of various tissues, immortalized cells, and fibroblast cells. This study suggested that various factors in the blood could stimulate rhythmic oscillations. Previous reports hewed that various factors such as such as EGF [39] calcium [7] glucose [36] PGE2 [75], 1 α , 25-dihydroxyvitaminD3 [29] and atomoxetine [51] can synchronize clock genes. Moreover, serum shock can induce Ser/Thr phosphorylation of CLOCK through the Ca²⁺-dependent PKC pathway [69] or activate the p42/44 MAPK pathway in a manner similar to that observed in response to light pulses [27][79] which may cause resetting of the clock. In addition, a previous report showed that blood-borne signals activate GTPase RhoA, which promotes G-actin polymerization into F-actin, resulting in release of MRTFs into the nucleus, thus regulating the transcription of clock genes [25].

Another common chemical synchronizing agent, FSK, has a similar mechanism to that of serum. FSK directly activates AC, which activates CREB through phosphorylation by promoting the synthesis of CAMP and activating PKA indirectly [79].

- **Mechanical Stimuli and Oxidative/Hypoxia Stress**

One of the recent study basically stated regarding the intermittent uniaxial stretching of the bone marrow which is basically derived from mesenchymal stem cells, DPSCs and adipose tissue derived from the mesenchymal stem cell which can basically be helpful in resetting the CR, which basically results in the synchronization effect which is as same to the one observed in response to the Dex Treatment [63]. The change in the media also helps in resetting the cellular CR. The mechanical stimuli basically help the researchers with other type of scenarios in order to reset the circadian clocks of cells, such as DPSCs, which cannot be synchronized by other way. The process by which the mechanical stimuli synchronization is done is still not clear, but it is stated that there is major involvement of the RhoA pathway, by which the short duration fluid shear force which bring change in the expression levels of the clock genes in osteoblasts (Hmamaura *et. al.*, (2012).

The hypoxic stimuli or the oxidative stimuli may basically lead to the entrainment of the circadian clock. In vitro, oxidative stimulation through the hydrogen peroxide basically synchronize the cellular circadian oscillations in dose and time dependent manner [73]. In the case of the vivo, there are the phase shifts in the peripheral clocks such as in the kidney and the liver which are basically observed after the penetration of the hydrogen peroxide injection (Geerdinke *et. al.*, (2016). There is that situation as well where the master clock response to the oxidative stress is of unknown manner. The oxygen cycles basically synchronize the cellular clocks through key transcription factors in the case of the culture fibroblasts, HIF1 α , which basically has same to same PAS domain to CLOCK and BMAL 1 (Adamovitch *et. al.*, (201). The onset of a 6-h-shifted dark period, the hypoxic stimulation for 2 h advanced phases of the activities of the locomotor basically in response to the new LD cycle which basically resulted that the peripheral oscillations and the central oscillations can be reset by the process of hypoxi stimulation. If combined together the oxygen signals may induce the circadian synchronization vitro.

I. MAINTAINING CIRCADIAN RHYTHM

There are different kind of studies made which state the major importance of maintain circadian rhythm for a healthy lifestyle (e.g., [5] [8] [42] [22] [5] stated that there are basically ten steps which one should follow in order to set a circadian clock which would basically help in the regulation of the functionality of the human organs which are mentioned as below:

- Embracing seasonal changes

- Healthy and eating on time
- Be social during daytime and intimacy during night
- Managing the food, drinks and blood sugar levels.
- Involving in regular physical activities
- Sleeping in comfortable dark room with healthy temperature
- Sleeping on time
- Managing mental stress
- Avoiding bright or blue light
- During day time getting proper exposure to blue light.

Ballayntyne (2014) further stated different other methods for fixing circadian rhythm which consist of having meal on time, maintaining sleeping patterns, light manipulation.

- ROUTINIZING: one of the best ways is to manage your routine as body gets regular pattern.
- LIGHT MANIPULATION- another method is exposure to the white blue light to your body in order to reduce melatonin, during daytime and setting lights in dim in the evening in order to make your body feel sleepy during sleeping time.
- TAKING MEALS ON TIME: Intake of the meals on the time between different time of interval and avoiding meals can basically affect circadian rhythm. [55] stated that there should be 16 hours fasting between dinner and next day breakfast which can help to keep the human body in healthy manner,
- MAINTAINING SLEEPING PATTERNS: it is good that if we avoid the daytime sleep more than 20 minutes in order to track on night sleeping. On time sleeping and awakening pattern can impact the lifestyle.

II. BENEFITS OF HEALTHY CIRCADIAN RHYTHM

People should enjoy a healthy life that have coincide circadian rhythm inside the body. This suggested that the one should sustain a 24-hr cycle inside time saving mechanism that controls the fundamental functions of sleep-wake and feeding figure. Circadian rhythm can also assist in sustaining various physiological modifications that comprised heart rhythm rate, control body temperature, produce of RBCs and hormone and control metabolism. So, it is very essential to hold circadian rhythm by a people to locate his or her to daily manner of living, behaviour and mind.

As per the explanation of [13], Disturbance of a coincide circadian rhythm has a connection to different sleep disorders, like sleeplessness and sudden changes in or infringe current circadian rhythm can likely result into health related issues of obesity, bipolar disorder, diabetes, depression and seasonal disorder. As per Dr. Michael Roizen, Circadian rhythm is very much alluring for sustaining teenage skin, high immunity, better blood sugar and more energy. Scholars specifically accept that circadian rhythm is a method of framing our life on daily basis in a healthy approach. Nonetheless, there is high probability that our circadian rhythm can get scatter due to the sudden changes in social, cultural, economic, technological, physical and political surroundings of our working place and state of living.

III. CIRCADIAN RHYTHM AND IMPACT IN HUMAN HEALTH

The circadian rhythm is an interior cycle that normally directs our biological cycles in a 24-hour time span. The word Circadian originate from Latin "Circa" means to "Circa" and "diēm" means to "day", subsequently changing "Circa diēm" into "Circadian" as a solitary word for "Around the day".

Human body gets energetic from arousing at a time and goes through a frame of 24 hours in a day. During this period, our body feels differing enthusiastic, behavioural and biological nature (like resting, urine passing, and hungry, dozing, thirsty and so forth.). At the point when a human body feels such experiences for a time of constant term, the body gets synchronized to the experience and that can get changed into our 24-hour schedule. The biological cycle that a human body follows as a daily practice inside a 24-hour cycle is currently known as the "Circadian Rhythm". In a straightforward term, this infers that for a model, everybody's routinized eating time greatly affects the manner in which our body cycle the food absorption. Essentially, dozing pattern of an individual likewise greatly affects the method of working our mind just as organs of human body.

As per the explanation of [22], As a human circadian rhythm is similar for everybody as unique as much as possible, it is a natural cycle of a person that can be clarified as a synchronized 24-hour inside clock that returns from of an individual's mind. Circadian rhythm processes become energetic consistently with normality among sluggishness and sharpness that is known as the sleep- wake cycle. The circadian rhythm is endogenous which implies that it's a process that is inherent to the body and should be support by them.

[42] underline the features of circadian rhythm as "The circadian rhythm is considered as a biological clock that is connected to the day/night cycles. It controls much in our bodies, also in other animals, plants, parasites and cyanobacteria" and shows the circadian rhythm with an expected biological

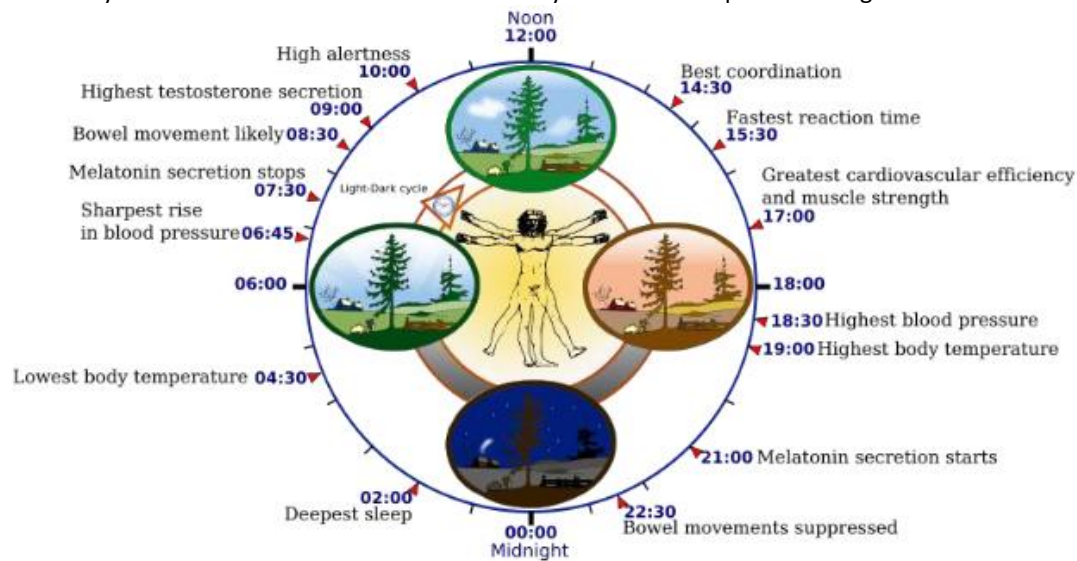


Figure 2: Potential human biological clock

All things considered, human circadian rhythm alludes to how body, organs and psyche of an individual do adapt into a synchronized cycle of our day by day way of life that incorporates our surroundings (e.g., light, climate condition, etc.), rehearses (e.g., dozing, food, food utilization time, and so forth.) and applications (e.g., portable, PC, and so on.) of different components. Regular changes in nature, practices and applications can seriously influences our synchronized circadian rhythm, hence causing sentiment of non-healthiness and strain once in a while.

As per the hypothesis of [5], "The term circadian rhythm represents the way that an immense exhibit of natural cycles inside the human body (and in fact all types of life on Earth) cycle as per a 24-hour clock. Circadian mood permits your body to allot capacities dependent on the hour of day (and whether you are snoozing); for instance, organizing tissue fix while you are resting, and organizing the quest for food, digestion, and development while you are awake.1Circadian rhythms are the means by which your body realizes what time it is (like when it's an ideal opportunity to get up toward the beginning of the day) – and appropriately controlled circadian rhythms are basic for wellbeing".

[8] proposed about the circadian rhythm that the disturbance of circadian rhythm can cause with more issues with unfortunate condition of a human body and brain. This investigation accordingly questions whether successive change in the body and brain related synchronizing cycle to have a superior circadian rhythm causes increment in ailment (like heart sicknesses, disease, diabetes, mental pressure, and so on.). This paper recommends this as an implications that future inspection can investigate this further, since increment in number of such ailments can correspond with successive changes in condition (e.g., truly changes in regular habitat, and progressed and quick changes in innovation). In this specific situation, this paper underlines the significance of keeping up steady encounters to frame a circadian rhythm as for our condition, practices and applications.

IV. CONCLUSION

As we know that the Circadian rhythm is considered as a biological clock which built in our brain and work entire day and night , It frame our body due to which it can work on daily basis in a healthy manner. So, the circadian rhythm turn up as a self-control system of human body to handle our eating habits, body function and other activities. In this context, our 24-hr daily working should have a trouble over food, exercise, work habits, physical environment and other activities. After considering everything, a mind clock in accomplishing even a common work should be accurately set with working on daily basis.

As circadian rhythm is very special and differ in each and every person, the cultural, political, economic, technological, sociological and environment features also affect the biological working, brain, thinking, mind and feelings of human. It is also feasible to proclaim whether a human can design a circadian clock in a coincide manner. Is will be very challenging for human because now-a-days, world mostly investigate with active socializing via the group, religion, culture, language, family, education, peers, economy, politics, law and

order etc., and this is due to sudden modification in etiquettes of human. Therefore, from the social cultural insight, as imputation for moreover examination, the paper consist this problem of sustaining a circadian rhythm because the working of the human body, mind and awareness are produced via social and cultural and various surroundings features; and the engagement of human with those modifying surroundings sudden take place probably.

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