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REVIEW

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Circadian mechanism disruption is associated with dysregulation of inflammatory and immune responses: a systematic review

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Abstract

The circadian rhythms are regulated by the circadian clock which is under the control of suprachiasmatic nucleus of hypothalamus. The central and peripheral clocks on different tissue together synchronize to form circadian system. Factors disrupt the circadian rhythm, such as irregular eating patterns, sleep/wake time, night shift work and temperature. Due to the misalignment of central clock components, it has been recognized as the pathophysiology of lifestyle-related diseases mediated by the inflammation such as diabetes, obesity, neurological disorder and hormonal imbalance. Also we discuss the therapeutic effect of time-restricted feeding over diabetes and obesity caused by miscommunication between central and peripheral clock. The genetic and epigenetic changes involve due to the deregulation of circadian system. The aim of the present review is to discuss the circadian mechanisms that are involved in the complex interaction between host and external factors and its disruption is associated with deregulation of inflammatory and immune responses. Hence, we need to understand the mechanism of functioning of our biological clocks so that it helps us treat health-related problems such as jet lags, sleep disorders due to night-time shift work, obesity and mental disturbances. We hope minimal cost behavioural and lifestyle changes can improve circadian rhythms and presumably provide a better health.

Keywords: Circadian rhythm, Suprachiasmatic nuclei, Central clock, Peripheral clock, Time-restricted feeding, Metabolism

1 Background

Circadian rhythm is derived from the Latin word: circa means 'approximate' and dies means 'day'. It is natural endogenous process of physiological, molecular and behavioural function throughout the day [1, 2]. Circadian rhythms are regulated by circadian clocks, which drive day–night oscillations with a free running period of 24 h [3]. The central and peripheral clocks on different tissues together synchronize to form circadian system. The whole body controller is situated on the hypothalamus of suprachiasmatic nucleus (SCN) in mammals [4]. However, the SCN acts more as a "master synchronizer" than a true pacemaker. The peripheral tissues and cells show similar gene expression of circadian rhythm as seen in SCN circadian rhythm [5, 6].

The mechanism of circadian rhythm is regulated by the transcription–translation feedback loop; CLOCK:BMAL1 are heterodimerized and bind to the promoted site of E-box to initiate the transcription of Per and Cry gene. These genes are translated and form PER:CRY heterodimer complex which inhibit the self-induced CLOCK:BMAL1 transcription [7]

Many factors affect the central clock and peripheral clock such as sleep/wake time, exercise, eating habits, light exposure and temperature. Eating habit is one of the factors that influence our metabolic process. Taking more

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than three meals in a day or prolonged eating is associated with metabolic syndrome. Restriction of diet in fixed time of period in a day that robust our circadian rhythm [8, 9]. TRF reduces body weight, improves lipid profile, increases insulin sensitivity, reduces glucose level, and decreases the oxidative stress and inflammatory markers [10–12]. Therefore, time-restricted feeding (TRF) is a therapeutic strategy for the treatment of metabolic disorders, such as obesity and diabetes [13].

The circadian clock disruption of pancreas-specific causes impaired glucose tolerance leading to increased glucose level in blood (hyperglycaemia), thereby resulting in decreased secretion of insulin [14]. In adipose tissue, the circadian clock disruption causes the reduction or abnormal secretion of fatty acid from adipocytes leading to obesity. This abnormal secretion from the adipose tissues regulates appetite centre of hypothalamus, which increases feeding throughout the day [15].

In jet lag and shift workers, the desynchronization of environment clock and tissue-specific circadian clock cause sleep disturbance and various metabolic disorders. This is because of miscommunication between feeding time and cellular metabolic process, which is directly linked with circadian rhythm [16]. For example, in pancreatic tissue, the loss of circadian gene, such as brain and muscle aryl hydrocarbon receptor nuclear translocator-like (Bmal1), results in decreased secretion of insulin, which leads to diabetes [17]. Circadian clock regulates many metabolic rhythms including glucose and lipid metabolism, and their disruption could promote diabetes, obesity and chronic heart disease (CHD) in many organisms [18–20]. The objective of our review is to create the awareness about the effect of circadian clock on the metabolic process and to deliver the message about the circadian clock management that improves the quality of life.

1.1 Method

We did all-inclusive literature search following PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analysis] guide (Fig. 1). A systematic electronic database search with NCBI, MEDLINE, Scopus, Google Scholar, PubMed and Web of Science databases was done to retrieve relevant research and review articles in English language only. All articles identified underwent a review to assess relevance against the eligibility criteria.

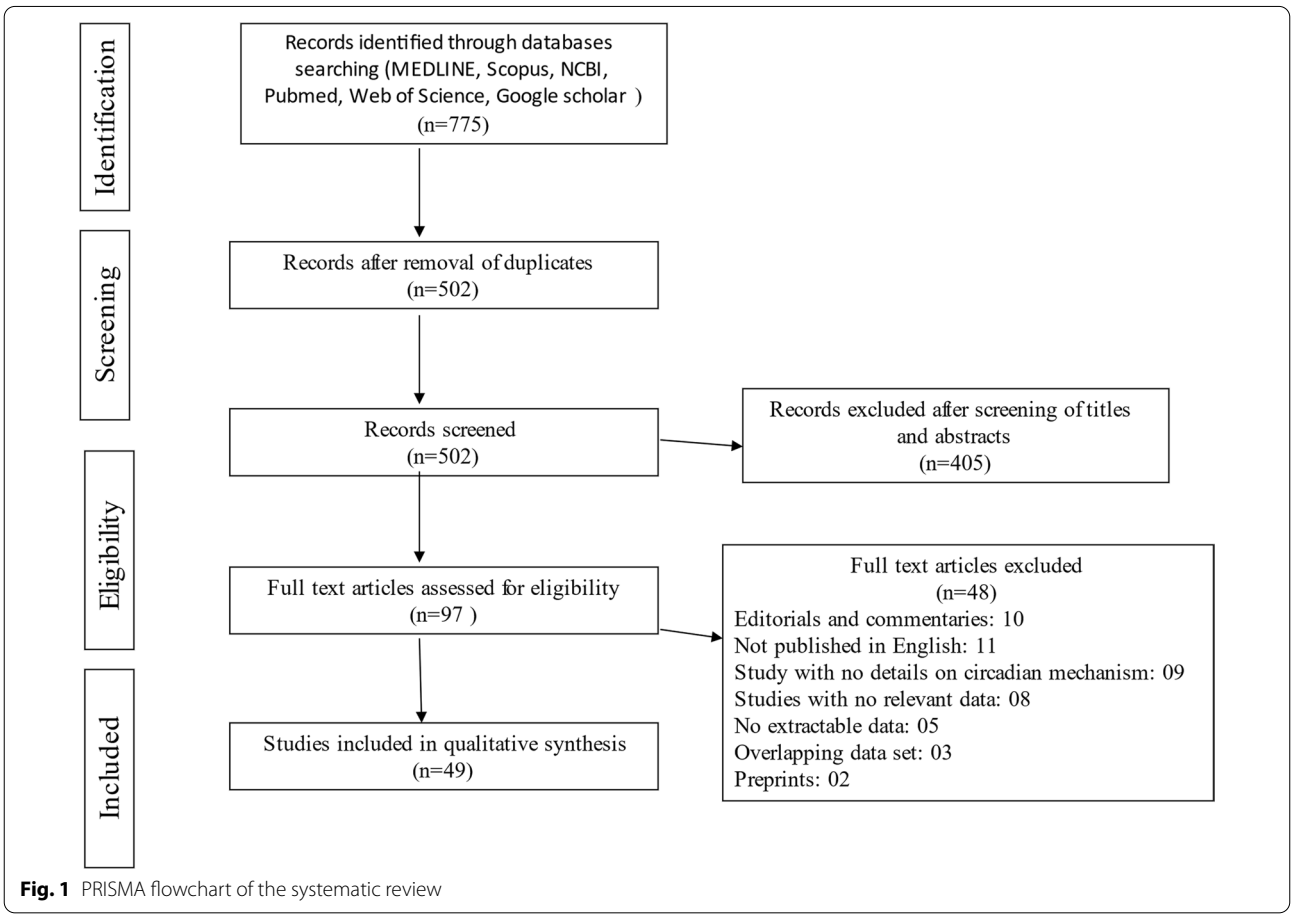

Fig. 1 PRISMA flowchart of the systematic review

This review process occurred in stages, which initially involved screening the article titles. We screened the articles using keywords like circadian rhythm, suprachiasmatic nucleus, BMAL1, CLOCK, PER, CRY genetics, epigenetics, time restricted feeding, temperature, diabetes, obesity and neurological disorders combined using Boolean operators AND and OR. This review article, which is submitted here as part of project, was approved by the ethical committee of the institution with reference no. 123/IAEC/2019 and project funded by ICMR, New Delhi.

2 Genetics and epigenetic basis of circadian rhythm

2.1 Genetics

Long-term changes in metabolism are directly linked to the chronological changes, such as alteration in glucose homeostasis, which are closely correlated to the clock gene function. In animal studies, a wide range of disturbance in metabolic process includes the deregulation of glucose metabolism that alters the insulin secretion resulting in impaired gluconeogenesis, obesity and metabolic syndrome [21, 22]. Alternative studies of genetically modified or transgenic mice model noticed the frequent change, due to alteration in clock gene function, resulting in abnormal metabolic phenotype [23].

These similar findings have been reported in many human genetic studies as well. The metabolic disorders like T2DM, obesity and metabolic syndrome have been associated with clock gene polymorphism and their associated haplotypes. Although these above studies reveal that the circadian rhythm gene and metabolism are functionally linked, and they are unable to differentiate the tissue-specific clock to overall phenotype. Due to this problem, there is a need for tissue-specific studies, creating local gene disruption by preparing BMAL1 knock-out model. Loss of function of BMAL1 in peripheral tissue is directly linked with change in glucose homeostasis, which leads to diabetes [24, 25].

Heterodimer formation of CLOCK and BMAL1 takes place to initiate transcription factor of core clock gene in mammals. This heterodimer binds rhythmically to the E-box of Period (Per1, Per2, Per3), Cryptochrome (Cry1 and Cry2), Rev-erb (Rev-erbα and Rev-erbβ) and Ror (Rorα, Rorβ and Rorγ) to initiate transcription. Translated PER/CRY repressive complex block the CLOCK: BMAL1-mediated transcription first on-DNA and then off-DNA [18, 19]. BMAL1 expression is regulated by the REV-ERBs and RORs through the repression and activation of its transcription, which promotes sturdiness of circadian oscillations [26, 27]. On rhythmic transcriptional activation of core clock components, CLOCK:BMAL1 regulates the expression of clock-controlled genes to generate the variations. Thus, it regulates the function of circadian rhythm system [28, 29].

It is interesting to know about the mechanism through which CLOCK: BMAL1 controls the expression of its core clock genes and target genes. Studies show that the rhythmic binding of CLOCK:BMAL 1 heterodimer to the promoter site of core clock gene DNA is required for the rhythmic transcription [24, 26, 30]. Recently, it has been shown that rhythmic binding of CLOCK: BMAL1 heterodimer to DNA initiates the removal of nucleosome, thereby generating a chromatin landscape that is favourable for the binding of second transcription factors at its enhancers [31]. Hence, this heterodimer promotes transcription of core clock gene by recruiting transcriptional co-activators, mediator complex and RNA polymerase II [16, 32]. The core clock gene activated by the CLOCK:BMAL1-mediated transcription mechanism is still unclear. Indeed, most of the clock target genes CLOCK:BMAL1 is expressed rhythmically, and a large fraction of the rhythmically expressed target genes are transcribed at night, in antiphase to maximal CLOCK:BMAL1 DNA binding [30]. These evidences suggest that different mechanisms are involved in CLOCK:BMAL1 regulation of transcription of core clock genes, which differ from the regulation of other clock-controlled genes. The circadian clock adds additional mechanisms for the activation of rhythmic gene expression. The binding of heterodimer CLOCK:BMAL1 to the DNA during transcription is capable for the uncoiling of chromatin and initiates transcription, whereas it is insufficient to produce transcriptionally active enhancers. The CLOCK:BMAL1 heterodimer generates a flexible chromatin landscape to rhythmically prime its enhancers for the recruitment of other transcription factors, rather than directly promoting transcription activation [33].

2.2 Epigenetic

The epigenetic changes influence the expression of gene without alteration in the nucleotide sequence leading to phenotypic change only. These epigenetic modifications include DNA methylation and modification of histone that amend the local chromatin and effect DNA accessibility and gene transcription (Table 1) [34]. DNA methyltransferase (DNMT) enzyme involves in methylation of DNA CpG sites of nucleotide, which is an important mechanism of transcriptional repression [35]. However, the DNA methylation performance remains ambiguous and disputed. To counter this, ten–eleven translocase (TET) enzymes catalyse DNA demethylation [36]. Another epigenetic modification includes acetylation and deacetylation of histone protein, which is catalysed by the histone acetyltransferases (HATs) and deacetylase (HDACs), respectively. HATs promote unfolding of

Table 1 Gene involved in metabolism and their mechanism of epigenetic modification

S. no.	Metabolic process	Gene		Epigenetic modification	Results	References
1	Glucose homeostasis	GLUT 4	Cell line	DNA hypomethylation Histone acetylation	Hypomethylation prevents the activation of its promoter	[109]
		ADIPOQ	Human	DNA hypomethylation Histone acetylation	Hypomethylation associated with high circulatory adiponectin level	[110]
		INS (Insulin)	Mouse and Human	DNA hypermethylation Histone acetylation	In both mouse and human hypermethylation at promoter site supress the activity of insulin gene	[111]
2	Inflammation	IFNG	Human	DNA hypomethylation	Hypomethylation leads to increases inflammation, in shift workers, cardiovascular disease and cancer	[112]
		INF	Human	DNA hypomethylation	Hypomethylation associated with increased plasma TNF-α level in PUFA intake	[113]
3	Lipid storage	FASN	Rats	DNA methylation	Hypomethylation at promoter region associated with obesity in HFD group	[114]
4	Adipogenesis	PPARA	Rats	DNA methylation	Methylation in promoter region of hepatic PPARα results in differential risk of disease	[115]
		CEBP β	Rats	Histone acetylation Histone methylation	Histone modification at promoter region alters its expression	[116]
5	Appetite regulation	LEP	Rats	DNA hypermethylation	Hypermethylation in CpG site 6–7 and 29–30 Hypomethylation at CpG site os 15 20-day intake HFs diet shift to chow diet till 10 weeks, reverse CpG site at 29–30	[117]
		MC4R	Human	DNA hypermethylation	CpGs 1–8—Hypermethylation (26%) CpGs 9–16—Hypomethylation (52–100%)	[118]
		NPY	Human	DNA hypomethylation	Hypomethylation at promoter site increases the risk of obesity	[119]
		POMC	Human	DNA hypomethylation Histone acetylation	Hypomethylation associated with the weight loss maintenance	[119]

chromatin during transcription, whereas HDACs are responsible for the chromatin condensation and hence represses transcription [25]. The repressors of gene transcription can access the acetylated open-chromatin structure [37]. Epigenetic modifications are unable to alter the DNA sequence and are not stable and undergo changes towards the exogenous stimuli such as light, diet [38], temperature [39, 40], social interaction [41] and maternal effect [42]. A recent study in mice model revealed that the time-restricted feeding (TRF) intervention decreased the HDAC activity and enhanced the histone acetylation [43]. During the light phase, CLOCK:BMAL1 binds to the DNA to initiate the chromatin modification by histone-modifying enzymes to the promoter region of core clock gene. The histone-modifying enzymes such as HATs and HMTs catalyse the acetylation and methylation, respectively. Histone acetyltransferase mediates the acetylation of histone lysine at positions H3K9 and H3K27 and methylation at H3K4 by histone methyltransferase. The feedback inhibition of clock gene through the binding of PER:CRY heterodimer to the DNA-bound CLOCK: BMAL1 complex is carried out by the additional recruitment of histone demethylases and deacetylases.

3 Time-restricted feeding (TRF) and circadian rhythm

The TRF has many physiological consequences [44]. A study in mice revealed that the everyday TRF for 4 h enhanced the glucose regulation and reduced weight gain [45]. Another study conducted in mice model showed that TRF for 8 h a day prevents high-fat-diet (HFD)-induced obesity [46], 9 h/day TRF results in reduced plasma glucose level and increased sensitivity and level of insulin in type 1 diabetes [47]. The circulatory level of glucose is lowered as well as the expression of PER 2 clock gene of adipose is delayed due to 5-h meal delay effects. Therefore, feeding time of shift worker may help to reset the circadian system. The effect of TRF on obese mice model induced by high-fat diet normalized the gene expression of lipid metabolism in hepatic tissue [46]. In diurnal organisms, TRF controls the expression of many clock control genes in peripheral tissues. It protects from the adverse effect of obesity induced by high-fat diet and also regulates the transcription factors that play critical role during fasting time in gluconeogenesis and deposition of fat in hepatic cells and multiple markers of inflammation are reduced. The complications were generated

by high-fat-diet-induced alteration in metabolic pathways, and generation of oxidative stress by reducing antioxidants is reversed by TRF [48].

It is described in the literature that metabolic parameters, i.e. glucose homeostasis, change every day and every time in humans. In healthy people, glucose tolerance decreases in the afternoon causing a condition called "afternoon diabetes". This metabolic pathway persists in controlled conditions, through changes in insulin signalling mechanism, which is governed by the internal circadian clock system [49]. Similarly, in night the triacylglycerol plasma level is elevated, if HFD has been taken in night as compared to the daytime meal, which is regulated by circadian rhythm [50].

Animal studies have shown the beneficial effect of TRF leading to improvement in the quality of life and provided protection against obesity and metabolic disorders due to consumption of high-fat diet [44]. Studies in rodents have proved that timely eating is a powerful tool for synchronizing peripheral clock. When animals are kept in a 12-h light/dark cycle, the restricted feeding time disrupts the internal synchronization of clocks [51]. In addition, the role of clocks in individual peripheral tissues provides a physiological insight to explain the temporal differences in postprandial responses. Hence, the meal time is very important as changing the life pattern may protect from various diseases and improve life quality and increases life span.

4 Temperature effects on circadian rhythm

Temperature also influences circadian clock, because of ubiquity of temperature regulatory mechanism and also potential target for therapeutics. All circadian rhythms are temperature-compensated. This important property allows the clock to maintain a stable period of oscillation regardless of the ambient temperature. The change in circadian rhythm with environmental condition is not reliable. Due to variation in the temperature of poikilothermic organisms, the oscillation of circadian rhythm is desynchronized. In hibernating animals, there is lack of day activity during hibernation period, and the internal body temperature of such animals undergoes circadian fluctuations with amplitudes of approximately 1 °C and 5 °C depending on the species [52].

In our biological system, the heat shock mechanism controls the effect of increasing temperature in our metabolic process and circadian clock. Many heat shock factors/proteins (HSF/HSP) such as HSF1, HSF2 and HSF4 initiate the transcription on increasing temperature. The heat shock element present in the promoter site of the stress response gene is transcribed by the binding of initiation HSF [53]. HSP genes contain heat shock elements (HSEs), and once translated, these proteins, chaperone, sequester the HSP from further transcription [54]. The Per2 gene expressions are reducing or lose their function on the exposure of high temperature [55]. Along with being a temperature sensor for phase setting, evidence proves that the circadian clock and heat shock factors are closely related. Although the levels of HSF have not been found to have circadian oscillation, their binding to target motifs certainly does in spite of the absence of temperature cycles [56]. HSEs located on the promoter region of Per2 gene are conserved among various species and expression of HSP gene synchronizes with the Per2 gene [55]. Finally, the temperature affects circadian rhythm through the heat shock response that exhibits both phase and period influence on the circadian clock.

5 Hormonal effects on circadian rhythm

In vertebrates, the photoperiod message is delivered by hormone melatonin, which is secreted during night/dark [57]. The secretion of melatonin is regulated by the light and dark cycle. This mechanism is present in SCN of hypothalamus [58, 59]. The data from other studies showed that permanent light period affects the significant decrease in melatonin and increase during permanent dark in healthy animals. During afternoon, leptin plasma concentration starts increasing and reaches its peak between midnight and approximately 2:30 a.m. with considerable inter individual variations [60]. The evidence shows that photoperiod influences the circulatory level of leptin and changes in circadian rhythm change the plasma leptin concentration. Many studies conducted on secretion of leptin and melatonin in healthy subjects showed that there is significant negative correlation [61, 62]. Contrary to it, a study conducted by the Cardoso et al. showed that melatonin had a positive role in the production of insulin-stimulated leptin in adipose tissue of rats. In this mechanism, melatonin binds to Gi protein-coupled MT1 (melatonin transporter 1) membrane receptor and potentiates the phosphorylation of insulin receptors and Akt (Protein Kinase B) [63]. Melatonin performs its action by binding to MT1 and MT2 membrane receptors found on the cell membrane which is coupled with G-protein. After binding, it initiates the signal transduction mechanisms. In human beings, these mechanisms have been found in many organs such as brain, heart, hepatic tissue, kidney, intestine, genital organs, adipocytes and skin (Fig. 2) [64–66].

Melatonin also enhances the antioxidant potential of cells by stimulating the synthesis of enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx), glutathione reductase (GRd) and augmenting glutathione levels. Melatonin protects, whereas leptin elevates the generation of reactive oxygen species (ROS) (Fig. 3) [67, 68].

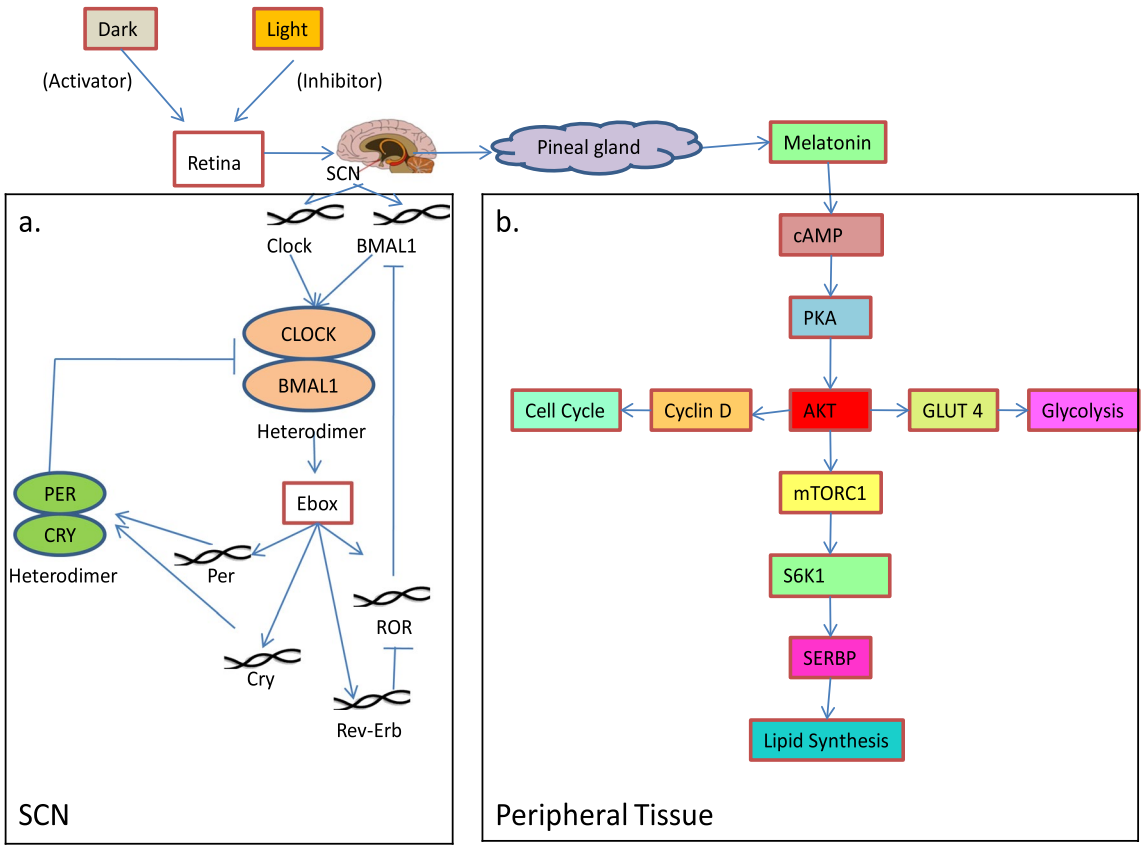

Fig. 2 Correlation between circadian rhythm and metabolism. **a** In SCN, circadian clock composed of interlocking feedback loops consists of transcription activators and repressors. **b** In peripheral tissue, the activation of metabolic pathway by melatonin secretion. cAMP—cyclic AMP, PKA—Protein kinase A, AKT—Protein kinase B, S6K1-S6 protein kinase 1, SERBP—sterol regulatory element binding protein

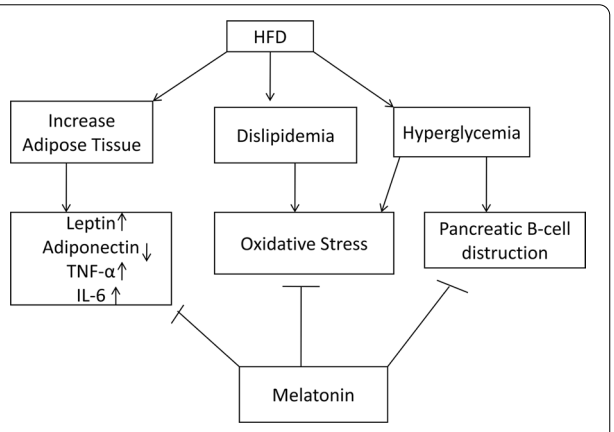

Fig. 3 Protective effect of Melatonin

In healthy animals, the photoperiod is responsible for the significant drop of antioxidant enzymes and it shows opposite effect in the dark in which it increases in circulation. Thus, light affects adversely on healthy animals by decreasing the level of antioxidant and elevates the lipoperoxide level, whereas it shows opposite effect during dark period. It is reported that ROS which is responsible for the disruption of lipid membrane initiates the activation of pro-inflammatory cytokine genes (TNF-α, IL-1, IL-6) by the stimulation of transcription factor NF-kB [69, 70].

The light enters in the brain via a monosynaptic pathway from intrinsically photosensitive retinal ganglion cells in the inner retina to the SCN [71]. In turn, from the SCN the light travels through the multi-synaptic router to the pineal gland. The photoperiodic information circulates from the pineal gland to the organs and regulates day/night cycle [72]. In dark/night, the pineal gland synthesizes melatonin, also known as sleep hormone and improves sleeping tendency. Photoperiodic information travels through the expression of receptors, which synchronously contributes to the circadian rhythm in peripheral tissue and central tissue [73].

6 Molecular mechanism

In mammals, the molecular mechanism of biological clock is governed by feedback loops of transcriptional–--translational processes (Fig. 2). The primary loop of circadian rhythm consists of two proteins, namely BMAL1 and CLOCK, which stimulate the transcriptional activity of clock control genes—Per1, Per2, Per3 and Cry1, Cry2. After appropriate temporal delay caused by post-translational modifications, these PER and CRY proteins form heterodimer, which enter into the nucleus and prevent their own transcription process through feedback inhibition. The CLOCK and BMAL1 protein interaction inhibit the transcription. The primary loops of these 'clock genes' are involved in many interactions between their translated proteins and key biochemical mechanism that regulates intracellular metabolism [23, 74]. In turn, the circadian gene/protein expression is regulated by most of the nuclear factors. It forms a feedback loop and links the biological clock to the cell metabolism. In the peripheral tissue, the rhythmic expression of 50% nuclear receptors is derived from the transcription factors of circadian rhythm protein [23].

7 Circadian rhythms and its effect on health:

Table 2 shows the effect of circadian rhythm in various metabolic diseases. Circadian clock regulates metabolic rhythms of glucose and lipid metabolism and their disruption could promote diabetes and other related complications [75, 76].

7.1 Diabetes and obesity

The impairment in sugar uptake leads to reduced insulin sensitivity and hyperglycemia [17]. It is feasible that starting from decreased postprandial glucose tolerance at night, the dysregulation of sugar intake may lead to increased use of fatty acid from triglyceride stores in hepatic and adipose tissue [77]. Many human and animal studies revealed that the imbalance absorption between carbohydrate and triglyceride leads to dyslipidaemia and hypertriglyceridemia. This modification in uptake

Table 2 Effect of circadian rhythm in associated diseases

S. no.	Study	Gene studied	Animal	Outcome	References
1	KO	CLOCK	Mice	Hypertension	[120]
2	KO	CLOCK	Mice	Mild diabetes insipidus	[121]
3	KO	Per1	Mice	Lower blood pressure	[122]
4	Double KO	Cry1/2	Mice	Hypertension	[123]
5	KO	BMAL1	Mice	Reduced blood pressure	[124]
6	Mutant	CLOCK	Mice	Obesity and hyperlipidemia	[19]
7	Triple KO	Period 1/2/3	Mice	Obesity	[125]
8	KO	BMAL1	Mice	Obesity and hyperlipidemia	[126]
9	KO	REV-ERB-γ	Mice	Increased adiposity and deregulated fatty acid/glucose utilization	[127]
10	Double KO	REV-ERB-α/ β	Mice	Deregulation lipid metabolism	[128]
11	KO	BMAL1 and CLOCK	Mice	Diabetic with reduced plasma insulin levels	[12]
12	SNPs	Bmal1	Human	Gestational diabetes mellitus	[129]
13	KO	BMAL1	Mice	Reduced plasma insulin levels	[130]
14	KO	Pancreas-specific BMAL1	Mice	Hyperglycaemia	[12]
15	KO	Cry1/2	Mice	Hyperglycemia	[131]
16	Adrenalectomy	Per1	Mice	Reduce glucocorticoid signalling	[132]
17	KO	Per1	Mice	Higher plasma and pineal melatonin	[133]
18	Melatonin intervention	-	Human prostate cancer cells	Increased expression of Per1 and CLOCK, decreased BMAL1	[134]
19	Mutant	Per2	Mice	TLR9 upregulated in spleen	[135]
20	KO	Cry1/2	Mice	Upregulation (NF)-κB	[136]
21	KO	BMAL1	Mice	Decreased fertility and implantation defects	[137]
22	KO	CLOCK	Mice	Decreased fertility	[138]
23	TRF (10 h/day for 12 weeks) intervention	–	Human	Reduced body weight, visceral fat, lowered blood pressure and decreased HbA1c	[139]

KO knock-out mice, *SNP* single nucleotide polymorphism, *TRF* time restricted feeding

of calorie and its storage decreases the energy balance imposed by sleep debt [78].

Studies have revealed changes in the circadian rhythm between obese and lean subjects. A worldwide study reported that the adverse effect of obesity on biological clock reduces the molecular and physiological rhythm, which largely depends on the target molecule [44]. The routine biological rhythm also exists in the level of many hormones such as adipokine, melatonin and leptin, which follow the circadian clocks that are likely to be driven by endogenous circadian physiology [79, 80]. Early reports indicated that in the obese subjects the concentration of leptin decreased rhythmically, but this work has not been found in recent studies [81]. Furthermore, some endocrine rhythms such as in insulin sensitive obese the circulating melatonin exhibits increased amplitude in obese insulin-sensitive men [82]. At the molecular level, a study in mice reported that obesity reduces clock gene expression, resulting in the alteration in clock gene rhythm or consumption of fatty diet [83, 84]. Obesity is the major factor for developing cardiovascular disease, dyslipidaemia and hypertension [85]. It has recently been reported that changes in daily rhythm in high-fat-diet-induced obese animal model may reject acute effects of the dietary intervention without any long-term changes in energy balance [86]. Only few studies have been reported in humans for routine profile of gene expression in obesity. However, in one of the study using human gluteal subcutaneous fat, there were no differences in gene expression level between lean versus obese individuals [87]. As a part of the strategies proposed for reducing energy intake and for increasing energy output [88], meal intervention at time and frequency could exert a significant influence on weight loss [89–91]. Thus, the risk of metabolic syndrome is a major cause by the wrong time sleep/wake and eating.

7.2 Neurological disorders

Ageing is a major risk factor for generating the neurological disorders such as Parkinson's disease (PD), Alzheimer's disease (AD) and stroke [92]. In each disorder, neuron death and degeneration occur by the involvement of mitochondrial function, oxidative damage, impaired lysosome function and dysregulation of cellular calcium homeostasis [93]. The evidence proved by animal experimental models of various neurological disorders/neurodegenerative diseases, prepared by the intervention of neurotoxins resulting in degeneration of one or many neurons. For example, in PD the animal model was prepared by the induction of MPTP dose, 6-hydroxydopamine and rotenone. These drugs are responsible of neuron degeneration by inhibiting mitochondrial complex I. In the 1990s, studies were initiated to test the general hypothesis that, ageing is the major risk factor for developing neurological disorders; it may be reduced or reversed aging process due to the intermittent fasting (IF). Studies prove that the (IF) protects against these disorders in animal models [94]. A study revealed that when animals are kept on alternate day fasting (ADF) for few months before the intervention of Kainic memory deficit improved [95]. It was also noticed that if mice model kept for few months on ADF acid, the neurons of the hippocampal region are resistant to degeneration and their learning capacity and are resistant to the MPTP, the indication of the improvement in PD model by preventing the degeneration of dopaminergic neurons [96].

7.3 Inflammation and immune response

Circadian rhythm disruption causes the metabolic disorders leading to diabetes and obesity, and is also responsible for the alteration in immune system [97]. Immune system plays a key role in the defence mechanism of an organism and maintains the tissue homeostasis. Weak response of immunity causes infection, inflammation and develops autoimmune diseases [98]. Clinical studies revealed that the inflammatory markers have tendency to alter the clock gene expression. In T2DM, the IL6 expression decreases the PER1, CRY1 and BMAL1 expression, whereas this circadian gene shows negative correlation with TNF-α [98, 99]. Central clock controls the metabolism, physiology and temperature of the peripheral clock [100, 101]. Circadian rhythm-associated diseases caused by the inflammation are cardiovascular disease [102], hypertension, chronic kidney disease [103], osteoporosis [104], chronic obstructive pulmonary disease [105], intestinal disease [106], diabetes [107] and obesity [108]. The disrupted circadian clock associated with the peripheral clock generates tissue-specific diseases, mediated by the inflammation (Fig. 4).

8 Conclusions

The circadian system of all organisms contains a core oscillator, away by which this clock can be set by the environment and output behaviours or processes whose phases are determined by the core clock. We conclude that the TRF is the potential intervention on the chronic disrupted circadian rhythm and correlated with the alteration in biological function leading to metabolic syndrome. The therapeutic strategies can be developed and implemented by changing the feeding pattern. There is a need of clinical trial study for a large scale to determine the sustainability and efficacy of TRF intervention. For future prospective, it is important for the clinicians to advice the dietary interventions for the general population. Studies are required using knockout model to understand the exact mechanism of specific gene.

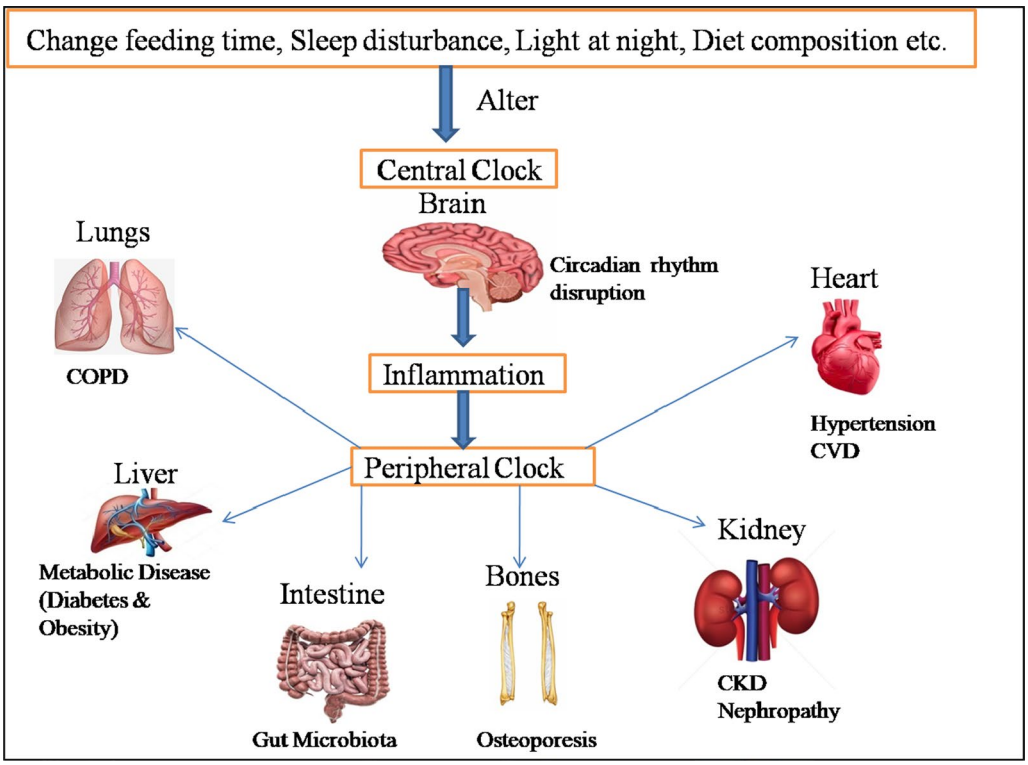

Fig. 4 Tissue-specific disease developed by the disrupted circadian rhythm mediated by inflammation

Further, the researchers have to develop various studies in combination of in vitro and in vivo experiments.

Abbreviations

SCN: Suprachiasmatic nucleus; CHD: Chronic heart disease; NCBI: National Center for Biotechnology Information; Per: Period; Cry: Cryptochrome; DNMT: DNA methyltransferase; TET: Ten–eleven translocase; HAT: Histone acetyltransferases; HDAC: Histone deacetylase; TRF: Time-restricted feeding; HMT: Histone methyltransferase; HSF: Heat shock factors; HSP: Heat shock proteins; MT: Melatonin transporter; Akt: Protein kinase B; SOD: Superoxide dismutase; GPx: Glutathione peroxidise; GRd: Glutathione reductase; ROS: Reactive oxygen species; TNF-α: Tumour necrosis factor alpha; IL: Interleukin; cAMP: Cyclic AMP; S6K1: S6 protein kinase 1; SERBP: Sterol regulatory element binding protein; IF: Intermittent fasting; MPTP: 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

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Author contributions

All authors were involved in conception and design of the work. NF, GKS, SS performed screening and selection of articles. NF drafted the manuscript. All authors were involved in editing and revision of the manuscript and final approval of the version submitted for publication. All authors agree to be accountable for all aspects of the work and in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors read and approved the final manuscript.

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Availability of data and materials

Not applicable.

Declarations

Ethics approval and consent to participate

This review article which is submitted here as part of project was approved by the ethical committee of the institution with reference no. 123/IAEC/2019.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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