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When time stands still: an integrative review on the role of chronodisruption in posttraumatic stress disorder

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Purpose of review

The human circadian system creates and maintains cellular and systemic rhythmicity essential to homeostasis. Loss of circadian rhythmicity fundamentally affects the neuroendocrine, immune and autonomic system, similar to chronic stress and, thus, may play a central role in the development of stress-related disorders. This article focuses on the role of circadian misalignment in the pathophysiology of posttraumatic stress disorder (PTSD).

Recent findings

Sleep disruption is a core feature of PTSD supporting the important supraordinate pathophysiological role of circadian system in PTSD. Furthermore, direct and indirect human and animal PTSD research suggests circadian system linked neuroendocrine, immune, metabolic and autonomic dysregulation with blunted diurnal rhythms, specific sleep pattern pathologies and cognitive deficits, as well as endocannabinoid and neuropeptide Y system alterations and altered circadian gene expression, linking circadian misalignment to PTSD pathophysiology.

Summary

PTSD development is associated with chronodisruption findings. Evaluation and treatment of sleep and circadian disruption should be the first steps in PTSD management. State-of-the-art methods of circadian rhythm assessment should be applied to bridge the gap between clinical significance and limited understanding of the relationship between traumatic stress, sleep and circadian system.

Keywords

autonomic nervous system, chronodisruption, circadian system, cognition, cortisol, glucocorticoids, hypothalamic-pituitary-adrenal axis, immune system, melatonin, memory, posttraumatic stress disorder

INTRODUCTION

The primary role of the human circadian system is the temporal organization and coordination of physiological processes and rhythmic changes to promote homeostasis and environmental adaptation [1]. Loss of cellular and systemic rhythmicity is implicated in a wide range of pathophysiological mechanisms and consequences in a both molecular and macrophysiological level [2,3]. Numerous human and animal studies suggest that acute and chronic stress affects the circadian system [4,5], implying a central role of circadian dysregulation in stress-related disorders.

Posttraumatic stress disorder (PTSD) is an anxiety disorder with distinctive symptoms following a psychologically distressing event outside the range of usual human experience. According to DSM-V, sleep disturbances are prominent clinical

features of PTSD [6], often resistant to first-line treatments and closely related to severity of PTSD psychopathology [7–10]. Nevertheless, sleep disturbances are still often clinically assessed as

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KEY POINTS

- Although sleep disruption is a core feature of PTSD, relevant clinical literature is neglecting the potential superordinate pathophysiological role of the circadian system.
- There are almost no studies using state-of-the-art circadian rhythm assessment in PTSD.
- Direct and indirect human and animal research suggests numerous symptoms, and comorbid medical conditions and pathophysiological research findings, also related to sleep deprivation and circadian disruption.
- PTSD pathophysiology could, thus, be mediated by sleep and circadian disruption.
- Evaluation and treatment of sleep and circadian disruption should be the first steps in PTSD management, although appropriate assessment of circadian rhythms should be urgently applied in clinical research.

secondary symptoms in PTSD. This article focuses on the role of the sleep and circadian disruption in the pathophysiology of PTSD, underlining common neurobiological underpinnings of PTSD and circadian misalignment.

CIRCADIAN SYSTEM AND CHRONODISRUPTION

The suprachiasmatic nucleus (SCN) is the primary pacemaker of the central circadian system, coordinating sleep and other physiological functions such as immune and autonomic activity, metabolism, neuroendocrine hormone secretion and thermoregulation [1,11,12]. The major effector of the central circadian system and, thus, fundamental synchronizing hormone is pineal melatonin, whose secretion is tightly controlled by the SCN [13]. However, recent research has shifted the model paradigm towards a more complex circadian hierarchy, including central and peripheral oscillating networks of different Zeitgebers that orchestrate biological functions [14]. A critical loss of this time order at different organizational levels is defined as chronodisruption and denotes an inappropriate adaptation to external stimuli resulting in a breakdown of harmonious functioning of internal biological systems that can lead to chronobiological disorders [15].

ASSESSMENT OF CIRCADIAN RHYTHMICITY

The assessment of circadian rhythms in human research is challenging [16]. State-of-the-art circadian

assessment methods such as measurement of melatonin secretion (e.g. dim light melatonin onset, cortisol/melatonin onset phase angle), core body temperature and circadian gene expression are sparsely used in clinical research. In PTSD, only two studies have measured melatonin. McFarlane *et al.* [17] found lower urinary melatonin levels after traumatic injury predicting higher risk for PTSD, while van Liempt *et al.* [18^{*}] reported undisturbed melatonin, cortisol and adrenocorticotrophic hormone (ACTH) nocturnal profiles in PTSD patients. No human, and only few animal studies have assessed the diurnal fluctuations of core body temperature as a marker of circadian rhythmicity in stress-related disorders, suggesting that chronic stress models or juvenile stress exposure lead to blunted diurnal core body temperature rhythm in rats [19,20].

Instead, other methods that provide a more indirect approach to circadian rhythmicity, such as assessment of sleep and activity patterns or neuroendocrine/physiological diurnal profiles (e.g. cortisol, heart rate, blood pressure), are used more frequently [21].

Sleep

Sleep homeostasis not only acts synergistically and bidirectionally with the central circadian system but also independently to restore an optimal internal temporal order [22]. Specific sleep stages are associated with CLOCK gene expression in the SCN and, thus, are tightly ruled by the circadian system, although sleep deprivation is normally associated with chronodisruption [12,22,23].

Acute and chronic stress exposure may cause both prompt and long-lasting alterations in sleep patterns, while sleep disruption can contribute to maladaptive stress [24,25]. Sleep disturbances are prominent clinical features of PTSD. Insomnia, nightmares and anxiety dreams, hyperarousal state, sleep avoidance, sleep terrors and nocturnal anxiety attacks, body movement and breathing-related sleep diseases are all frequently observed in PTSD [8,26,27]. However, polysomnographic findings in PTSD are complex and in part controversial, although many studies demonstrated heightened sympathovagal tone during rapid-eye movement (REM) sleep, fragmented REM sleep patterns and reduced REM theta activity [7,28^{*},29–31]. These findings are similar to those observed in animal and human sleep deprivation studies [32,33]. Evidence suggests that not only REM sleep disruption is the immediate aftermath of a trauma, but also sleep deprivation even prior to trauma may be associated with PTSD development [34,35].

The hypothalamic-pituitary-adrenal axis

The hypothalamic-pituitary-adrenal (HPA)-axis activity and cortisol secretion are characterized by circadian rhythmicity and are closely linked to the circadian system and melatonin [36,37]. The central circadian system enforces signal rhythmicity of the HPA axis by directly influencing hypothalamic neuroendocrine neurons, adrenal sensitivity to ACTH and the peripheral rhythms of the adrenal gland itself [36,38–40]. Melatonin has been shown to directly influence ACTH responses in the human adrenal gland and cortisol plasma concentration, although cortisol and HPA activity are suggested to stimulate the synthesis of melatonin and modulate the pineal gland activity, interfering in the daily adjustment of the light/dark cycle [41–43]. Accordingly, pathophysiological consequences of circadian disruption and HPA-axis dysregulation are highly overlapping [37].

Sleep deprivation has been repeatedly associated with various HPA-axis dysregulations (e.g. flattened amplitude of cortisol rhythm, decreased cortisol awakening response and reactivity, not only increased but also decreased diurnal cortisol levels, higher corticotropin-releasing hormone (CRH) levels) and vice versa [44–46]. Traumatic exposure and PTSD have been also linked to decreased peripheral concentrations of cortisol, increased cerebrospinal fluid (CSF) CRH levels, altered HPA reactivity with enhanced negative feedback inhibition and, most importantly, blunted diurnal cortisol rhythm and awakening response [47–50].

Enhanced HPA-axis negative-feedback sensitivity found in PTSD is consistent with increased glucocorticoid (GC) sensitivity and altered glucocorticoid receptor responsiveness and density in various cell types [51–53]. GC pathways (e.g. acetylation of GC receptor, GC receptor translocation to the nuclei and transcriptional activity, GC toxicity and sensitivity, and so on) display clear circadian patterns, moderated by melatonin, although sleep deprivation affects the response to stress through altered GC signalling [36,40,54,55]. In addition, animal studies demonstrate a melatonergic regulation of peripheral clock genes oscillation in the adrenal gland [56,57], thus confirming an influence of the circadian system on GC responsiveness and suggest that HPA-axis specific neuroendocrinological alterations in PTSD may be partially mediated by sleep disruption.

On the contrary, GC reset peripheral clocks by influencing the expression of circadian-related (CLOCK) genes [37]. Sleep disturbances and circadian misalignment have been associated with alterations of the physiological oscillations of CLOCK gene expression in humans, affecting the

neurobiological response to stress [58,59]. Animal stress models of PTSD have shown disrupted gene expression of *CLOCK* genes in several tissues including the hippocampus [60–62], although melatonergic treatment directly after exposure may be protective against these stress-related changes [61]. Interestingly, a genome-wide association study in PTSD identified the retinoid-related orphan receptor alpha (*RORA*) gene, a *CLOCK* gene, as a significant risk focus [63*].

IMMUNE AND METABOLIC SYSTEM

The human circadian and immune systems are closely and bi-directionally connected through a complex autonomic, endocrine and molecular network [41,64–66]. Immune system reactivity follows circadian rhythms, while sleep and circadian dysregulation have been associated with altered immune functions and diurnal rhythms, as well as increases in inflammatory cytokines and immune disorders [64,67,68].

The physiologic immune function is particularly altered in the presence of chronic stress [69]. Accordingly, there has been growing evidence suggesting peripheral immune dysregulation and low-grade inflammation in PTSD, which even correlates with symptom levels [70–74]. PTSD was repeatedly associated with increased circulating concentrations of interleukin (IL)-1b, IL-6, C-reactive protein (CRP), tumour necrosis factor (TNF)-alpha, altered mononuclear cell functions and lower levels of lymphocytes, T-cells, natural killer (NK)-cell activity, interferon (IFN)-gamma and IL-4 [71,74–77].

In addition, the circadian system is closely interconnected with metabolic regulatory circuits by regulating expression and activity of key metabolic players towards cellular homeostasis [78,79]. Sleep deprivation and chronodisruption can lead to pro-orexic alterations of lipid and glucose metabolism and consequently to pathological conditions such as insulin resistance, dyslipidemia, metabolic syndrome and obesity [78,80]. Such clinical manifestations have been repeatedly reported in PTSD patients [81–83] and are partly associated with disrupted endocrine rhythms [84].

Sympathoadrenal and autonomic nervous system

Central and peripheral circadian rhythmicity modulates the cardiovascular autonomic control through projections to preautonomic neurons of the hypothalamus and is essential for the physiologic diurnal fluctuations seen in humans [38,85,86].

Both animal and human studies show that sleep deprivation is associated with increases in autonomic sympatho-adrenal activity and blunting of cardiovascular autonomic rhythmicity and autonomic responsiveness, and thus constitute a major cardiovascular risk factor [45,79,87].

Similarly, patients with PTSD exhibit increased autonomic responses to traumatic stimuli, elevated baseline central and peripheral concentrations of norepinephrine, greater baseline heart rate, increased baseline sympathovagal balance, blunted salivary alpha-amylase awakening response and, most importantly, blunted autonomic differences between day and night-time measures [18^a,88,89^a, 90–92], suggesting central neuroautonomic dysregulation leading to higher cardiovascular risk in PTSD. Sleep and circadian disruption may, thus, constitute a possible link between stress-related disorders, such as PTSD and cardiovascular disease [45,93].

Memory and cognitive function

Both animal and human studies demonstrate sensitivity of cognitive performance to the circadian system [94,95]. Memory processing, formation and consolidation are directly influenced by the circadian clock and melatonin, especially under stress [94,96,97]. Sleep promotes memory consolidation, particularly for emotionally salient information, although sleep and circadian deprivation may reduce the connectivity between amygdala and prefrontal cortex and disrupt this process [98–100]. Accordingly, several neuropsychological deficits have been repeatedly reported in association to sleep disruption in humans [101–103].

Apart from sleep disruption, acute stress also affects neural correlates of memory formation [104,105]. Accordingly, PTSD is associated with several cognitive deficits, very important for the development and maintenance of the disorder [106,107]. Neuroimaging studies in PTSD have reported hypo-responsive medial prefrontal cortical regions, hyper-responsive amygdala and smaller hippocampal volume with decreased activation [50,108,109], similar to findings of human and animal sleep deprivation studies [110–112]. In addition, animal studies suggest a significant role of circadian rhythmicity and melatonin on homeostasis, neurogenesis and neural activation in these brain regions [113,114].

Pain

Sleep and pain interact bidirectionally, with sleep deprivation leading to hyperalgesic states and, on the contrary, acute and chronic pain being associated with alterations in sleep continuity, sleep architecture and chronodisruption at molecular level

[115–118]. This fact, as well as the systematic diurnal variations in pain modulation [119,120] closely link nociception to the circadian system. Chronic pain syndromes have been associated with HPA-axis alterations, such as hypocortisolism and negative-feedback sensitivity, similar to PTSD [121,122]. Chronic pain syndromes and hyperalgesia are also often reported in PTSD, although trauma history is linked to chronic pain syndromes [123–125], thus suggesting a common chronobiological background of both conditions.

Endocannabinoids

Central and peripheral endogenous cannabinoid signalling plays a modulatory role in many fundamental physiological processes, although it is particularly involved in the circadian HPA-axis activity and glucocorticoid signalling [126,127]. Most importantly, there is evidence supporting an endocannabinoid modulation of the circadian system through a strong expression of CB1 receptor (CB1R) in the SCN [128,129], but also an effect of the circadian system on diurnal profiles of the endocannabinoid system and CB1R gene expression [130,131]. Clinical studies suggest changes of plasma endocannabinoid levels and elevation in amygdala-hippocampal-cortico-striatal CB1R availability in PTSD patients [132,133], indicating a main role of the endocannabinoid system in the pathophysiology of stress-related disorders and PTSD. The close connection between chronodisruption, PTSD and endocannabinoids is also demonstrated by nabilone, a synthetic cannabinoid, which was found efficacious in the management of treatment-resistant nightmares in PTSD [134].

Neuropeptide Y

Neuropeptide Y (NPY) has been implicated in the regulation of several physiological functions such as metabolism, memory and cognition, thermoregulation, sleep and stress regulation [135,136]. Central NPY is involved in circadian entrainment by mediating both photic and nonphotic influences on the SCN and moderating phase-shifting and melatonin secretion [137–139]. Conversely, light and melatonin have been suggested as modulators of central NPY synthesis [140,141]. Repetitive administration of NPY has been shown to lead to sleep disruption and blunted nocturnal cortisol and ACTH levels in healthy humans [142].

Impaired NPY signalling regulation may impact neuroendocrinological adaptation to stress and be involved in the pathophysiology of stress-associated disorders [143,144]. Acute stress increases plasma NPY in humans and is positively associated with

cortisol and norepinephrine release, although chronic stress leads to a distinctive NPY system downregulation [145,146]. Accordingly, lower plasma and CSF concentrations of NPY, as well as blunted NPY reactivity have been reported in PTSD [50,147,148] and could be explained by circadian dysregulation.

Discussion

The human circadian system creates and maintains cellular and systemic rhythmicity, although loss of circadian rhythmicity leads to adverse pathophysiological and epigenetic consequences [2,149]. Chronic circadian disruption may gradually change the fundamental properties of brain systems regulating neuroendocrine, immune and autonomic stress systems, similar to chronic stress [12]. Chronodisruption may, thus, sensitize individuals to stress-related disorders and play a central pathogenetic role in the development of stress-related disorders [45]. However, the literature is relatively sparse on the potential effect of circadian system on the pathophysiological findings in PTSD. However, there is evidence that sleep disruption occurring after trauma exposure may represent a core, rather than a secondary feature of PTSD and, thus, mediate the neurobiological correlates of the disorder through impaired homeostatic balance [7,8,24,26,34,150].

Evidence of circadian dysregulation in PTSD mostly originates from findings on blunted endocrine, autonomic and immune rhythmicity. However, there are only very few studies using state-of-the-art methods of circadian rhythm assessment in human PTSD research. Many findings originate from sleep research. Sleep disturbances are prominent clinical features of PTSD, often resistant to first-line treatments [7–10], although their effective treatment is associated with significant improvement of overall PTSD symptom severity [7,151,152]. Nevertheless, sleep disturbances are still often clinically assessed as secondary symptoms in PTSD.

Sleep regulation should be an integral part of PTSD treatment [153–155] and PTSD assessment should include a careful analysis of sleep disturbance [10,30]. Cognitive-behavioural therapies for insomnia and nightmares in PTSD constitute widely acceptable, effective treatment options with durable gains and beneficial effects also on other PTSD symptoms [10,156,157]. In addition, pharmacotherapy remains an important treatment option [10], although the unique neurobiological background of PTSD may require rather specific pharmacotherapies than standard pharmacological sleep management. For example, prazosin, clonidine, nabilone

and trazodone have been shown to be effective for PTSD-related sleep disturbances and trauma-specific nightmares [134,158–160]. Recent experimental findings emphasize on a specific role of melatonin in mechanisms of consciousness, memory and stress [161], as well as restoring circadian gene expression after traumatic stress [61], thus suggesting a potentially beneficiary effect of an add-on melatonergic treatment in PTSD. Further options targeting a pharmacological manipulation of the circadian pathway in order to prevent chronodisruption are of theoretical interest and deserve further study [162].

CONCLUSION

Current evidence suggests that sleep and circadian disruption play a causal role in PTSD pathophysiology. Evaluation and treatment of sleep and circadian disruption should therefore be first steps in PTSD management. State-of-the-art methods for assessment of circadian rhythmicity should be applied to increase our knowledge on the supraordinate role of circadian system in trauma and the associations among trauma exposure, sleep, circadian system and PTSD. Understanding the mechanisms susceptible to disruption following trauma exposure and the effects of a dysregulated circadian network in PTSD could provide new insights into disease mechanisms, advancing psychoneurobiological treatment possibilities and enabling preventive strategies of the disorder.

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Conflicts of interest

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