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REVIEW ARTICLE

Could Timed Targeting of the Circadian-Controlled NLRP3 Inflammasome Be a Potential Therapeutic Strategy for Treatment of COVID-19–Induced Encephalitis?

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The new coronavirus disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has several manifestations including neurological complications like encephalitis. The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasomes, which are regulated by the circadian clock genes, are key signaling proteins that detect pathogenic microorganisms and sterile stressors and activate the pro-inflammatory cytokines such as interleukin-1β and -18 (IL-1β and IL-18). The disruption of circadian rhythms following SARS-CoV-2 binding to angiotensin-converting enzyme 2 (ACE2) receptors in the capillary endothelium could lead to hyperactivation of the NLRP3 inflammasome, contributing to an enhanced inflammatory response in the central nervous system, thereby increasing susceptibility to or severity of coronavirus disease 2019 (COVID-19)-induced encephalitis. This review highlights the role of the circadian-controlled NLRP3 inflammasome in the pathogenesis of COVID-19-induced encephalitis and suggests targeting the NLRP3 circadian axis for timely intervention as a potential therapeutic target for the treatment of COVID-19-induced encephalitis.

Keywords: Circadian rhythm; NLRP3 inflammasome; BMAL1; SARS-CoV-2; Encephalitis

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INTRODUCTION

The primary target of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is believed to be the respiratory system [1]. However, this novel virus has been linked to other severe acute disease conditions including electrolyte and neurologic abnormalities [2,3]. Hence, clinicians have been on the look for more neurological manifestations of this novel virus since the first case of coronavirus disease 2019 (COVID-19)-induced encephalitis was reported in China, where the researchers used genome sequencing to validate the presence of SARS-CoV-2 in the cerebrospinal fluid of the infected patient [4,5]. SARS-CoV-2 has been reported to invade the nervous system bound to angiotensin-converting enzyme 2 (ACE2) receptor [6] or through the neural pathways [7], to cause neurological damage. The innate immune system response to invading microorganisms is to activate immune signaling complexes to induce sterile inflammation that is adequate for tissue injury resolution and regeneration. The NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome is one of the innate signaling complexes that is activated by a diverse range of stimuli, including ion fluxes, toxins, and various pathogens. As a key defense mechanism, activation of the NLRP3 inflammasome pathway in response to these stimuli leads to caspase-1-dependent secretion of pro-inflammatory cytokines interleukin-1β and -18 (IL-1β and IL-18) [8]. However, aberrant NLRP3 inflammasome activation has been linked to several metabolic and inflammation-mediated diseases [9].

The circadian clock regulates the pattern of expression and activation of NLRP3 inflammasome in various tissues including the macrophages [10]. This biological clock influences both the prim-

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ing of the inflammasome, by controlling the expression of components of the NLRP3 signaling pathway, and the extent of the subsequent inflammatory response, by regulating the production of inflammatory cytokines [11]. While the rhythmic pattern of some of the proposed clock-mediated effects on the NLRP3 inflammasome and inflammation is well established, dysregulation of the NLRP3 inflammasome signaling cascade can amplify the activities of pro-inflammatory cytokines that contribute to the pathogenesis of inflammatory diseases [9].

This review summarizes the current evidence on the link between circadian rhythms and the NLRP3 inflammasome in the context of COVID-19-induced encephalitis. The review explores how circadian rhythm disruption can amplify NLRP3-mediated neuroinflammation and proposes targeting the NLRP3-circadian axis by synchronizing treatment with circadian rhythms as a potential innovative therapy for COVID-19-induced encephalitis.

CIRCADIAN CONTROL OF NLRP3 INFLAMMASOME AND THE IMMUNE SYSTEM

Circadian rhythms are generated by biological clocks, with the core region of the mammalian biological clock located in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus [12]. The stability of an organism's overall rhythmicity requires the coordinated action of the SCN and peripheral clocks, involving the participation of both the endocrine system and autonomic nervous [13]. The molecular mechanisms of circadian rhythms involve complex feedback loops composed of clock genes [14]. The core clock genes brain and muscle Arnt-like 1 (*BMAL1*) and circadian locomotor output cycles kaput (*CLOCK*) function as heterodimer transcription factors, forming the positive limb of this loop. The negative limb of the circadian clock comprises the inhibitory factors cryptochrome (*CRY*) 1–2 and period (*PER*) 1–3 [15]. The *CRY* and *PER* proteins induced by the binding of the *BMAL1*/*CLOCK* heterodimer to E-box sites rhythmically inhibit the transcriptional activity of the *BMAL1*/*CLOCK* heterodimer [16]. In addition, *BMAL1*/*CLOCK* is known to regulate the expression of pro-inflammatory genes, including the NLRP3 inflammasome, which is involved in the immune response [17].

The immune system is designed in a way that it can detect and clear disease-causing organisms including accumulated cellular debris. Immune cells use specialized proteins called pattern recognition receptors (PRRs) to distinguish non-infectious from infectious agent-derived molecules [18]. When these molecules are detected, it triggers the activation of the immune system, and secretion of inflammatory factors, especially IL-1β, which is controlled by cytosolic PRR-constituted inflammasome complex [18].

The inflammasome is an organized multi-protein complex comprising a sensor protein like NLRP3, an adapter protein, and an effector protein. Activation of this complex involves a two-step process [19]. The first step, referred to as the priming step, results in the transcription of the NLRP3 inflammasome components, following the binding and activation of the PRRs by ligands from endogenous or exogenous sources such as the cell wall components. The second step involves the recognition of the trigger molecules which may be associated with either the pathogens or damaged cells, and this would ultimately result in the activation of the NLRP3 inflammasome that promotes the maturation of caspase-1 mediated pro-inflammatory IL-1β, and release of mature cytokines [20]. This two-step process is believed to be modulated by *BMAL1*/*CLOCK* heterodimer [11].

The *BMAL1*/*CLOCK* heterodimer modulates the expression of nuclear receptors *Rev-erbα/β* and retinoid-related orphan receptors α, β, and γ (*RORα/β/γ*), which subsequently regulate gene expression through interactions with co-repressors and co-activators. *Rev-erbα/β* acts as a transcriptional repressor of NLRP3, while *RORα/β/γ* functions as an activator [19]. According to Popov et al. [21], exposure to monosodium urate (MSU) crystals disrupts circadian clock function in macrophages by downregulating both *BMAL1* and *Rev-erbα*, key negative regulators of NLRP3 inflammasome. However, unstimulated human leukemia monocytic cell line (THP-1) derived macrophages exhibit stable *Rev-erbα* levels and rhythmic *BMAL1* expression. It is noteworthy that the effect of MSU crystals on *Rev-erbα* expression was dependent on the time of day, with greater repression occurring when *BMAL1* levels were naturally low and less repression occurring when *BMAL1* levels were naturally high [21]. Thus, this disruption may affect NLRP3-mediated inflammation, with a more pronounced effect during the *BMAL1*-low phase.

In an in vivo model of acute sterile peritonitis induced by intraperitoneal administration of lipopolysaccharide together with alum to specifically activate the NLRP3 signaling pathway, results showed that the mRNA expression of the components of the NLRP3 inflammasome oscillates in a daily manner under the control of *Rev-erbα* in peritoneal mouse macrophages, reaching a peak during the active phase, corresponding to the lowest expression (or nadir) of *Rev-erbα* mRNA [22]. Studies have also shown that impaired expression of the nuclear receptor *Rev-erbα* disrupts the NLRP3 signaling pathway, leading to increased maturation and release of the pro-inflammatory cytokines IL-1β and IL-18 via NLRP3-induced caspase-1 activation [22,23]. Conversely, activation of *Rev-erbα* by heme or pharmacological ligands suppresses the release of these cytokines by binding to specific regulatory elements within the NLRP3 and IL-1β gene promoters, thereby inhibiting their expression and regulating caspase-1 maturation and NLRP3 inflammasome assembly [22,24]. Taken together, these studies indicate that NLRP3 inflammasome activity is influenced by circadian rhythms, and conversely, excessive NLRP3 activation can disrupt circadian clock function, creating a potential feedback loop that exacerbates inflammatory conditions.

THE NLRP3-CIRCADIAN AXIS AND COVID-19-INDUCED ENCEPHALITIS

Circadian rhythms exert significant control over various as-

pects of the immune system, spanning from molecular to cellular and organelle levels [17,25,26]. Exposure to pathogens, including SARS-CoV-2, could directly or indirectly disrupt the body's biological clock functions [27], compromise the integrity of the nervous system, and contribute to neuroinflammation that results in life-threatening complications like encephalitis [28,29]. Viral encephalitis is an inflammation of the brain parenchyma caused by a viral infection. Viruses initially infect tissues outside the central nervous system and subsequently spread to the brain via two primary routes: retrograde transport along nerve pathways or hematogenous dissemination through the bloodstream. Once in the brain, the virus and the host's inflammatory response impair the activity of the nerve cells [18].

Elevated cytokines levels are established biomarkers that positively correlate with the severity of COVID-19 [30,31] and encephalitis [32,33]. Encephalitis has been reported in some COVID-19 patients, where it is believed to be due to the activation of the NLRP3 inflammasome which exacerbates the inflammatory response in the brain [4,34]. Current understanding of SARS-CoV-2 infection indicates that the virus enters host cells through ACE2 receptors, which exhibits circadian expression patterns across various tissues [31,35]. The dissemination of SARS-CoV-2 in the systemic circulation facilitates the interaction of the virus spike (S) protein with ACE2 expressed in the capillary endothelium. This may lead to damage to the endothelial lining, thus access to the brain and neurological manifestations of COVID-19 [3].

When the S protein of SARS-CoV-2 binds to the ACE2 receptor, the virus is internalized by endocytosis, leading to translation and RNA replication of genomic and sub-genomic RNA including the viral structural E protein. The E protein is involved in calcium (Ca^{2+}) release from the Golgi apparatus into the cytosol, and this Ca^{2+} activates NLRP3 inflammasome [36]. Activation of NLRP3 inflammasome provokes the release of biologically active danger-associated molecular patterns (DAMPs), and several proinflammatory cytokines, including IL-1β [37]. Studies have shown that NLRP3 inflammasome activation triggered by Ca^{2+} flux is a common denominator across various viral infections [36,38-40].

TARGETING THE NLRP3-CIRCADIAN AXIS IN THE TREATMENT OF COVID-19-INDUCED ENCEPHALITIS

The interplay between inflammation and disease progression has become a cornerstone of understanding the pathophysiology of both COVID-19 and encephalitis. Encephalitis involves a complex inflammatory cascade within the central nervous system, while in COVID-19, hyperinflammatory responses, often manifested as a cytokine storm, significantly contribute to disease severity [30].

Chronotherapy is proposed as an effective intervention for hospitalized COVID-19 patients. This intervention involves carrying out disease- and symptom-related interventions during the optimal time of the day, and the administration of circadian rhythm modulators like melatonin [41]. Melatonin, primarily produced in the pineal gland, regulates sleep-wake cycle and immune function [42]. Adequate sleep supports the regular expression of immune components, over a 24-hour period; however, chronic sleep deprivation disrupts this regulation, leading to asynchronous expression of various immune factors [43,44].

Research has shown that melatonin inhibits NLRP3 inflammasome activity, thereby preventing pyroptosis [45]. This inhibitory effect of melatonin on the NLRP3 inflammasome has been demonstrated in several in vitro and in vivo models of diseases and injuries [46]. Inhibiting NLRP3 activity with melatonin has been reported to mitigate brain damage by downregulating NLRP3, apoptosis-associated speck-like protein (ASC), and caspase-1 levels [47,48], reducing reactive oxygen species through mitophagy [49], and inhibiting nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) [50]. As a result, melatonin has been proposed as an adjuvant option for the treatment of COVID-19 and related diseases [51]. To optimize melatonin levels, supplementation should be aligned with the body's natural circadian rhythm. It is generally recommended to take melatonin a few hours before the desired sleep onset. This helps regulate sleep patterns, supports the body's natural melatonin production, and mitigates the negative effects of NLRP3-induced chronic inflammation associated with sleep deprivation.

Several selective NLRP3 inflammasome inhibitors have been developed and tested in preclinical and early phase clinical studies, showing potential for efficacy across a wide range of inflammatory disorders with no safety concerns [52,53]. Preclinical studies have shown that selective inhibition of the NLRP3 inflammasome attenuates COVID-19-like immune system overactivation and pathology, suggesting that such a therapeutic approach could be beneficial for humans [54,55]. Interleukin-6 (IL-6) antagonists like tocilizumab, sarilumab and interleukin-1 (IL-1) antagonists like anakinra have been repurposed for COVID-19 [56-59]. However, the results on the effectiveness of these interventions were generally favorable, albeit inconsistent [60].

This raises important considerations about the role of chronotherapy and circadian rhythms in the treatment of hyperinflammation in COVID-19. For instance, anti-inflammatory therapies could be detrimental if administered too early in the course of disease, as they may favor viral replication and reduce immune competence and memory. In contrast, delayed immunomodulation may be ineffective when massive cytokines are released, and organ injury already occurred. This timed intervention has been demonstrated with antihypertensive agents [61], antiviral drugs during COVID-19 [62], and corticosteroids [63], all of which have shown better efficacy when aligned with biological rhythms.

In diseases like COVID-19-induced encephalitis, where hyperactivation of the immune system is likely driven by inflammasomes and IL-1 cytokines, the diurnal nature of inflammatory processes becomes particularly relevant. As NLRP3 inflammasome activity may peak during periods of heightened vulnerabil-

ity, such as early morning hours or sleep-wake transitions, aligning therapeutic interventions with peak periods of NLRP3 activity may be sufficient to mitigate hyperinflammation and optimize therapeutic outcomes.

CONCLUSION

NLRP3 inflammasome, which is crucial for the immune response, can exacerbate inflammation when it is overactivated, especially when circadian rhythms are disrupted. The circadian clock regulates NLRP3 inflammasome activity, and its disruption by SARS-CoV-2 can amplify neuroinflammation and exacerbate conditions such as encephalitis. NLRP3 has emerged as a promising therapeutic target due to its key role in inflammatory diseases, and as a result, several inhibitors with high therapeutic value have been developed. While these inhibitors have shown potential, inconsistencies in efficacy hinder their clinical translation, particularly in diseases such as encephalitis. Since circadian clock genes regulate the physiological outcomes of the immune system, targeting the NLRP3-circadian axis by aligning interventions with the peak times of the NLRP3 inflammasome could maximize treatment efficacy. Therefore, further clinical research is needed to elucidate the specific modulation of NLRP3 inflammasomes within the circadian regulatory network in order to successfully implement targeted interventions for the treatment of COVID-19 induced encephalitis.

Conflicts of Interest

The author has no potential conflicts of interest to disclose.

Availability of Data and Material

Data sharing not applicable to this article as no datasets were generated or analyzed during the study.

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