



## Review

## A time to fight: Circadian control of aggression and associated autonomic support

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## ABSTRACT

The central circadian clock, located in the suprachiasmatic nucleus of the mammalian hypothalamus (SCN), regulates daily behavioral rhythms including the temporal propensity for aggressive behavior. Such aggression propensity rhythms are regulated by a functional circuit from the SCN to neurons that drive attack behavior in the ventromedial hypothalamus (VMH), via a relay in the subparaventricular zone (SPZ). In addition to this pathway, the SCN also regulates sleep-wake and locomotor activity rhythms, via the SPZ, in a circuit to the dorsomedial hypothalamus (DMH), a structure that is also known to play a key role in autonomic function and the sympathetic “fight-or-flight” response (which prepares the body for action in stressful situations such as an agonistic encounter). While the autonomic nervous system is known to be under pronounced circadian control, it is less apparent how such autonomic rhythms and their underlying circuitry may support the temporal propensity for aggressive behavior. Additionally, it is unclear how circadian and autonomic dysfunction may contribute to aberrant social and emotional behavior, such as agitation and aggression. Here we review the literature concerning interactions between the circadian and autonomic systems and aggression, and we discuss the implications of these relationships for human neural and behavioral pathologies.

## 1. Introduction

Circadian clocks prepare the brain and body to execute particular physiological and behavioral processes during different times of day, conveying an evolutionarily adaptive advantage for an organism's survival. Indeed, the central circadian clock regulates baseline rhythms of the autonomic nervous system (Buijs et al., 2013), which is the system that primarily controls another adaptive mechanism, the so-called “fight-or-flight” response. This term was coined by Cannon to refer to physiological responses induced by stress that prepare the body to face adversity, such as an agonistic encounter (Cannon, 1929), and thus the autonomic system's role in situations that promote aggressive behavior has long been recognized. We recently demonstrated that the central circadian system directly regulates a rhythm in the propensity for aggressive behavior through a novel neural pathway (Todd et al., 2018). However, it is less apparent how the circadian control of autonomic regulation and its underlying circuitry may support this temporal propensity for aggression, as well as the implications of these connections for human disorders in which circadian and autonomic dysfunction are comorbid factors with agitation and aggressive behavior. Here we review the literature on interactions between the circadian system, the

autonomic system, and aggressive behavior, and we present opportunities for new lines of research that could potentially inform human disorders characterized by circadian and autonomic disruptions and aberrant social and emotional behaviors such as aggression.

## 2. Anatomy of the circadian system and its direct neural control of aggression

The suprachiasmatic nucleus (SCN) of the hypothalamus is the central circadian clock of the mammalian brain and is required for daily rhythms of physiology and behavior (Reppert and Weaver, 2002). The SCN entrains such rhythms to the daily light-dark cycle (Rusak et al., 1990), via photic input from the retina by way of the retinohypothalamic tract (Gooley et al., 2003; Todd et al., 2012). SCN neurons, which are highly coupled in vivo, can function as individual oscillators with rhythmic electrical activity on a period of about 24 h (Welsh et al., 1995). This rhythmic activity is under the control of clock genes, via a transcriptional-translational-posttranslational negative feedback loop (Jin et al., 1999). While this same genetic machinery is present in cells throughout the brain and body, the SCN is necessary to synchronize peripheral oscillators and maintain rhythmic behavior

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(Mohawk et al., 2012). Importantly, axonal output appears to be the primary method by which the SCN establishes such synchrony in vivo (Gall et al., 2012; Saper, 2013), and the majority of SCN axons target a nearby region known as the subparaventricular zone (SPZ) (Watts et al., 1987; Watts and Swanson, 1987; Vujovic et al., 2015). Indeed, circadian rhythms of sleep-wake, locomotor activity, and feeding behavior are known to be regulated by a pathway from the SCN, through the SPZ, to the dorsomedial nucleus of the hypothalamus (DMH) (Lu et al., 2001; Chou et al., 2003; Saper, 2013). Pathways by which the circadian system directly regulates more complex behaviors, such as particular social and emotional behaviors, have remained more elusive. For example, while evidence from rodents (Sofia and Salama, 1970; Landau, 1975b; Haller et al., 2000a) and humans (Manfredini et al., 2001) previously demonstrated temporal differences in aggressive behavior, it was unclear whether the SCN clock directly regulates a rhythm in aggression (Bronsard and Bartolomei, 2013; Hood and Amir, 2018). However, we recently demonstrated that the propensity for aggressive behavior follows a daily rhythm in male mice, with the highest levels during the early active phase and the lowest during the early resting phase, and we showed that this rhythm is contingent on proper functioning of GABAergic SPZ (SPZ<sup>GABA</sup>) neurons (Todd et al., 2018). Genetic deletion of the vesicular GABA transporter (VGAT) in these neurons, which renders them unable to release GABA, results in increased behavioral aggression during the early light period, the resting phase for nocturnal mice. Importantly, while these deletions reduce locomotor activity and plasma corticosterone levels during the early dark period, when both are normally high in intact mice, they do not increase them during the early light period, suggesting that the increase in aggression at that time results from a direct neural effect. Attack behavior in male mice is known to be directly regulated by neurons within the ventromedial nucleus of the hypothalamus (VMH), and specifically those that express estrogen (Esr1) and progesterone receptors in the ventrolateral VMH (VMHvl) (Lin et al., 2011; Yang et al., 2013; Lee et al., 2014; Yang et al., 2017). We showed that SPZ<sup>GABA</sup> neurons make functional synaptic connections onto Esr1-expressing VMHvl neurons, and that vasoactive intestinal polypeptide (VIP) neurons of the SCN make functional connections onto SPZ<sup>GABA</sup> neurons that project to the VMH (Todd et al., 2018). We showed that these SPZ neurons are also more active during the early light period compared to the early dark period, and acutely inhibiting these neurons using a novel inhibitory chemogenetic vector reversibly increased aggression in a phase-dependent manner. Altogether, the SCN → SPZ → VMH circuit constitutes a critical pathway through which the central circadian clock gates aggression propensity across the 24 h day (see Fig. 1). While this circuit represents the basis for the central circadian control of aggression, the circadian system is also known to modulate the autonomic system, and through these pathways likely supports the body's ability to respond accordingly during an aggressive act.

### 3. Circadian regulation of the autonomic system

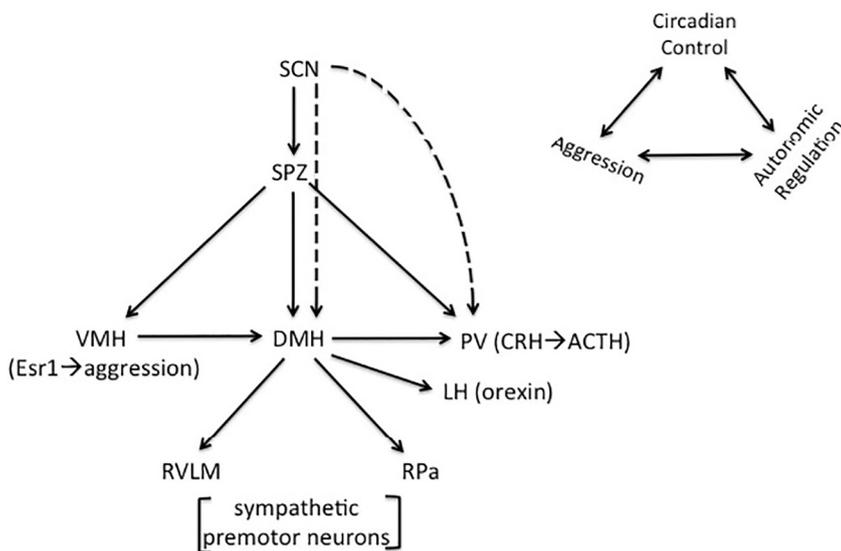
The autonomic system exhibits a distinct circadian pattern, as shown by the early rise in sympathetic nerve activity, blood pressure (BP), heart rate (HR) and increases in body temperature (Tb), cortisol release, and glucose levels that prepare the body for the daily active phase (Buijs et al., 2013; Smolensky et al., 2016). In humans, the well-known phenomenon of cardiovascular events, such as ventricular tachycardia, ventricular fibrillation and sudden cardiac death, most commonly occurring in the morning after waking, reinforces a critical role for the circadian system in autonomic function (Takeda and Maemura, 2016). Additionally, professions involving night-shift work, which causes chronic circadian disruption, are associated with increased risks of cardiovascular disease (Thosar et al., 2018). HR regulation appears to transition from the influence of high sympathetic nerve activity in the early active phase to a state of relative vagal dominance during the resting period (Verrier and Tan, 2009; Takeda

and Maemura, 2016). Changes in autonomic regulation are also found during sleep. For instance, non-rapid eye movement (NREM) sleep is characterized by vagal dominance, while sympathetic nerve activity is stable, and during this stage individuals show relative hypotension, bradycardia, and reduced cardiac output and systemic vascular resistance. This pattern is disrupted during rapid eye movement (REM) sleep, which is characterized by vagal withdrawal, while sympathetic nerve activity can reach even higher levels than during wake (Verrier and Josephson, 2009).

Circadian control of the autonomic system has been shown to be coordinated by the SCN, as bilateral thermal ablation of the SCN in mice abolishes HR circadian rhythms, an important indirect indicator of autonomic control (Warren et al., 1994). Additionally, global knockouts of the clock genes *Clock* and *Bmal1* result in a loss of the HR circadian rhythm (Rahman et al., 2018). However, cardiomyocyte-specific knockout of *Clock* or *Bmal1* reduces but does not abolish the HR circadian rhythm, suggesting that the local cardiac clock contributes, but is not essential for this rhythm (Bray et al., 2008; Schroeder et al., 2011). These results support the hypothesis that the SCN works as an autonomous clock regulating HR rhythmicity. Indeed, VIP neurons within the SCN, which represent only about 10% of all SCN neurons (Mazuski et al., 2018), have specifically been shown to modulate circadian rhythmicity in the heart, but do not appear to eliminate the circadian rhythm of Tb (Schroeder et al., 2011).

The pathway by which the SCN regulates circadian rhythms of Tb is unclear (Saper, 2013), but one possibility could be through the SCN's modulation of brown adipose tissue (BAT) activity (Amir et al., 1989). BAT thermogenesis is regulated by the sympathetic system and exhibits an ultradian rhythm (less than 24 h) that corresponds to phase-linked changes in Tb (Ootsuka et al., 2009). Indeed, the DMH region, and specifically the glutamatergic neurons within the dorsal hypothalamic area (DHA<sup>Vglut2</sup>), regulates BAT activity and thermogenesis induced by stressful stimuli, as part of the fight-or-flight response (Morrison, 2004; Machado et al., 2018; Kataoka et al., 2014). However, DMH/DHA lesions do not abolish circadian rhythms of Tb (Chou et al., 2003), and thus a neuro-circuit for the circadian control of Tb remains to be determined.

In addition to its role in modulating sleep-wake centers and Tb, there is substantial evidence that the DMH projects to sympathetic outflow areas to regulate cardiovascular and respiratory function (see below, and Fig. 1). It is therefore likely that the SCN → SPZ → DMH pathway also underlies circadian cardiac and respiratory autonomic rhythms, although this remains to be demonstrated definitively. What is clear is that the hypothalamus regulates the fight-or-flight stress response, and in this context, the DMH is thought to be the critical hypothalamic region mediating the sympathetic activation and cardiovascular responses induced by stressful stimuli in humans and animals (DiMicco et al., 2002; Fontes et al., 2011; Fontes et al., 2017; Lisa et al., 1989; James et al., 2013; Dampney, 2015). Injection of muscimol (an agonist of GABA<sub>A</sub> receptors) into the DMH of rats prevents increases in BP, HR, and adrenal corticotrophic hormone (ACTH) induced by air-jet stress (Stotz-Potter et al., 1996), and reduces psychogenic fever induced by the resident-intruder protocol (Kataoka et al., 2014). DMH neurons innervate brainstem regions also critically involved in the regulation of the autonomic system. The rostral ventrolateral medulla (RVLM) and raphe pallidus (RPa), which have premotor neurons that regulate sympathetic output, are considered to be key relays of the stress-induced autonomic responses. Several lines of evidence suggest that the DMH/DHA modulates RVLM and RPa activity in order to produce stress induced fight-or-flight responses, wherein the RVLM provides vasoconstrictor drive to muscle, splanchnic, and renal vascular beds while the RPa provides the cardiac drive and the sympathetic drive to BAT (Fontes et al., 2001; Cao and Morrison, 2003; Horiuchi et al., 2004; Kataoka et al., 2014; Machado et al., 2018). Evidence for a similar DMH mechanism in humans has been demonstrated by the strong resting fMRI signal coupling between the DMH and the RVLM, suggesting



suggested to regulate the hyperarousal during fight-or-flight responses. Finally, DMH neurons also receive innervation from the region of the VMH associated with promoting aggression, representing the possible pathway by which aggressive behavior reciprocally influences circadian autonomic regions. Hatched lines represent relatively sparser projections from the SCN to the DMH and PV, compared to SCN projections to the SPZ.

strong DMH-RVLM connectivity (Macefield and Henderson, 2016). In addition to its direct pathways to the RVLM and RPa, the DMH may also regulate circadian autonomic rhythms via its projections to orexin neurons within the lateral hypothalamus (LH) (Saper, 2013). These LH orexin neurons regulate wakefulness and been shown to project to cardiovascular and respiratory centers (Geerling et al., 2003), and they also play a key role in hyperarousal during fight-or-flight responses (Kuwaki et al., 2008).

#### 4. Autonomic support during aggressive behavior

Aggression is considered a normal component of a species' behavioral repertoire, whether it be used to ward off predators, catch prey, or compete for resources or mates, and in both animals and humans, aggressive acts are associated with a state of hyperarousal (Falkner and Lin, 2014). However, in most experimental studies that assess aggression in association with autonomic indicators, these two variables are usually temporally segregated (Haller et al., 2014). For example, human studies often examine individuals with violent criminal pasts or children with a history of antisocial behavior, but such subjects are almost always peaceful during the actual autonomic tests. Other studies that do assess real-time aggression and autonomic function usually employ symbolic or mild forms of aggressive responding, due to the obvious ethical and technical constraints of such work. However, Haller et al. devised a highly realistic model of human aggression in real world scenarios with the concomitant measurement of cardiac autonomic variables (Haller et al., 2014), involving police trainees performing operations under extreme stress. Under these conditions, high levels of inappropriate aggression (in the form of unprovoked gun use) were associated with high HR and low heart rate variability (HRV), whereas refraining from unprovoked aggression under such circumstances was associated with low HR and high HRV. HRV is a valuable tool for investigating changes in autonomic function in humans, as it is an indirect and noninvasive measure of parasympathetic and sympathetic influences on the sinoatrial node. In this regard, parasympathetic activity is indexed by the high-frequency component of HRV, while sympathetic activity can be determined through lower frequency components (Verrier and Tan, 2009). Since changes in autonomic function are highly associated with neuropsychiatric conditions, HRV has become an emerging measure that links physiological responses and cognitive features (Cohen and Benjamin, 2006; Cohen et al., 2000;

Ulmer et al., 2018).

Although the autonomic aspects underlying pathological aggression (such as in individuals with violent criminal pasts) are not fully elucidated, the majority of human studies have demonstrated physiological patterns that suggest a correlation of low baseline HR with previous aggressive behavior. One meta-analysis identified that aggression is consistently associated with low resting HR and high HR reactivity in adults (18 years or older) and low HR in child aggression (1–11 years old), when data from 16 different studies was analyzed (Lorber, 2004). In this regard, and as described above, cardiac autonomic function is thought to be a valuable external indicator of internal motivational states and raises the possibility that cardiac measurements could be used as predictors of the responsiveness and potential agitation of individuals to stressful stimuli. HR is shown to be lower in aggressive adults and children, but the mechanisms underlying this phenomenon are not well elucidated. Experiments in rats do not support the idea that vagal tone/parasympathetic activity is higher in aggressive animals. A study identified that highly aggressive rats show resistance in response to vagal blockade administration and are more susceptible to stress-induced tachyarrhythmias and pharmacologically-induced arrhythmias compared to non-aggressive rats (Carnevali et al., 2013). These results suggest that an impairment of the cardiac autonomic modulation occurs in aggression that is likely due to a vagal dysfunction, which may also be the basis for the low HR associated with aggression in humans. The results from this rodent model also suggest that the disruption of vagal regulation may facilitate the sympathetic action on the heart, leading to arrhythmic events. Supporting this argument, a study using post-weaning social isolation as a stressor model demonstrated that stressed rats exhibit autonomic overreaction, in the form of higher increases in HR and corticosterone levels, during aggression compared to non-stressed rats (Toth et al., 2011). In humans, there is evidence that suppressed vagal control and anger can contribute to arrhythmogenesis and predict premature cardiac morbidity and mortality (Tsuji et al., 1994; Tsuji et al., 1996; Lampert, 2010). These observations suggest that in aggressive individuals a vagal disruption associated with overreaction of the sympathetic arm of the autonomic system can increase propensity to arrhythmogenic events and even sudden death.

It is important to note that none of the studies mentioned above assessed time of day as a primary factor when measuring aggressive outcomes or autonomic output. Given that, as described above, circadian and autonomic circuits clearly influence neural processes

underlying aggression, as well as each other, we argue that assessments which incorporate real-time measures of autonomic output during tests of aggressive responding at different circadian time points will be crucial to better understand such interactions. Additionally, strong evidence suggests a reciprocal influence from neural processes underlying aggression upon the circadian circuit regulating autonomic rhythms, as repeated aggressive arousal has been shown to be able to entrain HR rhythms (Tornatzky et al., 1998). Indeed, the VMHvl, which contains the neurons that promote attack behavior, sends a strong input to the DMH (Canteras et al., 1994), and this is likely the pathway by which aggression itself can influence circadian autonomic function (see Fig. 1). Finally, because agitation and aggression are difficult to quantify in humans, experiments in animal models delineating the various interactions between circadian, autonomic, and aggression systems could prove vital in determining the efficacy of autonomic measures (which are readily assessed with wearable devices) as indicators of underlying agitated states in disorders associated with circadian disruption and aggressive behavior. Such work could thus lead to future examinations that reveal the mechanisms underlying these neural and behavioral pathologies.

### 5. Circadian and autonomic regulation of hormonal modulation and aggression

The circadian and autonomic systems both modulate a number of hormonal rhythms, and there is a large body of evidence to support various hormonal influences on aggression across the animal kingdom (Haller et al., 1998; Nelson and Trainor, 2007; Haller, 2014). The paraventricular nucleus (PV) of the hypothalamus is the primary neural regulator of the hypothalamic-pituitary-adrenal (HPA) axis (Whitnall, 1993), which plays a complementary role in modulating the fight-or-flight stress response via neuroendocrine output (Li and Sawchenko, 1998). Indeed, the circadian, autonomic, and neuroendocrine systems are highly interconnected and each plays a role in influencing emotional state and likely behavioral outcomes of an agonistic encounter.

PV neurons expressing corticotropin-releasing-hormone (CRH) regulate the release of plasma corticosterone (Vale et al., 1981), which as mentioned above, demonstrates a pronounced circadian pattern (Engeland and Arnhold, 2005). These CRH neurons stimulate the synthesis of ACTH by the pituitary gland, which further stimulates the secretion of glucocorticoids by the adrenal cortex. This rhythm has been shown to be regulated by the SCN (Engeland and Arnhold, 2005), however the SCN sends only sparse direct projections to the PV (Vrang et al., 1995). Instead, the SCN → SPZ → DMH circuit appears to modulate the corticosterone rhythms through DMH projections to the PV (Chou et al., 2003), and perhaps by direct projections from the SPZ (Vujovic et al., 2015; Todd et al., 2018) (see Fig. 1). In our assessment of the circadian control of aggression, SPZ VGAT deletions did not increase plasma corticosterone during the early resting period, when they are normally low in intact mice, in conjunction with the increase in aggression seen at this time point. However, these deletions did decrease corticosterone levels during the early active phase, when they are normally high in intact mice. This suggests that the high levels of corticosterone in intact mice during the early active period may contribute to the normally high levels of aggression seen at this time point. Indeed, studies in rats and hamsters have shown that high levels of attack behavior correspond to the rising phase of these corticosterone rhythms (Landau, 1975b; Haller et al., 2000a), and that this pattern is disrupted by adrenalectomy (Landau, 1975a; Haller et al., 2000b). As further evidence of the interconnectedness of these systems, sympathetic preganglionic fibers project to the adrenal medulla and stimulate the release of catecholamines into the bloodstream to support bodily action during the fight-or-flight response (Kvetnansky et al., 1995). Indeed, lower than normal levels of catecholamine activity have been shown to be associated with greater levels of anger and agitation in adult humans (Schwartz and Portnoy, 2017).

### 6. Human neural disorders characterized by aggressive behavior and circadian and autonomic dysfunction

The autonomic system is regulated by the central nervous system and is tightly modulated by circadian rhythms, as discussed above. Because aggressive behavior is also under the influence of the circadian system, disruption of circadian rhythms may lead to facilitation of aggressive arousal. For instance, Alzheimer's disease and related dementias are associated by progressive circadian dysfunction, including “sundowning syndrome”, a poorly understood clinical phenomenon associated with agitation and aggression during the early evening that has been described in medical literature for over 70 years (Bachman and Rabins, 2006; Khachiyants et al., 2011; Bedrosian and Nelson, 2013; Canevelli et al., 2016). Interestingly, we found that disrupting the SCN → SPZ → VMH pathway leads to increased behavioral aggression during the early resting phase (Todd et al., 2018), which is temporally analogous to when patients that exhibit sundowning display increased agitation and aggression. Additionally, AD and dementia patients have also been found to exhibit autonomic dysfunction (Jensen-Dahm et al., 2015; Santos et al., 2017), although this has never been examined in the context of sundowning. Similarly, other behavioral disorders such as schizophrenia, autism, bipolar disorder, and post-traumatic stress disorder, are usually associated with autonomic imbalance as well as circadian/sleep-wake disruption, and these disorders often present with agitation and aggression (Boettger et al., 2006; Henry et al., 2010; Heiler et al., 2011; Panju et al., 2015; Tye et al., 2015; Cohen et al., 2018). In this regard, the identification of the autonomic profile of aggressive behavior may generate physiologically sensitive indices that could be used as possible markers for the neuronal conditions underlying aggressive behavior, pathologies associated with aggression, and behavioral states across the antisocial spectrum.

### 7. Conclusion and future directions

Interactions between the circadian and autonomic systems likely influence the behavioral outcomes of an agonistic encounter, and may shift a response closer to “fight” rather than “flight” depending on the time of day. Additionally, the degree of interconnectivity between these systems (Fig. 1) underscores the emotional and behavioral implications of circadian disruption in both healthy individuals and in pathological conditions. More work in both animal models and humans is needed to better understand such interactions. For instance, strategies for determining the directionality or relative weight of these interactions could be examined in shift workers, or in simulated shift work schedules in rodent models. Indeed, while shift work has been previously associated with autonomic dysfunction (Thosar et al., 2018), we are unaware of any studies examining agitation or aggression in shift workers. Additionally, studies in transgenic mice manipulating the synaptic terminals of particular SCN or SPZ cell types in regions involved with fight-or-flight responses, such as the DMH and the PV, will be critical in order to elucidate the central circuit of autonomic system rhythmicity. Such experiments are likely to inform our understanding of the regulation of autonomic rhythms and how they influence agitation and aggression in humans, considering the evidence that SCN projections are evolutionary conserved from rodents to humans (Buijs et al., 2013). Translational work could also more definitively establish circadian autonomic measures, which can be easily assessed in humans using wearable monitors, as reliable indicators of an underlying agitated state. Most importantly, such examinations could thus prove vital to a better understanding of human neural and behavioral pathologies where aggressive outcomes can be more difficult to study and quantify.

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## Declarations of interest

None.

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