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Sleep and circadian dysfunction in neurodegenerative disorders: insights from a mouse model of Huntington's disease

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Abstract

Sleep disorders are common in patients with neurodegenerative diseases and manifest early in the disease process. Among a number of possible mechanisms underlying the sleep disturbances, there is evidence that dysfunction in the circadian system is a contributing factor. Focusing on a mouse model of Huntington's disease has enabled us to determine that at the onset of symptoms, spontaneous electrical activity of neurons within the central clock is disrupted even though the molecular clockwork is still functional. These findings suggest that the fundamental deficit contributing to disordered sleep is reduced SCN output. The mechanism underlying this deficit is not yet known, but mitochondrial dysfunction and oxidative stress are likely involved. Disruption of circadian output from the SCN would be expected to have wide ranging impact on the body including SCN regulated brain regions and the heart. In fact, there is a great deal of overlap in the non-motor symptoms experienced by HD patients and the consequences of circadian disruption. This raises the possibility that the disordered sleep and circadian function experienced by HD patients may be an integral part of the disease. Furthermore, we speculate that circadian dysfunction may accelerate the pathology underlying HD. If these hypotheses are correct, we should focus on treating circadian misalignment and sleep disruptions early in disease progression.

Keywords

Circadian; Huntington's disease; Non-motor symptoms of Huntington's disease; Sleep; Suprachiasmatic nucleus

Introduction

Sleep disorders are common in Europe and the USA with an estimated 30 to 40% of the adult population reporting difficulty falling asleep at night and significant daytime sleepiness as a consequence^{1,2}. The National Health Interview Survey has found that an average night's sleep is 6.5 hrs with the trend shortening for working adults³. These data suggest that many of us are all too familiar with the symptoms of sleep deprivation, including feelings of fatigue, irritability, and difficulty concentrating⁴. There is also a growing awareness that sleep deprivation is associated with metabolic imbalances and compromised immune response⁵⁻⁷. Fortunately, these symptoms quickly recover with the restorative powers of a good night's sleep. Unfortunately, for many patients with chronic diseases of the nervous system, a good night's sleep is very hard to obtain⁸. There is

increasing evidence that in neurodegenerative disorders such as Alzheimer's, Huntington's and Parkinson's diseases, sleep disruptions are common and occur early in the disease progression⁹⁻¹¹. In some cases, patients will experience years of sleep disturbances before the onset of dementia or motor symptoms that characterize the specific disease^{12,13}. These sleep disturbances have significant negative consequences for both the patients and their caregivers. While there are a number of possible mechanisms underlying the sleep disturbances, we propose that dysfunction in the circadian system is a contributing factor.

Molecular clockwork common in cells throughout the body

Output from the master circadian clock regulates physiological rhythms through modifications of the phase and amplitude of "clock gene" rhythms measurable in many tissues. Most cells express robust rhythms in the transcription and translation of key clock genes through an autoregulatory negative feedback loop, which then synchronize with other functionally relevant cells. Over the past two decades, circadian rhythm researchers have identified the basic mechanism underlying the cell-autonomous molecular clockwork that generates and regulates circadian rhythms in gene expression^{14,15}. In short, CLOCK and BMAL1 are basic helix-loop-helix PAS-containing transcription factors that heterodimerize and enhance transcription of Period genes (Per1-3)¹⁶⁻¹⁹ and Cryptochrome genes (Cry1-2)²⁰ through E-box elements²¹⁻²³. Once translated, PER and CRY proteins form complexes that accumulate in the cytoplasm and are later translocated to the nucleus recruiting HDAC complex to repress BMAL/CLOCK-mediated transcription^{20,24-26}. To relieve this repression, CRYs are targeted for proteasomal degradation by an ubiquitin process which allows a new cycle to begin^{25,27,28}. The timing and stability of the core negative feedback loop is regulated by the phosphorylation state of clock proteins directing the protein for degradation or nuclear translocation²⁹⁻³¹, and additional stabilizing transcriptional loops regulate Bmal1^{32,33} and other clock genes^{34,35} through nuclear receptors from the REV-ERB and ROR families. Taken together, the network that drives circadian oscillations in gene expression output is a highly regulated, robust, and resilient timekeeper.

Circadian regulation of gene expression varies with tissue

Each of the major organ systems of the body is made up of a network of circadian oscillators, with each of the major organ systems (ie. brain, heart, liver, pancreas, etc) apparently having its own clockwork to regulate the transcription of genes important to the specific target organ¹⁴. Using DNA microarray expression profiling it has been found that approximately 8 to 12% of genes display circadian oscillations³⁶⁻³⁸. Many of these genes are involved in key rate-limiting steps of biochemical pathways^{36,39}. In the nervous system, a number of genes involved in peptide synthesis, secretion, and oxidative phosphorylation are transcribed with a circadian oscillation likely driven by the molecular clockwork present in each of these organs. For example, the genetic overexpression of REV-ERB alpha specifically in the liver shuts down the molecular clock locally and results in a loss of 90% of the transcriptional rhythms measured in mouse hepatocytes⁴⁰. These data indicate the predominant driver of gene expression rhythms in the liver is the molecular clockwork within hepatocytes, even though some liver rhythms are imposed by external signals such as cortisol⁴¹. In some cases, rhythms in mRNA expression do not lead to rhythms in protein levels^{42,43} and it is therefore important to confirm gene expression rhythms with protein measurements.

SCN output coordinates an array of rhythmic tissues

In mammals, the suprachiasmatic nucleus (SCN) of the hypothalamus contains the "master" oscillatory network necessary for coordinating circadian rhythms throughout the body^{15,44}(Fig.1) The SCN is a bilaterally paired nucleus made up of tightly compacted,

small-diameter neurons just lateral to the third ventricle atop the optic chiasm⁴⁵. Anatomical studies generally support the division of the SCN into at least two subdivisions including a ventral (core) and dorsal (shell) region^{46,47}. Ventral neurons are thought integrate environmental irradiance information and from three major input pathways: the retinohypothalamic tract (RHT), the geniculohypothalamic tract from the intergeniculate leaflet of the thalamus, and from the raphe nuclei⁴⁸. These input processing neurons then communicate environmental information to dorsal SCN neurons. Notably, ventral neurons exhibit relatively low amplitude rhythms in clock gene expression and the neuropeptides vasoactive intestinal peptide (VIP) or gastrin-releasing peptide (GRP) in addition to the neurotransmitter GABA. In contrast, neurons of the dorsal shell appear to generate robust circadian oscillations in gene expression⁴⁹⁻⁵¹, and express vasopressin (AVP) or prokineticin 2 (PK2) in addition to GABA.

The fact that many core neuronal projections terminate on shell neurons supports the idea that the interplay between these two regions is responsible for coordinating output of circadian information from the SCN⁵². SCN outputs from both core and shell subpopulations largely project to other hypothalamic regions, including the subparaventricular zone and other medial hypothalamic structures surrounding the SCN⁵³⁻⁵⁵. These hypothalamic relay nuclei send projections throughout the nervous and endocrine systems, providing multiple pathways by which the SCN output conveys temporal information about the environment to the rest of the brain and body^{14,55}. Additionally, output from physiological systems receiving circadian regulation can “feeds-back” to alter the master clock. For example, both sleep states⁵⁶ and locomotor activity⁵⁷⁻⁵⁹ “feedback” to regulate SCN neural activity recorded *in vivo*. These physiological studies demonstrate the difficulty in attempting to disentangle the role of the circadian system and sleep on behavior and physiology, because it may not be possible to alter sleep without impacting the circadian system.

Focus on Huntington’s disease

HD is caused by an expanded CAG repeat coding for polyglutamine in the huntingtin (HTT) protein⁶⁰. Onset of HD is typically in middle age but symptoms can start quite young. Generally, the larger the CAG repeat, the earlier the age of onset and the severity of the symptoms. The classical clinical features of HD are abnormal movements including both involuntary movements (chorea) and difficulty with motor coordination⁶¹. Pathologically, HD motor symptoms appear to be due to progressive neuronal cell loss in basal ganglia and cortex^{62,63}. HD patients also exhibit early-onset non-motor symptoms such as sleep disturbances, depressed mood, metabolic disorder, and cognitive dysfunction⁶⁴⁻⁷². In humans, many of these non-motor symptoms begin *before* the onset of motor symptoms, and are likely due to alterations in hypothalamic and endocrine system function^{73,74}, resulting in a cluster of neuropsychiatric symptoms. Common neuropsychiatric aspects of HD include cognitive impairment that progresses to dementia, anxiety, apathy, personality changes, and sleep disorders^{73,75,76}. Sleep disorders are extremely common in HD and have major detrimental effects on daily functioning and the quality of life of patients and their caregivers⁷⁷⁻⁸⁰. Since disruptions in sleep are common and often become apparent years before the onset of motor symptoms, an improved understanding of the mechanism underlying these disruptions has important implications for early diagnosis and treatment of HD.

Temporal components of several prominent non-motor symptoms of HD raise the possibility that SCN coordination of physiological and behavioral rhythms is dysfunctional. Most strikingly, sleep disruptions reported by HD patients include increased sleep latency, decreased sleep maintenance, fragmented sleep, and excessive daytime sleepiness. These

symptoms may reflect alterations in the temporal patterning of sleep which can be the result of circadian dysfunction. Similarly, the autonomic dysfunction related to cardiovascular function reported in HD is also consistent with possible circadian dysregulation. In order to explore the possible contribution of circadian dysfunction to HD disease progression, we examined mouse models of HD.

BACHD mouse model of HD

Previous work has shown that the R6/2 CAG150+ mouse model of HD exhibits a progressive and rapid breakdown of the circadian rest/activity cycle that mimics the condition observed in human patients typified by loss of consolidated sleep, increased wakeful activity during the sleep phase, and more sleep during the active/waking phase^{10,81}. We sought to extend this work by examination of bacterial artificial chromosome (BAC) HD transgenic mice that express the entire human *HTT* gene with stable expression of 97 mixed CAA-CAG repeats in somatic and germline tissues under the control of human HD promoter⁸². No single mouse model can be expected to recapitulate all aspects of the human disease, and we hence felt that it was important to explore possible circadian dysfunction in a sophisticated transgenic HD mouse model with stable CAA-CAG repeat expansion and the full-length human *HTT*.

Deficits in BACHD mouse circadian behavior and temporal distribution of sleep

The BACHD line was screened by monitoring daily rhythms of wheel-running activity, the method of choice for screening mutations that influence the circadian system of mammals⁸³. BACHD mice exhibit low amplitude, fragmented rhythms in wheel running behavior under both a light/dark photic environment and constant darkness (Fig. 2). Amplitude and coherence of behavioral rhythms progressively decline over the life of WT and BACHD mice; however, this decline occurs earlier in BACHD mice with young BACHD mice essentially exhibiting the circadian phenotype of an older WT mouse. By young adulthood (3-6 mo), BACHD mice exhibit deficits in circadian rhythm fragmentation, rhythm power, and activity amount as measured by wheel-running activity. With increasing age they show further deterioration in activity amount. Additionally, video recordings were used to measure sleep distribution in BACHD mice as measured by video recording. The effects of the mutation on sleep were subtle, with BACHD mice exhibiting significantly reduced sleep during the beginning of their rest phase. In other words, BACHD mice show deficits in the onset of sleep, a similar sleep phenotype to human HD patients.

Disrupted circadian regulation of the cardiovascular system

In addition to sleep related non-motor symptom in HD patients, poor cardiovascular health is also observed. Patient cardiac dysfunction is best evidenced by alterations in autonomic tone⁸⁴⁻⁸⁶. Heart rate variability (HRV) is a measure of variation in the beat-to-beat (R-R) interval and reflects the dynamic balance of sympathetic and parasympathetic control of heart function and displays a robust diurnal and circadian rhythm. BACHD mice fail to show day/night differences in HRV suggesting a loss of circadian control, as well as an overall decrease in HRV over a 24hr period when compared to WT controls⁸³. The decrease in HRV and autonomic dysfunction may be responsible for the elevated HR and body temperature measured during the rest phase (daytime) in BACHD mice. Notably, a similar decrease in HRV has also been reported in HD patients beginning during the presymptomatic and early stages of HD progression^{84,87}. Reduced HRV is generally considered an indication of poor cardiovascular health and a predictor for cardiovascular disease and mortality⁸⁸⁻⁹⁰. In this regard, it is worth considering that loss of temporal control

and autonomic imbalance may be promoting cardiac failure -- a leading cause of death among HD patients⁹¹⁻⁹². Electrocardiograph (ECG) parameters were also examined in WT and BACHD mice (Fig. 3). While most parameters were not different between the two genotypes, we detected a loss of day/night differences in the PR interval of BACHD mice, with a significant elongation during the active period when compared to WT mice. The PR interval reflects the time it takes for the cardiac electrical impulse to travel from the sinus node of the atria to the atrioventricular node, which is regulated by a number of factors, one being input from the autonomic system^{93,94}. Duration of the PR interval is also sensitive to K⁺ handling in cardiomyocytes, which could present as a potential mechanism for the loss of circadian regulation of heart function⁹⁵. Finally, we measured the baroreceptor reflex, a process dependent on proper autonomic function, in the BACHD mice⁹⁶. BACHD mouse showed a blunted response of the baroreceptor reflex that suggested dysfunction of both branches of the autonomic nervous system, as well as significantly higher daytime blood pressure in BACHD mice compared to WT controls, consistent with the observed increase in HR during the rest phase. Overall, BACHD mice showed a dramatic decrease in HRV, alterations in the PR interval, and an inability to appropriately decrease heart rate and blood pressure in BACHD mice during sleep, all of which are indications of compromised autonomic function.

The molecular clockwork is not obviously altered in the BACHD line

As a first screen for possible deficits in the molecular clockwork responsible for generating circadian oscillation (see above), we examined *Per2* expression in the SCN at peak and trough time-points (Fig. 4), but found no differences in BACHD mice⁸³. In contrast, prior work with the R6/2 line suggests that behavioral impairment *is* accompanied by disordered *in vivo* expression of circadian clock genes in the SCN and striatum^{81,97}. Additionally, livers from the R6/2 line lost rhythms in the core clock gene *Cry1* and the output gene *Dbp*, but not of the core clock genes *Bmal1* and *Per2*⁹⁷. Therefore, further work is required to definitively determine whether rhythms in clock gene expression are altered in the BACHD mice.

Reduced daytime firing rate of SCN neurons in BACHD mice during the early stages of HD progression

SCN neurons are spontaneously active and generate action potentials with peak firing rates during the day⁹⁸. Neuronal output from the SCN regulates physiological rhythms via the regulation of the autonomic nervous system⁵⁵, as well as other neural and hormonal pathways¹⁴. In the daytime (Fig. 5), BACHD mouse SCN neurons showed significantly reduced spontaneous firing rates⁸³. Decreased daytime electrical activity in the SCN would therefore weaken both neural and hormonal outputs. This observation is consistent with the hypothesis that the weakening of electrical output from the SCN is part of the pathology responsible for the circadian behavioral phenotypes observed in the BACHD mice.

Reduced daytime firing rates in the SCN of the BACHD line were measured from neurons embedded within a circuit. One mechanism by which HD may alter the function of the circadian system is by reducing the strength of inter-cellular coupling within the SCN circuit. Recent work in a variety of mouse models of neurodevelopmental and psychiatric disorders suggests that alterations in the balance between synaptic excitation and inhibition are at the heart of the pathophysiology⁹⁹⁻¹⁰³. Synaptic alteration in R6/2, and YAC mouse models of HD have been observed in cortex and striatum. During early stages of HD progression increased spontaneous inhibitory post-synaptic currents (IPSC) frequency are followed by late-stage decreases in spontaneous IPSC frequency in cortical pyramidal neurons¹⁰⁴. In striatal medium spiny neurons the amplitude of spontaneous excitatory post-

synaptic current (EPSC) increases in early stages, then in late stages there are decreased spontaneous EPSC frequencies¹⁰⁵. These changes may underlie observed increases in firing rates in both brain regions and decreased synchrony/coupling or correlated firing¹⁰⁶⁻¹⁰⁸. While we have no specific evidence that HD alters synaptic transmission or coupling within the SCN circuit, alterations in synaptic transmission remains a very plausible mechanism to explain the disruption in circadian function.

SCN spontaneous electrical activity is controlled by a set of currents that drives daily rhythms in action potentials. During the day, SCN neurons are relatively depolarized with a resting membrane potential (-50 to -55 mV) close to the threshold for generating an action potential (-45 mV). This relatively depolarized resting potential is the result of excitatory drive provided by multiple cation currents¹⁰⁹⁻¹¹¹. In response, SCN neurons exhibit sustained discharge for 4-6 hours in the subjective day without spike adaptation. Prior work suggests that 3 potassium (K^+) currents including fast delayed rectifier (FDR), A-type- K^+ current (I_A), and large-conductance Ca^{2+} activated K^+ (BK) currents are critical in the regulation of spontaneous action potential firing in SCN neurons during the day⁹⁸. Reduction in magnitude of the FDR and perhaps the BK currents would consequentially decrease SCN neuronal firing rates. Changes in these currents may therefore underlie the decreased daytime firing we observed in the BACHD mouse SCN.

The molecular basis for decreased firing rate of SCN neurons in HD is unclear

It is unclear if decreased SCN electrical activity is due to changes in synaptic signaling and/or alterations of intrinsic membrane currents; however, there is a third very appealing hypothesis – disrupted mitochondrial function may also reduce neuronal electrical activity^{112,113}. Membrane repolarization following action potential generation is extremely energetically demanding. The ATP-dependent sodium-potassium pump (Na^+/K^+ -ATPase) is critical for maintaining neuronal resting membrane potential. The pump is more active in the day than in the night¹¹⁴, and therefore its activity may be critical to the daily rhythm in membrane potential of SCN neurons. The use of this pump is very energy-expensive and insufficient ATP availability would depolarize membrane potential leading to an inability of neurons to generate action potentials.

Another possible mechanistic candidate causing decreased electrical activity is mutant huntingtin-driven increases in oxidative damage in SCN neurons. Mutant huntingtin aggregation has been found to inhibit mitochondrial trafficking¹¹⁵, and increase reactive oxygen species (ROS) production by decreasing complex I-dependent mitochondrial respiration^{116, 117}, both of which would decrease mitochondrial efficiency and thereby increase ROS byproducts. Notably, circadian transcriptional machinery coordinates anti-oxidant stress by controlling the transcription of anti-oxidant enzymes in many cells¹¹⁸. This suggests that disruption of the intracellular circadian clock may increase susceptibility to oxidative stress and subsequently compromise cellular function and survival¹¹⁹. This is supported by observations of disrupted ROS homeostasis in *Clock* mutant mice¹²⁰. Based on observations of disrupted clock gene expression in the R6/2 mouse model, a similar mechanism may cause neuronal dysfunction via reduced ROS homeostasis¹⁰. We did not observe deficits in circadian gene expression in BACHD mice, but we still expect to see an increase in ROS levels due to mitochondrial inefficiency. While oxidative stress damages a range of cellular processes, it is particularly relevant to neuronal currents because of K^+ channel sensitivity to oxidative damage^{121,122}. Increased daytime firing rates are dependent on K^+ channel currents, and therefore oxidative damage to the channels mediating these currents in the SCN may underlie the reduced daytime firing rates observed in the BACHD model.

Based on the literature, the most promising explanation for decreased SCN firing frequency in the BACHD model is decreased mitochondrial function and increased oxidative stress. Future examination of these targets provides new hypotheses to explore the mechanism underlying reduced SCN firing frequency and in turn may provide new insights into disease progression and disease prevention.

Future directions: does decreased SCN output contribute to the symptoms associated with HD?

Altered coupling within the SCN circuit would likely have profound consequences on patient health¹²³⁻¹²⁶. Many rhythms researchers believe that robust circadian rhythms depending on a coupled SCN circuit are essential to good health. In recent years, a wide range of studies have demonstrated that disruption of the circadian system leads to a cluster of symptoms including metabolic and cardiovascular disease, as well as cognitive deficits (Table 1). Many of these same symptoms are seen in HD patients. We therefore should consider circadian dysfunction is not just a symptom of HD, but also as a key part of the disease mechanism. We have good reason to think so, because sleep/circadian disruptions occur early in the HD patients and HD mouse models. If this hypothesis is correct, circadian disruption may make the symptoms of HD worse, while stabilizing the rhythm could delay the symptoms (Table 2). Recent work suggests that interventions that stabilize deteriorating daily rhythms can delay cognitive and motor symptom progression in the R6/2 line⁸¹. Whether this intervention improves rhythms in SCN output or is effective in other mouse models has yet to be determined.

Based on present understanding of the pathophysiology of the master oscillator in the BACHD mouse (Fig. 6), future work needs to focus on understanding how mutant huntingtin alters the electrical activity within the SCN and development of interventions that can treat these disruptions. Identifying new therapeutic targets to treat sleep and circadian deficits in HD patients may improve quality of life and potentially slow disease progression for this currently incurable disease.

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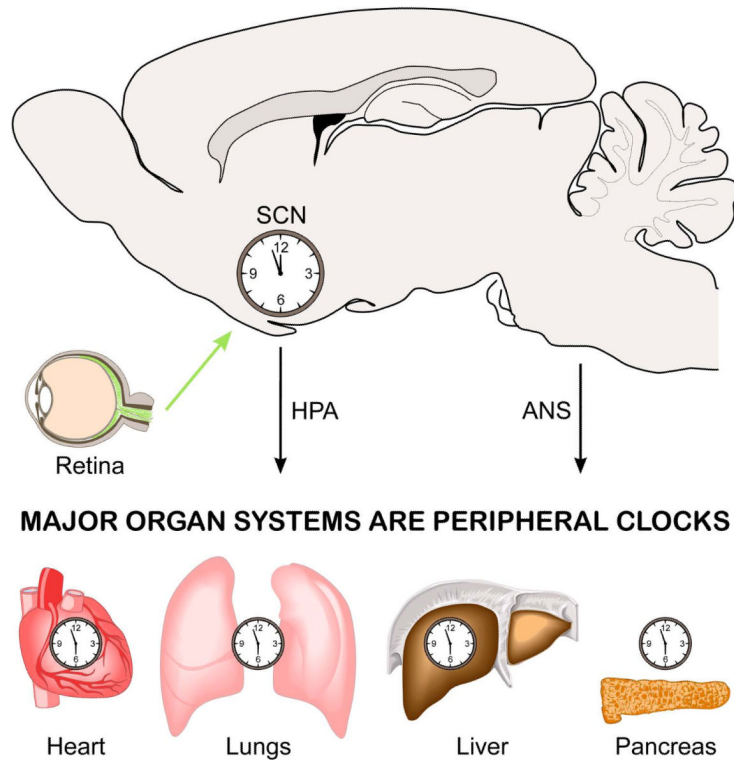


Fig. 1. Schematic illustrating key components of the circadian system. The circadian system consists of a network of circadian oscillators. The central clock is located in the suprachiasmatic nucleus (SCN). Neurons in this cell population receive light information from melanopsin-expressing retinal ganglion cells found in the retina. The axons of these ganglion cells make a direct synaptic connection onto cells in the SCN. These SCN neurons integrate this photic information with other timing cues to generate robust circadian oscillations that are synchronized to the environment. Signals from the SCN travel out via the hypothalamic-pituitary-adrenal (HPA) axis, as well as through the autonomic nervous system (ANS), to coordinate and regulate the independent circadian oscillations found throughout the body.

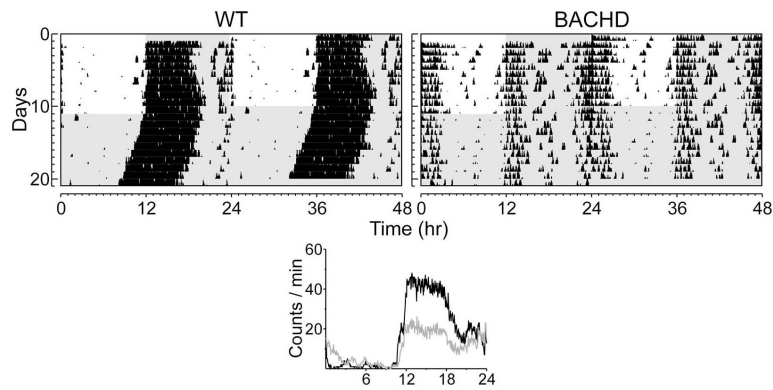


Fig. 2.

Circadian dysfunction is a common feature of mouse models of HD. Mice were placed individually in cages with running wheels, and locomotor activity was recorded under different lighting conditions. Each horizontal row represents an activity record for a 24-hr day. Successive days are plotted from top to bottom. The grey shading represents darkness. Mice were initially held in LD (12:12) and then released into DD. Panels show examples of the wheel-running activity recorded from WT (left), BACHD (middle). The average waveform of activity for each genotype (black line =WT; grey line = BACHD) as measured over 10-days in LD is also shown (right panel). The mice were 2-3 mo of age. Data from Kudo and colleagues⁸³.

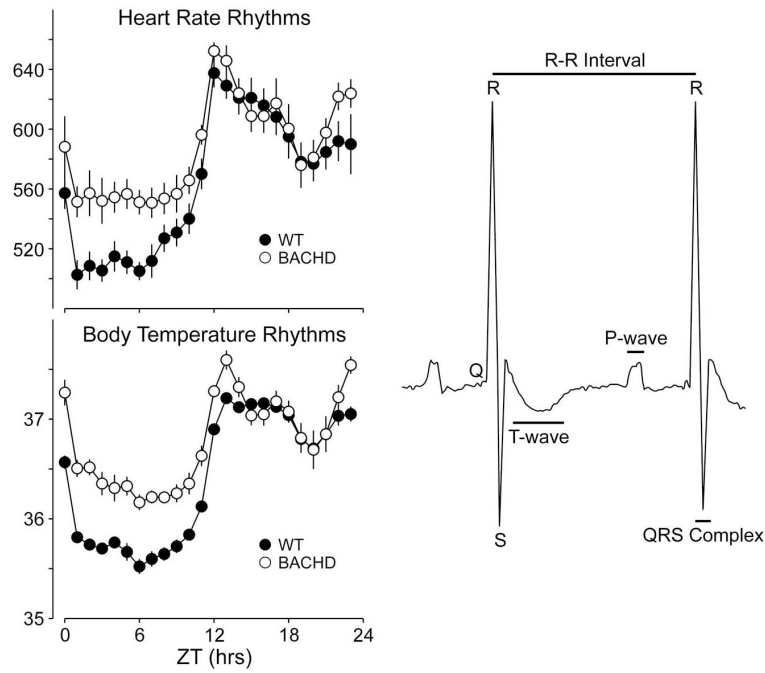


Fig. 3. BACHD mice exhibit a decrease in the amplitude in circadian rhythms as measured by telemetry. Examples of heart rate and body temperature measured from WT (left panels) and littermate BACHD (right panels) mice at ~6 mo of age are shown. Each horizontal row represents an activity record for a 24-hr day. Activity double plotted to aid detection of activity patterns. Successive days are plotted from top to bottom. The average waveform of activity for each genotype as measured over 10-days in LD is also shown (right panels). Representative example of an ECG tracing from a WT mouse labeled with features and intervals of the waveform. The PR interval was significantly increased in the BACHD mice. Data from Kudo and colleagues⁸³.

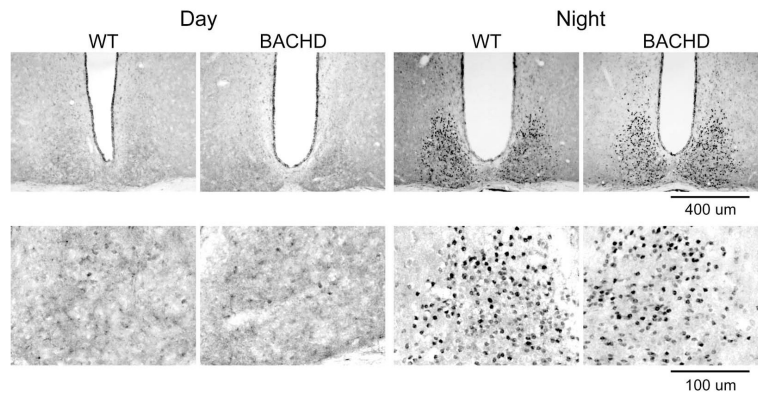


Fig. 4. PER2 rhythm within the SCN did not appear to be disrupted in BACHD mice. Mice were held in DD and wheel running activity measured to determine circadian phase. IHC was used to measure PER2 immunoreactivity in the SCN of BACHD and WT controls. Tissue was collected in subjective day (CT 2) or subjective night (CT 14). (top panels) Photomicrographs of SCN tissue of each genotype in low (10 \times) and higher (40 \times) magnification. (bottom panel). Data from Kudo and colleagues⁸³.

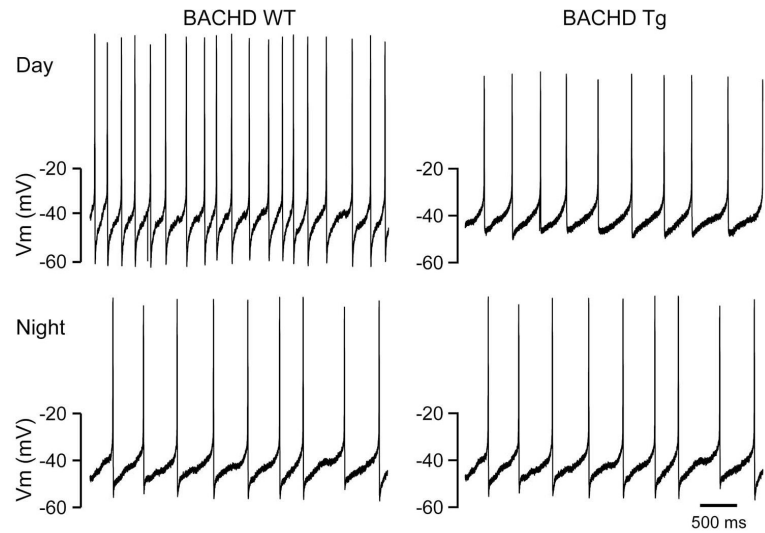


Fig. 5. Daytime spontaneous neural activity is reduced in the SCN of BACHD mice. Using the current-clamp recording technique in the cell-attached configuration, we measured the spontaneous firing rate (SFR) in dorsal SCN neurons during the day and night. The panels show representative examples of firing rate recorded from the WT and BACHD mice at each time point. Data from Kudo and colleagues⁸³.

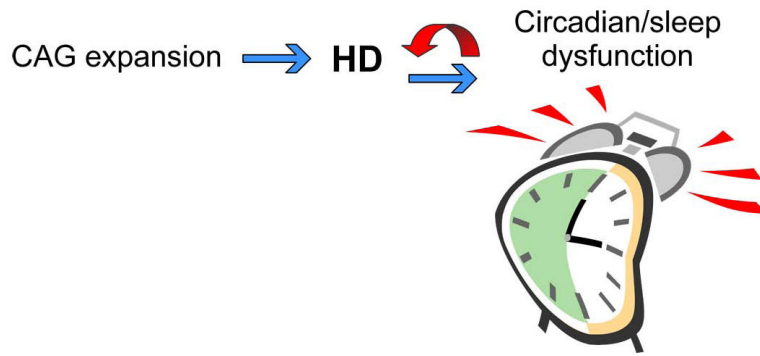


Fig. 6.

Speculation that circadian dysfunction could accelerate the pathology of HD. Work from several groups indicates that the mouse models of HD show a circadian phenotype. The circadian clockwork regulates mitochondrial function, reactive oxygen species homeostasis, DNA repair and immune response. Dysfunction of this timing system is likely to contribute to chronic inflammation, mitochondrial dysfunction, and DNA damage. These processes are all thought to contribute to the pathology of HD and contribute to age-related changes in the brain. Therefore, we raise the possibility that circadian dysfunction due to genetic or environmental perturbations can accelerate the pathology of HD.

Table I

Symptoms due to weakening of circadian output

-
- Cognitive dysfunction including memory problems.
 - Triggering affective disorders.
 - Metabolic dysfunction including increased risk of Type 2 diabetes.
 - Cardiovascular disease.
 - Gastrointestinal disturbances.
-

Table II

How to strengthen daily rhythms in HD.

-
- Maintain light/dark cycle with bright sunlight in daytime and darkness during nighttime
 - Scheduled timing of meals.
 - Scheduled timing of exercise.
 - Limit intake of psychostimulants, including caffeine.
 - Consider short-term use of sedative hypnotics.
 - Melatonin supplementation.
 - Cognitive behavioral therapy for insomnia and HD-related mood and/or anxiety disorders.
-