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Circadian biology and sleep in monogenic neurological disorders and its potential application in drug discovery

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Abstract

Sleep disturbances are common in people with monogenic neurological disorders and they dramatically affect the life of individuals with the disorders and their families. The associated sleep problems are probably caused by multiple factors that have not been elucidated. Study of the underlying molecular cause, behavioral phenotypes, and reciprocal interactions in several single-gene disorders (Angelman Syndrome, Fragile X Syndrome, Rett Syndrome, and Huntington's Disease) leads to the suggestion that sleep disruption and other symptoms may directly result from abnormal operation of circadian systems due to genetic alteration and/or conflicting environmental cues for clock entrainment. Therefore, because circadian patterns modify the symptoms of neurological disorders, treatments that modulate our daily rhythms may identify heretofore unappreciated therapies for the underlying disorders.

Introduction: single gene neurological disorders

The vast majority of neurological disorders are complex or multifactorial disorders. Those diseases include schizophrenia, depression, autism, epilepsy, Alzheimer's Disease, Parkinson's Disease, etc., all of which are influenced by multiple genetic and environmental factors. In contrast, single-gene neurological disorders are caused by variations/mutations in the DNA sequence of a specific gene [1]. For example, the core symptoms of Angelman Syndrome (AS), Fragile X Syndrome (FXS), Rett Syndrome (RTT), and Huntington's Disease (HD) are caused by single-gene variants [2,3]. Moreover, environmental factors often play important roles in the initiation and development of single gene disorders [4,5]. Although single-gene neurological disorders are not very common, they are extremely valuable to investigate the genetic and pathological causes of disorders because of the simpler genetic underpinnings as compared with complex genetic disorders [6●●]. Investigation of monogenic diseases can create a foundation for new preventive treatments and therapeutic drug discovery, as well as providing conceptual and technical bases for studying more complex disorders.

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Conflict of interest statement

Nothing declared.

Interplay of sleep and circadian rhythms

Many physiological processes display day–night rhythms, including sleep–wake behavior and metabolism. These daily oscillations are regulated and coordinated by the master circadian clock in the suprachiasmatic nucleus (SCN) of the hypothalamus and by tissue-specific clocks [7]. In mammals, the expression of approximately 50% of genes are circadianly regulated at primarily posttranscriptional levels in at least one tissue [8,9]. Those rhythmic transcripts are translated into proteins and processed by posttranslational modifications, and then act functionally and rhythmically in myriad cellular processes [10,11]. Disruption of these rhythmic gene expression patterns, as in human circadian desynchrony (e.g. from shiftwork, jet-lag, and/or sleep disruption) can have profound effects on mental health [12●,13]. Improper circadian entrainment is associated with the onset of neurological disorders, and circadian disruption may interact with other susceptibility factors to precipitate disease states [14].

Circadian rhythms also help determine our sleep patterns. The body's master SCN clock controls the production of melatonin and corticosterone, two hormones that are involved in sleep regulation [15,16]. The SCN receives environmental light/dark information via retinal-hypothalamic tracts from specialized ganglion cells in the eyes to the brain. The circadian clock is thereby enabled to anticipate, sense, and respond to light-dark changes so as to create physiological plasticity to predictable alterations in the external environment [4]. For decades, circadian rhythms have been thought to dictate sleep timing. In addition to affecting the timing of sleep, emerging evidence shows that circadian rhythms in the brain and even in peripheral tissues such as muscle [14,17●] are also able to regulate and coordinate the sleep quality and sleep duration by affecting 'sleep homeostasis.' Circadian rhythms and sleep therefore interact, balancing each other to fine-tune the daily cycles of behavior, metabolism and physiology in the body [18].

Ube3a imprinting and AS

AS is a neurodevelopmental disorder of imprinting characterized by mental disability, developmental delays, sleep disorders, epileptic seizures, motor difficulties, and speech impairment [19●●,20,21]. There is no specific therapy for AS and treatment for seizures usually becomes necessary. About 70% of AS patients have deletions of the maternal copy of chromosome 15 in the region of 15q11-q13 (Figure 1). The *Ube3a* gene within this region was identified as the genetic locus for AS [21]. *Ube3a* encodes a HECT-domain E3 ubiquitin ligase that adds ubiquitin to substrates, thereby targeting them for destruction in the proteasome. AS is an example of genomic imprinting that is caused by the deletion or inactivation of the maternal copy of *Ube3a*, while the paternal copy is imprinted and therefore silenced. It has been thought that the paternal imprinting involved in AS occurs only in the brain and is not imprinted in non-neural peripheral tissues or in glia [22,23]. However, detailed analyses in a variety of cell types using the *Ube3a::YFP* mouse as a tool demonstrated spatiotemporal confirmation of allele-specific *Ube3a* expression in neurons, astrocytes and oligodendrocytes [24–26]. Besides the allele-specific expression of *Ube3a* in different cell types, the three known isoforms of its transcript may play different and critical roles in the pathology of AS [27,28●●]. Therefore, improving our understanding of the

developmental parameters of paternal *Ube3a* imprinting, including its isoform-specific silencing and cellular basis could facilitate the therapeutic treatment of AS.

Sleep/circadian disruption in AS

Sleep syndrome in AS individuals

Sleep problems are very common in AS patients. Up to 75% of subjects with AS suffer from sleep disturbances [29,30], and these sleep disruptions are one of the syndrome's most stressful manifestations to families with an AS member [31]. Disrupted sleep phenotypes such as short sleep duration, frequent arousal during sleep, and increased sleep onset latency are observed very often in AS patients. In addition, snoring and parasomnias are frequent. These sleep problems in AS are most likely multifactorial, and include epilepsy, medication, anxiety, GI symptoms, etc. as contributing factors [32,33]. The severity of sleep problems varies with the extent of genetic disruption; for example, patients with a deletion of the entire 15q11-q13 region often have more severe sleep traits than patients with point mutations in *Ube3a* [30]. This observation suggests that other (adjacent) genes contribute to the severity. For instance, abnormal GABA transmission may be a direct effect of AS in the majority of cases in which a large portion of chromosome 15 is deleted so that maternal deletion of GABA receptors (e.g. *Gabrb3* in the 15q11-q13 region) could contribute to sleep anomalies in AS [34]. Interestingly, sleep problems are more severe and prevalent during childhood but improve in adolescence and adulthood, indicating developmental modulation [35]. However, AS children might naturally need less sleep than their typically developing counterparts [36,37].

In terms of sleep structure, polysomnography studies showed distinct intermittent rhythmic delta and theta waves, and interictal epileptiform discharges in AS individuals [38,39]. Recently, increased delta rhythmicity is observed as the most common EEG phenotype in AS (~84% of patients) [40]. Furthermore, children with AS exhibit increased long-range EEG coherence both during wakefulness and in the gamma band during sleep. In addition, sleep spindles (a thalamocortical oscillation in the sigma band that occurs during NREM sleep) are less frequent and briefer in children with AS indicating an impaired function of AS in memory consolidation [41].

Animal models and AS

The human sleep studies of AS subjects are confounded by the variety of methods for sleep assessment, medications used by the subjects, and the large age range of the subject population. In order to gain insight into the mechanisms underlying the AS disorder and to obtain preclinical data to evaluate drug/therapeutic treatment to AS, animal models have been developed [23,42,43]. Because the main cause of single-gene neurological disorders is due to the alteration of one gene, animal models are suitable and relevant tools to study the behavior and physiology of the disorder, as well as paving the way towards therapeutic and/or pharmacological treatments. Mouse, zebrafish, and fruit flies are commonly used animal models by virtue of their genetic malleability, although rats are increasingly the model of choice for disorders that involve cognitive dysfunction and metabolism [44].

Traditional gene targeting and transgene technologies have provided many useful animal models for human diseases. However, some diseases with genetic bases cannot be easily mimicked with those techniques [45]. Thus, new genetic engineering tools like CRISPR (Clustered Regular Interspaced Short Palindromic Repeats), TALEN (Transcription Activator-like Effector Nucleases) and ZFN (Zinc-finger nucleases) to create small *in situ* lesions, and the analytic capability of sequencing and precision medicine's 'big data' provide unprecedented opportunities to create animal models including nonhuman primate models that better resemble the genetic alteration of these disorders. These tools will enable basic research to be more relevant to the clinic.

Different mouse models have been able to recapitulate some but not all of the human symptoms of AS [23,42,43]. The phenotypic effects of AS models are influenced by multiple factors including knockout strategy, age, gender, diet, laboratory conditions, etc. In particular, there are pronounced differences in the AS phenotypes that depend upon mouse strain (e.g. C57BL/6 {B6}, 129, and mixed C57BL/6 and 129). For example, AS 129 mice performed poorly on contextual fear conditioning and exhibited a lower seizure threshold than do AS C57 mice [46[●]]. Noteworthy is the observation that gene expression and behavior in genotypically identical AS mice are influenced by whether their mothers are affected (m-/p+) or not (m+/p-) by the gene loss [47]. What's more, phenotypic analysis of C57BL/6J versus C57BL/6N substrains showed that even these subtle changes at the genomic level could lead to changes of circadian behavior (e.g. for the effects of cocaine on circadian behavior [48]).

Sleep phenotypes in AS animal models

Ube3a(m-/p+) mice have a markedly reduced capacity to accumulate sleep pressure both during their active period and in response to forced sleep deprivation [49]. The majority of AS human subjects have a large chromosomal deletion that removes multiple genes, including *Atp10a* and *Gabrb3*. *Atp10a* is not imprinted in mouse, and therefore it is insensitive to the AS imprinting center [50]. However, loss of *Gabrb3* in the AS mouse model is sufficient to cause EEG abnormalities and disturbed rest-activity cycles that are similar to the clinical features of AS, indicating that impaired expression of the *Gabrb3* gene in humans probably contributes to the sleep phenotypes of AS [51]. In agreement with this idea, an animal model with specifically GABAergic *Ube3a* deficiency showed an increase in cortical EEG total and delta power [52[●]].

Circadian disruption in AS animal models

Although it has been known for decades that sleep is disrupted in AS human subjects, only in the last few years have researchers started to investigate whether circadian rhythmicity is affected by *Ube3a* in AS. In a *Drosophila* model for AS based on a null mutation of the fly homolog of *Ube3a* (*dube3a*), circadian rhythmicity and activity/rest cycles were abnormal [53]. Consistent with that observation, knockdown of *Ube3a* in cultured mammalian cells lengthens the circadian period [54]. Further studies using two widely used AS mouse models (*Ube3a* m-/p+ and *Ube3a-Gabrb3* m-/p+ [19^{●●}]) reported lengthened behavioral period. In congruence with the previous observations of GABRB3 deficiency influencing circadian/sleep phenotypes, we found that 'big deletion' mice (i.e. *Ube3a-Gabrb3* m-/p+ mice)

appeared to have very significant circadian phenotypes [19^{●●}]. While we also found a significant lengthening of circadian period in the ‘small deletion’ (i.e. *Ube3a* m-/p+ mice) AS model [19^{●●}], a different research group using the same small deletion AS mouse reported a similar trend of lengthened circadian period, but their results did not achieve statistical significance [49] (they tested different ages and used a slightly different breeding protocol, and these differences might account for the discrepancies between their results and ours with the small deletion AS model).

Paternal imprinting involved in AS occurs mainly in neurons but is either not imprinted in non-neural peripheral tissues or is bi-allelic in non-neural brain cells such as glia [24,26]. A recent publication using small deletion *Ube3a* m-/p+ mice reported that SCN neurons maintain persistent expression of paternal UBE3A protein, which the authors interpreted to mean there is a relaxation of *Ube3a* imprinting in the SCN that is not typical of most neurons [55]. However, UBE3A still appeared to express in the SCN of *Ube3a*-null mice (~20%), suggesting non-specific binding of their UBE3A-antibody or leaky expression of *Ube3a* in the knockout animal. Both observations are common limitations of immunohistological cytochemistry and conventional knockout strategies. In contrast, we found that *Ube3a* is indeed imprinted in the SCN of both mice and rats (unpublished data). We concluded that *Ube3a* expression constitutes a direct mechanistic connection between symptoms of AS and the circadian mechanism [19^{●●}], suggesting that chronotherapeutics may be effective for AS sleep disorders [56].

In order to further explore the crosstalk between UBE3A and the core clockwork, we and others pinpointed a central component of the mammalian circadian clock, BMAL1 (ARNTL in humans), as a potential ubiquitinylation target of UBE3A [19^{●●},54]. These results imply that the BMAL1 protein in AS-model rodents may be under-ubiquitinylated (due to the deficiency in UBE3A levels) and therefore not degraded efficiently. The prediction, therefore is that BMAL1 abundance is increased in AS mouse neurons. If so, reduction of BMAL1 levels by experimental reduction of *Bmal1* gene dosage could rescue AS phenotypes in *Ube3a* m-/p+ and *Ube3a-Gabrb3* m-/p+ mouse models. Indeed, we find that the suppression of wheel-running activity by constant illumination in AS mice [19^{●●}] is rescued when maternal deletion of *Ube3a* (*Ube3a* m-/p+ AS model) is combined with lower gene dosage of *Bmal1* (accomplished by heterozygosity for *Bmal1*) (Figure 2). While we presume that this ‘rescue by reduction of *Bmal1* gene dosage’ is mediated in the SCN region (since it is the master coordinator of circadian behavior), we cannot exclude by this level of analysis the possibility that other brain regions may contribute to the behavioral rescue by *Bmal1* reduction depicted in Figure 2.

Sleep/circadian phenotypes in other single-gene neurological disorders

Like AS, most single-gene neurological disorders have significant sleep and circadian phenotypes. FXS is an X-linked disorder caused by a CGG repeat expansion in the 5'UTR of the *Fmr1* gene, resulting in gene silencing. Sleep problems are commonly observed, and the abnormalities appeared to be regulated by circuits involved in the dysregulation of melatonin and the circadian system. In animal studies, *Fmr1/Fxr2* double knockout (dKO) and *Fmr1*-KO/*Fxr2* heterozygous animals exhibit a loss of rhythmic activity in a light:dark

(LD) cycle, whereas *Fmr1*-KO or *Fxr2*-KO single knockout mice display a shorter free-running period of locomotor activity in constant darkness (DD) [57]. In addition, total sleep time in adult *Fmr1* KO mice are significantly different from wild-type mice and depend on age [58]. Remarkably, TALEN-edited *Mecp2* mutant monkeys (diurnal cynomolgus monkey) have more fragmented sleep, which is similar to the most prevalent sleep problem reported as night waking in RTT individuals [59,60●]. In line with those observations in primates, abnormal circadian rhythms were also reported in *Mecp2* mutant mice.

The most extensively studied example of a monogenic disorder that causes perturbed sleep and circadian rhythms is Huntington's disease (HD). HD is a neuro-degenerative disorder caused by a CAG repeat expansion in the HTT gene. Animal model studies demonstrate that changes in the molecular clock contribute greatly to the observed sleep/circadian phenotypes in a sex-dependent manner [61,62], and that when circadian or sleep function is restored pharmacologically, the rate of cognitive decline is reduced [63,64●,65].

Conclusions: application of sleep/circadian phenotypes to drug discovery and biomarker identification

Regarding neurological disorders, circadian and sleep abnormalities have generally been considered to be consequences of the associated pathological changes in the brain [66]. We suggest, however, that the circadian/sleep disruption is the *cause* of some of the pathologies, not just a consequence (Figure 3). With the development of new technologies to monitor circadian behaviors and sleep noninvasively (even at home in a subject's everyday environment [67●,68]), the patterns of daily rhythmicity and sleep may provide a more robust biological marker for determining the effects of novel therapeutic strategies relevant to neurological disorders and suggest new diagnostic approaches for these diseases. Emerging data show that sleep disruption may be a direct result of circadian disruption [19●●,57,61,69], and we contend that a disrupted clock network contributes directly to the pathology of many diseases. Consequently, our sleeping and circadian patterns might be a modifiable cause of neurological disorders, and therapies that manipulate our daily rhythms may tap into heretofore unappreciated therapies. Therefore, identification of disrupted circadian networks as novel targets (as in the case of AS [19●●]) may provide mechanistic and clinical insights into how the circadian clock and sleep interacts with pathological pathways that are mediated by genetic disorders.

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Figure 1.

Angelman Syndrome (AS) results from deletion (open box on chromosome 15 in lower right corner of the figure) of the *Ube3a* gene on maternal chromosome 15 and concomitant imprinting (X) of the *Ube3a* gene on paternal chromosome 15. In addition to motor and cognition deficits (middle panels), AS has significant effects on sleep and the circadian clock (note desynchrony of brain vs. peripheral clocks in left panels) [19^{●●}].

Figure 2.

Rescue of light-suppression of wheel-running activity by reducing *Bmal1* gene dosage. Constant light suppresses the wheel-running activity of AS mice [19^{●●}], as shown here in the comparison between panel A and panels B and E. Heterozygosity for the *Ube3a*-target clock gene *Bmal1* reduces the gene dosage of *Bmal1* and rescues the level of wheel-running activity in constant illumination (blue background) as shown by comparing panel D with panel B. Upper panels are actographs of circadian locomotor rhythms, and lower panels are quantifications of the activity on running wheels. (a) WT-m +/p+, *Bmal1*+/+; (b) ‘small deletion’ *Ube3a*-m-/p+, *Bmal1*+/+; (c) WT-m+/p+, *Bmal1*+/-; (d) ‘small deletion’ *Ube3a*-m-/p+, *Bmal1*+/-; (e) ‘big deletion’ *Ube3a*-Gabbrb3 m-/p+, *Bmal1*+/+ (unpublished data). WT = wild-type mice.

Figure 3.

Two views of the contribution of sleep/circadian disruption in genetics-based disorders. The traditional view is that sleep/circadian disruption is an endpoint symptom of the pathological consequences of a genetic disorder. Recent studies support the new view that the sleep/circadian disruption is a direct contributor to the severity of endpoint symptoms.