Mendoza-Viveros L, Obrietan K, Cheng HM. J Neurol Neuromed (2018) 3(1): 21-25
www.jneurology.com

Journal of Neurology & Neuromedicine

Commentary Open Access

Commentary: miR-132/212 Modulates Seasonal Adaptation and Dendritic Morphology of the Central Circadian Clock

Lucia Mendoza-Viveros[1,2], Karl Obrietan[3], Hai-Ying M. Cheng[1,2*]

1Department of Biology, University of Toronto Mississauga, Mississauga, ON, L5L 1C6, Canada
2Department of Cell and Systems Biology, University of Toronto, Toronto, ON, M5S 3G3, Canada
3Department of Neuroscience, Ohio State University, Columbus, OH, 43210, USA

Article Info

Article Notes
Received: February 05, 2018
Accepted: February 27, 2018

***Correspondence:**
Dr. Hai-Ying Mary Cheng
Associate Professor
Department of Biology, University of Toronto Mississauga,
Email: haiying.cheng@utoronto.ca

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Keywords:
Circadian rhythms
Dendritic morphology
microRNA
miR-132/212
Seasonal timekeeping
Suprachiasmatic nucleus

ABSTRACT

Daily rhythms in behavior and physiology are coordinated by an endogenous clock located in the suprachiasmatic nucleus (SCN) of the hypothalamus. This central pacemaker also relays day length information to allow for seasonal adaptation, a process for which melatonin signaling is essential. How the SCN encodes day length is not fully understood. MicroRNAs (miRNAs) are small, non-coding RNAs that regulate gene expression by directing target mRNAs for degradation or translational repression. The miR-132/212 cluster plays a key role in facilitating neuronal plasticity, and miR-132 has been shown previously to modulate resetting of the central clock. A recent study from our group showed that miR-132/212 in mice is required for optimal adaptation to seasons and non-24-hour light/dark cycles through regulation of its target gene, methyl CpG-binding protein (MeCP2), in the SCN and dendritic spine density of SCN neurons. Furthermore, in the seasonal rodent *Mesocricetus auratus* (Syrian hamster), adaptation to short photoperiods is accompanied by structural plasticity in the SCN independently of melatonin signaling, thus further supporting a key role for SCN structural and, in turn, functional plasticity in the coding of day length. In this commentary, we discuss our recent findings in context of what is known about day length encoding by the SCN, and propose future directions.

Main Text

The suprachiasmatic nucleus (SCN) of the hypothalamus houses a central circadian pacemaker in mammals. The ~20,000 neurons in this bilateral structure coordinate internal daily rhythms in behavior and physiology with external cycles, the most predominant one being light availability due to the Earth's rotational movement[1]. The so-called "molecular clock" is a ubiquitous machinery that sustains near 24-hour (circadian) rhythms in expression of "clock" genes *via* interlocking transcription and translation feedback loops (TTFLs). In the primary feedback loop, the positive limb, comprised of the transcription factors CLOCK and BMAL1, promotes the transcription of elements in the negative limb, the *period* and *cryptochrome* genes[2,3].

Although cells in the SCN can autonomously sustain molecular oscillations, to produce a robust, coherent output to peripheral clocks, they need to maintain synchrony at the tissue level: this intra-SCN synchrony is achieved through paracrine communication[4]. The neuronal population of the suprachiasmatic nucleus is predominantly GABAergic[5] and densely interconnected. Although it is heterogeneous in terms of the neuropeptides that are synthesized, there are two main anatomical and functional clusters: the "core" (ventrolateral region) and the

"shell" (dorsomedial region)[6]. Neurons in the core express vasoactive intestinal polypeptide (VIP), and receive direct input from retinal ganglion cells[6]. Upon photic stimulation at critical time windows, core neurons quickly reset the phase of their molecular clock, which is essential for shifting behavioral cycles[7,8]. Neurons in the shell SCN secrete arginine vasopressin (AVP); unlike cells in the core, they take longer to re-adapt the phase of clock gene oscillations to changes in the external light/dark cycle[9].

In addition to maintaining 24-hour rhythms, the SCN can also encode variations in photoperiod or day length (i.e., a long day in the summer vs. a short day in the winter), allowing organisms to prepare for the environmental demands characteristic of each season throughout the year. The SCN relays photic information through a multi-synaptic pathway to the pineal gland, which produces and secretes melatonin during the nighttime. This is required for physiological seasonal adaptation[10,11]. In photoperiodic mammals, distinct patterns of melatonin signaling acting in the pituitary gland and various hypothalamic nuclei allow for season-appropriate changes in appearance, reproductive physiology and metabolism[12–14]. Whether other mechanisms independent of melatonin signaling also contribute to seasonal changes in physiology and behaviour remains unclear. Mice of the C57BL/6 background exhibit photoperiod-dependent changes in circadian activity/rest cycles and SCN physiology despite their inability to produce melatonin[15]. This suggests that there may well be other mechanisms at play besides melatonin signaling that influence seasonal adaptation.

As is the case in other species, structural plasticity could also play a role in how the murine SCN network alters its properties to encode photoperiodic information. In *Drosophila*, seasonal adaptation requires axonal plasticity in brain clock neurons[40]. In seasonal songbirds, the higher vocal center in the brain undergoes remarkable morphological changes to enable song production, which is essential for breeding during the long photoperiod[41].

Seasonal time has been proposed to be a meta-property encoded within the network of circadian oscillators that comprise the SCN[16]. Overall, under short days there is a higher degree of synchrony among SCN neurons, and under long days cell clusters are out-of-phase with each other[16]. This has been reported between the rostral and caudal SCN[17–20], and between the core and shell sub-compartments[18,21,22]. VIP signaling appears to have a role in seasonal adaptation, as *Vip*$^{-/-}$ mice do not show photoperiod-dependent changes in SCN electrical activity[23]. Some electrophysiological mechanisms have been investigated in the context of seasonal adaptation. A switch in GABAergic transmission from inhibitory to excitatory, due to changes in the equilibrium potential of GABAergic currents, has been suggested to mediate adaptation to long photoperiods[24]. Moreover, Cl^- transporter abundance and intracellular Cl^- concentration can regulate the polarity and strength of GABAergic transmission. These processes were implicated in maintaining the phase disparity between the core and shell regions of the SCN under long days[25]. Additionally, changes in the properties of K^+ currents have been shown in the SCN of long day-housed animals[26]. Beyond these studies, the mechanisms for photoperiodic plasticity in the SCN remain elusive.

MicroRNAs (miRNAs or miRs) are short, non-coding RNAs that recognize elements within the 3'-untranslated regions (UTRs) of target mRNAs through base complementarity with their "seed sequence", hindering translation and/or promoting transcript degradation. miRNAs have been increasingly recognized as regulators of circadian rhythms[27,28]. In regard to the mammalian central pacemaker, *miR-132* and *mir-219* have been examined before[29,30]. In our recent study[31], we investigated the role of the microRNA cluster *miR-132/212*. Although *miR-132* and *miR-212* are encoded in a single locus and their seed sequences are identical, their patterns of expression and putative target genes do not overlap entirely[32]. Previously, expression of *miR-132* was shown to be light-responsive in the SCN, and to downregulate the behavioral phase-shifting response to acute photic stimulation by modulating the expression of genes implicated in chromatin remodeling and translational control[29,30]. However, in our study, a global deletion of the *miR-132/212* cluster did not affect the behavioral response to acute photic stimulation under constant darkness, at nine different time points assessed throughout the circadian cycle[31]. The discrepancy between our previous investigations, where only levels of *miR-132* were tonically or transiently manipulated[29,30], and our recent study, where both *miR-132* and *miR-212* were genetically ablated, might indicate that *miR-132* and *miR-212* have different or opposing roles in regulating acute phase resetting of the clock. This question could be addressed by either deleting or transiently inhibiting *miR-212* alone without altering *miR-132* expression. Since our study used a germline disruption of the *miR-132/212* locus, an alternative explanation is that compensatory changes arising throughout development counteract the effects of *miR-132/212* deletion on the phase shifting response. Using an inducible *miR-132/212* knock-out model would help to clarify if this is the case.

Given that the expression of *miR-132* and *miR-212* are induced by neuronal activity[33,34], we hypothesized *miR-132/212* ablation may affect "activity"-dependent plasticity of the circadian system, in particular in the context of exposure to different environmental light cycles. To address this, we examined the locomotor behavior of *miR-132/212*-deficient (*miR-132/212*$^{-/-}$) mice under long and short photoperiods as well as under non-24-hour cycles (T-cycles). *miR-132/212*$^{-/-}$ mice entrained better and

more precisely to short days and short T-cycles than wild-type controls. Furthermore, a shortening of the behavioral period following exposure to a short T-cycle (also known as "after-effect") was more pronounced in *miR-132/212*$^{-/-}$ mice compared to wild-type controls. To date, there is not a clear explanation for the persistent effects of T-cycles or photoperiod on the circadian clock, although some molecular events have been proposed. In one study, maternal exposure to T-cycles during pregnancy had long-lasting effects in the progeny, pointing to epigenetic mechanisms imprinting the central clock[35]. In hamsters, reversible methylation of the promoter region of *Dio3*, a gene encoding for a melatonin-dependent thyroid hormone enzyme, underlies reproductive activation under long days[36]. Two other studies analyzed DNA methylation programs in the SCN of animals adapted to long or short T-cycles[37,38]. Remarkably, changes in the DNA methylome were region-specific, and communication between the core and shell SCN was required to produce those changes[37,38]. The identities of those genes whose expression in the SCN is regulated by the photoperiod or T-cycle remain elusive, but are likely to reveal important insights on the cell-autonomous mechanisms that underlie the network-level changes involved in this type of circadian plasticity. In our study, expression of the *miR-132/212* target gene, MeCP2, was dysregulated in the SCN of *miR-132/212*$^{-/-}$ mice in a circadian- and photoperiod-dependent manner. The MeCP2 protein is capable of binding to methylated DNA, and we speculate that its association with methylated gene promoters may be important for regulating the gene expression programs underlying SCN network plasticity.

In another experiment, we found that long-term exposure to constant light had a milder period-lengthening effect on *miR-132/212*$^{-/-}$ mice than it did on wild-type animals. Disruption of synchrony among SCN neurons has been suggested to underlie the effects of constant light[39], although the mechanisms for this are not clear. In this scenario, SCN lacking *miR-132/212* could be more resistant to desynchronization, leading to stronger coupling between clock neurons. This idea is supported by the higher amplitude of clock protein oscillations in *miR-132/212*$^{-/-}$ SCN under constant dark conditions compared to wild-type controls. We also examined PER2 expression throughout the rostral-caudal axis of the SCN after adapting mice to either short or long days. Circadian PER2 oscillations after adaptation to a summer-like photoperiod showed a widened peak, which was advanced in the caudal portion of the SCN in wild-type but not in *miR132/212*$^{-/-}$ mice. Under short days, PER2 rhythms had a narrow peak (compared to a 12h light:12h dark cycle) irrespective of genotype, although the amplitude was higher in *miR-132/212*$^{-/-}$ SCN relative to wild-type controls, another indication that intercellular synchrony may be greater in *miR-132/212*$^{-/-}$ animals. These results roughly correlate with the behavioral phenotypes of our knockout mice under short and long photoperiods, although a future study could address in more detail the progression of changes in PER2 rhythms during the process of photoperiodic adaptation.

An important consideration for our experiments is the difference in spatiotemporal dynamics between the rostral-caudal and the ventral-dorsal axes. In our experiments, we did not find consistent phase differences under the long photoperiod between the shell and core SCN, as has been reported by other groups[22]. The reason for this discrepancy is unclear, but it may be due to the light:dark (LD) cycle that we used in our study (16:8 LD, in hours), in contrast with the more extreme cycles under which ventral-dorsal phase differences were previously observed (i.e., 18:6, 20:4 and 22:2 LD)[22]. Although phase differences across both axes have been described in the context of photoperiodic adaptation, in recent years more emphasis has been given to the shell-core subdivision because of the functional implications of the peptidergic profiles of cells within each cluster. However, it is worth pointing out that the ventral-dorsal subdivision is most prominent in the central SCN, which contains both VIP and AVP neurons, whereas in the most rostral and caudal extremes the cells are predominantly AVPergic shell neurons. For most *ex-vivo* studies of SCN network properties, thin slices containing central SCN are generally used, unless otherwise specified. In our rhythmic profiles, we did not co-label PER2 with AVP or VIP; this may be important for further conclusions about the role of *miR-132/212* in the spatiotemporal dynamics of clock protein expression within the SCN.

The *miR-132/212* cluster has been implicated in regulation of neuronal morphology in the hippocampus and cortex[43–45]. In our study, we characterized dendritic spine density of SCN neurons from wild-type and *miR-132/212*$^{-/-}$ mice maintained under different photoperiods. Relative to wild-type controls, we found a downregulation of spine abundance in *miR-132/212*$^{-/-}$ SCN at all time points and under all photoperiods examined. These data seem counterintuitive with our previous observation of enhanced intercellular synchrony in the *miR-132/212*$^{-/-}$ SCN. However, the network dynamics that maintain the organization and phase distribution of individual oscillators are just beginning to be unveiled[46]. Hence, the degree of structural connectivity might not necessarily translate to enhanced or diminished synchrony. In the future, this question might be examined in our model by using *ex-vivo* approaches with single-cell resolution. Interestingly, regardless of genotype, daylength altered the prevalence of different protrusion types. Under long days, we noted an increase in the number of spines and a decrease in varicose protrusions. When we analyzed SCN neuronal morphology in a seasonal rodent, the Syrian hamster, we found a similar effect of photoperiod on SCN spine density, namely, a reduction under short days

when compared to long days. Importantly, this effect was independent of melatonin signaling, since it was still present in pinealectomized hamsters. We were able to correlate this morphological change with a strong suppression of *miR-132* expression in short-day adapted hamsters compared to those housed under long days. These data suggest that the SCN can undergo structural changes that make its network flexible and adaptable to different photoperiods, and that *miR-132/212* plays a role priming the SCN for seasonal changes in day length. Mice lacking *miR-132/212* adapt more readily or more efficiently to short days, have difficulty entraining to long cycles, and resist the period-lengthening effects of constant light. Altered SCN connectivity may underlie all these phenotypes. It is worth noting that in our study we focused on two time points (middle of the day and middle of the night), hence we are unable to draw conclusions about the potential rhythmic changes in spine density in the SCN. Future investigations could examine this aspect, as well as other morphological parameters such as dendritic complexity and neurite length. The physiological implications of the structural plasticity that we observed in our study are also fertile ground for future research.

In terms of the molecular players that could potentially mediate the phenotypes of *miR-132/212*$^{-/-}$ mice, we focused primarily on MeCP2, a target gene for both microRNAs[30,47–49]. In our investigation, ablating MeCP2 expression *in vivo* and *in vitro* rescued the morphological phenotype of *miR-132-212*$^{-/-}$ SCN cells. The role of MeCP2 in dendritic structure is, by all accounts, complex. Analysis of neuronal morphology of MeCP2 mutant mouse lines have yielded contradictory results[50–53]. Some studies have found increased spinogenesis in the mutant mice whereas others have found the opposite. Effects seem to depend on gene dosage, developmental stage, and even brain region. Beyond the need for the spatiotemporal expression of MeCP2 to be tightly regulated, there is much to be learned about this gene in regard to neuronal morphology. A puzzling finding that emerged from our study is the SCN neuronal phenotype of *mecp2*$^{+/-}$ female mice. We found a considerable upregulation of spine density in these animals, regardless of their *miR-132/212* status ($^{-/-}$ or $^{+/+}$). Since *Mecp2* is located on the X chromosome, *mecp2*$^{+/-}$ females exhibit a mosaic pattern of MeCP2 expression at the cellular level. Unfortunately, our technical approach to studying neuronal morphology did not allow us to distinguish MeCP2-expressing cells from those with null expression. Being able to discriminate between these two cell populations in MeCP2 heterozygous females would enable us to determine whether this dendritic phenotype was cell-autonomous or a consequence of altered SCN network connectivity in MeCP2 mutant animals.

In conclusion, our study found a novel role for the *miR-132/212* cluster in seasonality of the SCN, and a new dimension of structural plasticity in the central circadian clock allowing for adaptation to environmental challenges.

Acknowledgments

This work was supported by operating grants to H.-Y.M.C. from the Canadian Institutes of Health Research (CIHR) (MOP#126090) and the Natural Sciences and Engineering Research Council (NSERC) of Canada (RGPIN-2016-05563), and to K.O. from the National Institutes of Health (R01MH103361). H.-Y.M.C. is a Tier II Canada Research Chair (CRC) in Molecular Genetics of Biological Clocks. L. M.-V. was supported by a graduate scholarship from Consejo Nacional de Ciencia y Tecnologia (CONACyT) of Mexico. The authors declare no conflict of interest.

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