Journal of Physiology - Paris xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Journal of Physiology - Paris

journal homepage: www.elsevier.com/locate/jphysparis

Are circadian rhythms new pathways to understand Autism Spectrum Disorder?

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ARTICLE INFO

Article history:
Received 27 July 2016
Received in revised form 18 March 2017
Accepted 14 June 2017
Available online xxxx

Keywords:
Circadian rhythms
Autism Spectrum Disorder
Sleep

ABSTRACT

Autism Spectrum Disorder (ASD) is a frequent neurodevelopmental disorder. ASD is probably the result of intricate interactions between genes and environment altering progressively the development of brain structures and functions. Circadian rhythms are a complex intrinsic timing system composed of almost as many clocks as there are body cells. They regulate a variety of physiological and behavioral processes such as the sleep-wake rhythm. ASD is often associated with sleep disorders and low levels of melatonin. This first point raises the hypothesis that circadian rhythms could have an implication in ASD etiology. Moreover, circadian rhythms are generated by auto-regulatory genetic feedback loops, driven by transcription factors CLOCK and BMAL1, who drive transcription daily patterns of a wide number of clock-controlled genes (CCGs) in different cellular contexts across tissues. Among these, are some CCGs coding for synapses molecules associated to ASD susceptibility. Furthermore, evidence emerges about circadian rhythms control of time brain development processes.

1. Introduction

1.1. Autism Spectrum Disorder: a neurodevelopmental disorder

ASD is a neurodevelopmental disorder associating a deficit in social communication skills and a restricted repertoire of interests, behaviors, and atypical sensory reactivity (American Psychiatric Association, DSM-V, 2013). ASD ranges from mild personality traits to severely impaired functioning. Intellectual disability is observed in more than half of ASD cases (Charman et al., 2011), along with several others neurodevelopmental disorders (in particular Attention Deficit Hyperactivity Disorders, specific motor and language disorders), and neurological diseases. ASD is also frequently associated with sleep disorders and low levels of melatonin.

Although the exact mechanisms are still unknown, as a neurodevelopmental disorder ASD probably results from intricate interactions between genes and the environment progressively altering development of brain structures and brain functions. According to this developmental hypothesis, the first observed symptoms, such as social orientation deficits, poor eye contact, atypical object manipulation, deficit in flexibility, emerge in early infancy, involve different experiences of the environment at each time, and progressively divert the development from the usual pathway (Klin et al., 2015; Jones and Klin, 2013). ASD symptoms impact social reciprocity, a platform for social and language skills development, and thus social brain specialization (Klin et al., 2015). Similarly ASD symptoms impact very early flexibility (tested with e.g. attention disengagement task), and thus attention brain specialization (Jones and Klin, 2013; Elsabbagh et al., 2012, 2013a,b). However, the complete clinical picture, observed after 3 years, does not result only from early neurodevelopmental atypicalities, but also from adaptations and compounded effects (Gliga et al., 2014). Brain structures and brain functions development are dynamic processes, dependent on genetic and social/physical environmental cues, involving keeping homeostasis at each time, and allowing maturation of new functions in time.

1.2. Circadian rhythms: a complex biological timing system

Biological rhythms are complex timing systems. In interactions with environmental cues (e.g.: fluctuation in light intensity) they control a variety of physiological (e.g.: endocrine factor levels) and behavioral processes (e.g.: rest-activity) (Dibner et al., 2010), but also, as highlighted by recent literature, time brain development (Kobayashi et al., 2015). Circadian rhythms, probably the most important of all biological rhythms, are composed of a complex and hierarchical network of biological clocks. These rhythms

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http://dx.doi.org/10.1016/j.jphysparis.2017.06.002
0928-4257/

last approximatively 24 h but have to be periodically resynchronized with geophysical time. The brain's master clock is located in the Hypothalamic Suprachiasmatic Nucleus (SCN). There are other circadian clocks in the brain. Aside from that, circadian rhythms are functional in most body cells; in others words, each of these cells have a clock for themselves. The light-dark cycle is the most important environmental *Zeitgeber* (time giver) for the phase entrainment of all circadian oscillators. Because of its particular properties, Dibner et al. (2010) raise the hypothesis that the SCN could be best viewed as a "conductor of an orchestra of clocks" synchronizing all clocks and integrating information from periphery to generate coherent systemic rhythms in organisms. The SCN transmits information about rhythms via different and various outputs such as neuronal connections, endocrine signals, body temperature, cellular redox state, and other more indirect cues such as the rest-activity cycle. However, other clocks in the brain and the peripheral cells can be reset by many parallel signals (such as nutriments-food intake or microbiota in intestinal cells) (Asher and Sassone-Corsi, 2015). This redundancy results in a huge complexity in the circadian clock network.

1.3. Molecular level of circadian rhythms: large fraction of the genome under clock control

Circadian rhythms are largely generated by auto-regulatory genetic feedback loops driven by transcription factors CLOCK and BMAL1. CLOCK and BMAL1 factors heterodimerize and drive daily patterns of transcription of a large number of clock-controlled genes (CCGs) in different cellular contexts across tissues (Janich et al., 2011; Marcheva et al., 2010; Paschos et al., 2012). They also drive the transcription of their own repressors PER and CRY. Accumulation of PER and CRY during the day and controlled degradation during the night allow cells to establish cycles in circadian gene expression (Lowrey and Takahashi, 2011; Crane and Young, 2014). Additional levels of circadian regulation exist with the Orphan Nuclear Receptor ROR and the Nuclear Receptor subfamily 1, group D, member 1 called NR1D1 or REV-ERB α (Triqueneaux et al., 2004). Both controls transcription of bmal1 gene. There are many other clock genes involved in circadian regulation, such as npas1, npas2 and Timeless (tim). However, the purpose of this paper is not to compile an exhaustive list. Furthermore, proteins clocks are modified in post-translation in various ways. This complex and, not completely elucidated regulation of clock machinery, allows organisms to circadian regulation of cellular, physiologic and behavioral output functions. Recent transcriptome studies have shown that a large fraction of the genome is under this clock control. Moreover, the overlap of CCGs in different tissues is relatively marginal, questioning the contribution of tissue specific factors to clock control (Masri and Sassone-Corsi, 2010; Asher and Sassone-Corsi, 2015). In this paper, we will first review how circadian rhythms are intricate with the sleep cycle and how these circadian-sleep rhythms may be implicated in ASD. Secondly, we will review how circadian rhythms are implicated in the timing of the brain development and may suggest new insights in the etiology of an atypical neurodevelopment disorder such as Autism Spectrum Disorder.

2. From sleep-circadian disorders to ASD

2.1. Reciprocal influence of circadian rhythms, sleep-wake pattern and melatonin

The sleep-wake pattern is regulated by two broad mechanisms: circadian rhythms and wake-dependent homeostatic build-up of sleep pressure. Sleep pressure increases during wake and dissipates during sleep. Sleep-wake pattern is also modulated by the light-darkness cycle, mood and cognition, and social time (such as meal time, sport time etc...) (Wirz-Justice et al., 2005). Reciprocally, the sleep-wake pattern also transmits information to circadian rhythms. The sleep-wake pattern can be view as an interface between different environmental variables (cognition, mood, social time) and circadian rhythms (Wulff et al., 2010). The sleep-wake pattern and circadian rhythms are influenced by melatonin rates and reciprocally. Melatonin synthesis release is regulated by a multi-synaptic pathway originating in the SCN and including the pineal gland. Melatonin levels depend on the light-dark exposure. Melatonin is correlated with the initiation of sleep. Consequences of circadian rhythms on the sleep-wake system can be difficult to untangle at a behavioral level. However, mutations in Clock, Bmal1, Cry1, Cry2 genes result in alterations in sleep time and sleep fragmentation (Laposky et al., 2005; Naylor et al., 2000).

2.2. Sleep and circadian rhythms disorders in ASD: role of melatonin

ASD is frequently associated with sleep initiation and maintenance disorders, as highlighted in Kotagal and Broomall (2012) review. Surveys of parents show that the sleep problems prevalence in ASD is 50 to 80% compared to 9–50% in age-matched typically developing children. These results are independent of cognitive impairments (Allik et al., 2006; Richdale et al., 2009; Polimeni et al., 2005; Doo and Wing, 2006; Giannotti et al., 2008; Kotagal and Broomall, 2012). Interestingly, ASD is more associated with anxiety about falling asleep, limit-setting disorders, sleep-onset association disorders, and circadian rhythm sleep disturbances compared than with general intellectual disability (Kotagal and Broomall, 2012).

Importantly, several studies show that a large population of ASD patients (about 65%) has less than half the average values of melatonin. This deficit in melatonin concerns diurnal as well as nocturnal melatonin levels, suggesting a global deficit in melatonin production in autism and not just a delayed phase or and inverted day-night rhythm (Nir et al., 1995; Tordjman et al., 2005, 2012, 2015; Kulman et al., 2000; Bourgeron, 2007). Melatonin is produced by the conversion of serotonin to N-Acetylserotonin (NAS) by the rate-limiting enzyme AA-NAT (Arylalkylamine N-Acetyltransferase), followed by the conversion of NAS to melatonin by HIOMT (Hydroxiindole O-Methyltransferase). Abnormal melatonin synthesis in ASD is frequently due to the deficiency of HIOMT (Melke et al., 2008). Melatonin is often reported as an efficient treatment of sleep onset disorder in ASD. A recent review highlighted that the literature supports the existence of a beneficial effect of Melatonin on sleep in individuals with ASD, with only few and minor side effects. However there is no randomized controlled trials with a representative population of ASD and these conclusions cannot be regarded as evidence-based (Guénolé et al., 2011).

Nicholas et al. (2007) aimed to test the implication of circadian rhythms in ASD and screened single-nucleotide polymorphisms (SNPs) in 11 clock/clock-related genes in 110 individuals with ASD and their parents. A significant allelic association was detected for clock gene per1 and npas2. However, it was a small population and results were not significant after correction for multiple testing. Yang et al. (2016), in a population of 28 ADS (14 with sleep disorders 14 without) and 23 controls, detected only in the population of ASD with sleep disorders, 2 kinds of mutation p.F498S in TIMELESS and p.R366Q in PER3 which were considered to affect gene function. Some of their results suggested also involvement of NR1D1 in autism etiology (Goto et al., 2017).

Please cite this article in press as: Geoffray, M.-M., et al. Are circadian rhythms new pathways to understand Autism Spectrum Disorder?. J. Physiol. (2017), http://dx.doi.org/10.1016/j.jphysparis.2017.06.002