Pharmacology, Biochemistry and Behavior 162 (2017) 55–61

Contents lists available at ScienceDirect

Pharmacology, Biochemistry and Behavior

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

Review

Circadian neurons in the lateral habenula: Clocking motivated behaviors

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ARTICLE INFO

Keywords:
Lateral habenula
Circadian
Clock genes
Motivation
Feeding
Depression

ABSTRACT

The main circadian clock in mammals is located in the hypothalamic suprachiasmatic nucleus (SCN), however, central timing mechanisms are also present in other brain structures beyond the SCN. The lateral habenula (LHb), known for its important role in the regulation of the monoaminergic system, contains such a circadian clock whose molecular and cellular mechanisms as well as functional role are not well known. However, since monoaminergic systems show circadian activity, it is possible that the LHb-clock's role is to modulate the rhythmic activity of the dopamine, serotonin and norephinephrine systems, and associated behaviors. Moreover, the LHb is involved in different pathological states such as depression, addiction and schizophrenia, states in which sleep and circadian alterations have been reported. Thus, perturbations of circadian activity in the LHb might, in part, be a cause of these rhythmic alterations in psychiatric ailments. In this review the current state of the LHb clock and its possible implications in the control of monoaminergic systems rhythms, motivated behaviors (e.g., feeding, drug intake) and depression (with circadian disruptions and altered motivation) will be discussed.

1. Introduction

Many, if not all, physiological functions follow rhythmic patterns. Hence, a "chronostasis" process overlaps the classical homeostatic concept of physiology to regulate the temporal organization in the organism (Aguilar-Roblero, 2015). The presence of daily fluctuations of diverse biological functions allows organisms to adapt to daily changes in their environment (e.g., light-dark transitions, temperature changes, food availability, and predator avoidance) to assure survival and successful reproduction (Pittendrigh, 1993). These variations are under the control of a timekeeping system organized in a hierarchical manner in which the hypothalamic suprachiasmatic nucleus (SCN) in mammals acts as the main orchestrator clock for the other oscillators in the brain and body (Albrecht, 2012; Welsh et al., 2010). Thus, circadian clocks have an important role in our lives, giving us harmony with our environment. A perturbation of this timekeeping system (as seen in jet lag exposed-people and shift workers) can lead to severe health consequences, ranging from metabolic (e.g., obesity, diabetes) to psychiatric (e.g., depression, addiction).

The capacity of SCN to oscillate, as well as other timed-organs, is dependent on a series of genes called "clock genes" having cycles of around 24 h. These cycles are organized into positive and negative feedback loops in the transcription and translation of certain genes, namely *Clock/Npas2*, *Bmal1*, *Per1–3*, *Cry1–2*, *Rev-Erbα* and *Rorβ*, which modulate and regulate each other in order to establish the 24 h rhythm of the clock output genes (Takahashi, 2015). Circadian gene expression allows clocks to oscillate in the absence of any external stimulation giving them their autonomous capability. Despite this ability to oscillate independently, the SCN needs to be set daily by external cues in order to synchronize with environmental changes. For this, solar time is the most important and reliable synchronizer for the clock (Meijer and Schwartz, 2003). Light reaches the SCN via a monosynaptic tract (i.e., the retinohypothalamic tract) that connects the retina with the ventral part of the SCN clock (Moore et al., 1995) (Fig. 1). In the retina, melanopsin-expressing ganglions cells, or ipRGC's (intrinsic photoreceptor ganglions cells), transmit the external light information to the SCN clock (LeGates et al., 2014). Light induces clock gene expression (e.g., *Per1–2* genes) in the SCN, mainly in the ventromedial region of the nucleus (containing VIP), as well as phase changes in behavioral and molecular rhythms in a time-dependent manner (Takahashi et al., 1984). Principal effects are observed when light is applied during the early and late night period in both diurnal and nocturnal species, while no effects of light on molecular or behavioral rhythms are observed when light is applied during the day (Golombek and Rosenstein, 2010).

Abbreviations: 5-HT, 5-hydroxytryptamine/serotonin; βCaMKII, βeta calmodulin-dependent protein kinase type II; DA, dopamine; DBS, deep brain stimulation; FR, fasciculus retroflexus; GABA, gamma-aminobutyric acid; GLT-1, glutamate transporter 1; GLUT, glutamate; ipRGC's, intrinsic photoreceptor ganglions cells; IGL, intergeniculate leaflet; LUC, luciferase; LH, lateral hypothalamus; LHb, lateral habenula; ORX, orexins; PER2, Period 2 protein; REM, rapid eye movement; RMTg, rostromedial tegmental nucleus; SCN, suprachiasmatic nucleus; SN, substantia nigra; Vglut2, vesicular glutamate transporter 2; VIP, vasointestinal peptide; VTA, ventral tegmental area

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http://dx.doi.org/10.1016/j.pbb.2017.06.013
Received 31 January 2017; Received in revised form 30 March 2017; Accepted 26 June 2017
Available online 28 June 2017
0091-3057/

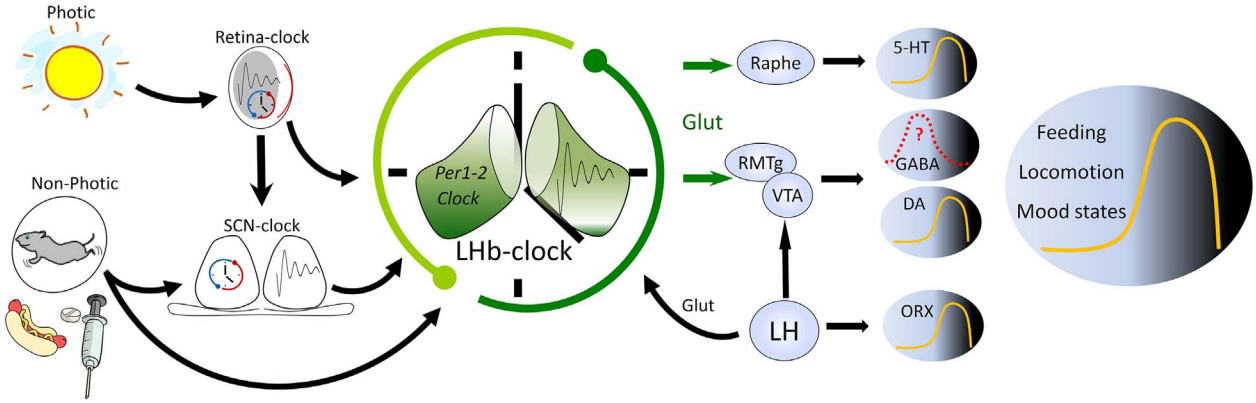

Fig. 1. Putative role of the LHb clock in the timing of motivation. The circadian clock in the LHb receives timing information from the light-dark cycle via the retina-LHb pathway and from the SCN clock. Moreover, other external non-photic cues (e.g., exercise, food, drugs) reset the SCN pacemaker and may have as well a setting effect on the LHb clock. The LHb cells (mainly glutamatergic) may set in time the neurochemistry (DA, 5-HT, GABA) of their principals targets (VTA, raphe, RMTg) and regulate the release of DA and 5-HT in the forebrain. However, whether GABA release from the RMTg and VTA shows a circadian profile is unknown. Thus, behaviors dependent on monoaminergic neurotransmission, which show circadian variability (locomotion, mood states) may in some way be modulated by the clock in the LHb closely coupling with the main clock in the SCN, and with the LH glutamatergic pathway (feeding).

In addition to light, other cues, called non-photic synchronizers, are able to affect the SCN clock at both the molecular and behavioral levels (Fig. 1). Among these synchronizers, food, exercise and drugs all have a strong impact on the SCN clock (Mendoza, 2007; Mistlberger, 1994; Mrosovsky, 1996). Non-photic entrainment is also time-dependent, but unlike light effects, these affect the clock during the day, advancing the phase of behavioral and physiological rhythms and down-regulating the expression of clock genes in the SCN (Hughes and Piggins, 2012; Maywood and Mrosovsky, 2001; Mistlberger and Skene, 2004). While physical activity may be the critical aspect of synchronization through exercise, some correlated variables, such as the state of arousal or motivation could also be involved (Antle and Mistlberger, 2000). In behavioral synchronization by food, the metabolic state of the organism appears to be the most important condition to allow entrainment. However, the hedonic reward properties of food also appear to be important determining factors for the synchronization of circadian clocks, including the SCN (Mendoza et al., 2005; Mendoza et al., 2010). Thus, when external time-cues contain a reward background the whole circadian system (the SCN, along with extra-SCN and peripheral oscillators) becomes susceptible to entrainment. The question then being, what are the central mechanisms involved in circadian reward-entrainment? Since the circadian system is composed of a functional network of brain pacemakers, those networks regulating reward and motivation might be the principal areas implicated in the synchronization to hedonic cues.

2. A clock in the LHb

To be qualified as “circadian pacemaker”, an organ or brain structure firstly has to show a rhythmic activity. Two other features are the presence of clock genes working in a rhythmic manner and a self-sustained capacity to oscillate (Guilding and Piggins, 2007). Beyond the SCN, circadian rhythmicity has been found in several peripheral organs, such as the liver, kidney and heart (Stratmann and Schibler, 2006). In the central nervous system, the retina was identified as an important circadian oscillator independent of the SCN (Jaeger et al., 2015; Ruan et al., 2008; Tosini and Menaker, 1996). Later, the olfactory bulb joined this group of self-sustained oscillators when it was reported that it also contains a SCN-independent circadian timer (Granados-Fuentes et al., 2004) which regulates day-night olfactory responses (Granados-Fuentes et al., 2006).

The lateral habenula (LHb) in the epithalamus is another of these self-sustained circadian oscillators in the central nervous system in addition to the SCN, retina and olfactory bulb (Guilding et al., 2010). Extracellular activity of LHb neurons, both in vivo and in vitro, shows a higher firing rate during the day than at night (Sakhi et al., 2014; Zhao and Rusak, 2005). Moreover, c-Fos protein expression shows a day-night activity difference in diverse rodent species such as mice, rats and hamsters (Tavakoli-Nezhad and Schwartz, 2006). In rats the c-Fos response to stressful stimuli at nighttime is significantly increased in the LHb compared to daytime, suggesting a circadian sensitivity of this structure to stress cues (Chastrette et al., 1991).

What makes the LHb clock tick? Although clock gene expression has been reported in many other brain regions, only some of them show a rhythmic expression pattern (Abe et al., 2002; Guilding and Piggins, 2007). Nevertheless, the presence of all of the molecular machinery (i.e., positive and negative loops of gene expression), as seen in the principal SCN clock, has not been fully described in other brain nuclei. In the rat habenula, first reports showed an expression of *Clock* and *Per1–2* genes, however, the rythmicity of this expression was not described as animals were euthanized at only one time point (Shieh, 2003). Moreover, in this study the mRNA expression of clock genes (by radioactive in situ hybridization) was not specifically localized in the LHb, but rather in the whole habenular complex, including the medial and lateral habenula (Shieh, 2003). Using PER2:luciferase (LUC) transgenic mice, circadian rhythmic activity was demonstrated in the mouse habenula ex vivo, indicating for the first time the presence of circadian oscillations of clock genes in the LHb (Guilding et al., 2010). Daily expression of the clock gene *Per2* (mRNA and protein) in the LHb in vivo was recently reported in rats, with higher levels during the day than at night (Zhao et al., 2015a). Interestingly, clock activity has been showed in the habenular region of lower vertebrates (e.g., fishes) as well (Sanchez-Bretano et al., 2015); in zebrafish, the ventral habenula is the fish homolog of the mammalian LHb (Aizawa et al., 2011; Amo et al., 2014). In goldfish, *gPer1b* mRNA expression in the habenular nucleus shows a day-night difference with the strongest activity at nighttime (Sanchez-Bretano et al., 2015). Thus, a functional circadian clock in the LHb is present throughout vertebrates, likely with a conserved similar role.

As for the SCN in rodents, there is a projection from the retina to the LHb. Using fluorescent retrograde or anterograde tracers it was reported that retina ganglion cells project to the rat and hamster LHb, suggesting that this epithalamic structure may integrate visual information (Qu et al., 1996; Reuss and Decker, 1997). In mice retinal cells expressing the photopigment melanopsin, ipRGC's, project their axons to several non-visuals brain targets (e.g., SCN, IGL, subparaventricular zone) including the LHb (Hattar et al., 2006). These contacts, however, are limited to the border of the dorsal region of the LHb (Hattar et al., 2006). Furthermore, the electrical activity of LHb cells is light-responsive. In fact, in rats, light can stimulate or inhibit