Frontiers in Neuroendocrinology 38 (2015) 50–64

Contents lists available at ScienceDirect

Frontiers in Neuroendocrinology

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

Review

Structural plasticity of the circadian timing system. An overview from flies to mammals

Olivier Bosler *, Clémence Girardet [1], Jean-Louis Franc, Denis Becquet, Anne-Marie François-Bellan

Aix-Marseille Université, CNRS, CRN2M, UMR 7286, Faculté de médecine, secteur nord, Boulevard Pierre Dramard, CS 80011, F-13344 Marseille cedex 15, France

ARTICLE INFO

Article history:
Available online 20 February 2015

Keywords:
Rhythm
Circadian clock
Suprachiasmatic nucleus
Cell network
Structural plasticity
Glial plasticity
Synapse remodeling
Paraspeckles

ABSTRACT

The circadian timing system orchestrates daily variations in physiology and behavior through coordination of multioscillatory cell networks that are highly plastic in responding to environmental changes. Over the last decade, it has become clear that this plasticity involves structural changes and that the changes may be observed not only in central brain regions where the master clock cells reside but also in clock-controlled structures. This review considers experimental data in invertebrate and vertebrate model systems, mainly flies and mammals, illustrating various forms of structural circadian plasticity from cellular to circuit-based levels. It highlights the importance of these plastic events in the functional adaptation of the clock to the changing environment.

1. Introduction

The circadian timing system allows living organisms to achieve temporal homeostasis with their environment, giving rise to daily biological rhythms which are generated at cellular level by oscillating gene expression and are orchestrated on a 24-h basis by networks of "master clock" neurons. These neurons continually integrate information from the outside world and send rhythmic temporal cues throughout the organism using neural, endocrine and metabolic signaling pathways (Dibner et al., 2010; Albrecht, 2012) (Fig. 1).

Over the last decades, the molecular mechanisms underlying circadian rhythmicity have been the subject of considerable research effort in different model systems, more specifically in flies and mammals. It is now well established that the core circadian time-keeper is composed of interlocked transcriptional/translational feedback loops that involve the products of circadian clock genes (Hardin and Panda, 2013). These autoregulatory loops are remarkably conserved across species and operate not only in central master clock cells but also in nearly every body cell (Ozkaya and Rosato, 2012; Partch et al., 2014). Major advances have also been made in our understanding of the anatomo-functional organization of clock neurons in the invertebrate and vertebrate brain. While in flies, the clock neurons belong to networks that involve different subsets of neurons in the lateral and dorsal brain serving different aspects of circadian behavior, in mammals, they are gathered into a small paired structure of the anterior hypothalamus referred to as the suprachiasmatic nucleus (SCN).

The mechanisms through which the circadian system is synchronized to external cycles (input pathways) and orchestrates coherent physiological and behavioral responses (output pathways) are central to biological timing. Synchronization to day/night and seasonal cycles is fundamental for adaptation of physiology and behavior. It permits anticipation to changes in the environment through entrainment of endogenous rhythmic outputs with intrinsic period length close to 24 h to daily cycles of exactly 24 h and their adjustment to day length. Various forms of plasticity are involved in the underlying mechanisms. They account, in particular, for physiological processes such as resetting clock neurons at appropriate phase of the circadian cycle, entrainment-induced adjustments in clock period to permit an accurate representation of solar time or rapid recovery after circadian rhythm disruption (Amir et al., 2002). The plasticity of the circadian timing system results not only in fine tuning of the multioscillatory molecular machinery in individual clock neurons but also in daily changes at cellular and network levels (Girardet et al., 2010a). These rhythmic changes, referred to as structural circadian plastic rearrangements (Muraro et al., 2013), may involve reorganization of subcellular elements in individual clock cells or

* Corresponding author. Fax: +33 (0)491698920.
E-mail addresses: olivier.bosler@univ-amu.fr (O. Bosler), girardetc@slu.edu (C. Girardet).
[1] Present address: Pharmacological & Physiological Science, Saint-Louis University School of Medicine, 1402 S. Grand Blvd., St. Louis, MO 63104, USA.

http://dx.doi.org/10.1016/j.yfrne.2015.02.001
0091-3022/

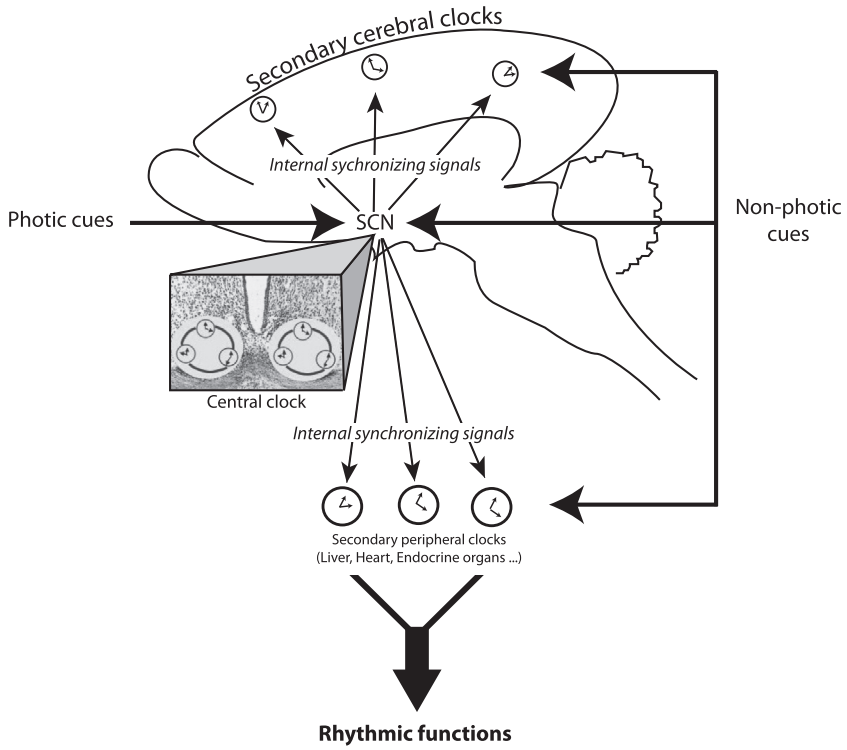

Fig. 1. Hierarchical organization of the circadian system in mammals. The central master clock is located in the suprachiasmatic nucleus (SCN) and sends rhythmic synchronizing signals of nervous and humoral nature to cerebral and peripheral secondary clocks. Elaboration of a rhythmic message from the SCN results from the coordinated functioning of its multiple cellular oscillators organized into networks. Intercellular coupling mechanisms allow SCN individual cell oscillators to retain determined phase relationships between each other. The SCN integrates a wide range of temporal cues from the environment, among which light is the most potent (photic cues). Non-photic cues such as meal timing may also synchronize secondary clocks. This has been shown in particular for the liver as well as extra-SCN cerebral clocks (see Mendoza and Challet, 2009). Hormonal and metabolic signaling is used to synchronize peripheral clocks to each other and to send feedback modulatory messages to the SCN and extra-SCN clocks (not shown).

remodeling at a circuit-based level, to adapt intercellular coupling within clock neuron networks and/or to reshape the circadian message. They are observed both in clock brain structures and in any brain region under the control of the circadian clock. Structural circadian plasticity is known to coexist with circadian changes in neuronal excitability and synaptic efficacy within and outside clock structures but the precise relationship between these two forms of plasticity remains poorly understood (Frank and Cantera, 2014).

In this review we consider the current experimental evidence supporting the idea that the mechanisms of the brain's structural plasticity play major roles in circadian timing and that glial cells are importantly involved. First we will present the main organizational features characterizing the circadian system of *Drosophila* and mammals, the two model systems that are commonly used in circadian research. We will then discuss how structural plastic events may occur at different cellular and network levels of the circadian system to adjust temporal adaptation of the organism.

2. Overview of the circadian timing system

2.1. The circadian network in Drosophila

The *Drosophila* brain comprises some 150 clock neurons (out of the estimated 250,000 neurons) which have been classified into readily identifiable groups designed according to their anatomical locations (for reviews, see Nitabach and Taghert, 2008; Allada and Chung, 2010). Two major groups with specific functional attributes regarding the control of the bimodal activity rhythms characterizing the fly (morning and evening peaks) have been recognized in the lateral part and the dorsal part of the *Drosophila* brain (Grima et al., 2004). An additional group made of lateral posterior neurons has also been described. These cells have been implicated specifically in temperature entrainment of circadian activity (Miyasako et al., 2007).

The lateral group (15–16 neurons in each brain hemisphere), consists of a ventral lateral cluster (LNv) comprising small (s-LNv) and large (l-LNv) neurons and a dorsal lateral cluster (LNd). The s-LNv neurons would be at the top of the hierarchy, directing locomotor rhythms through dorsal projections toward other clock neurons and putative downstream circuits. They would have a special role in regulating the morning activity peak (M oscillators) and in driving rhythmic activity under constant darkness. In contrast, the contribution of the l-LNv is not well defined. Together with a so-called "5th s-LNv neuron" residing in the vicinity of the other LNv neurons, the LNd neurons would be involved in regulating the evening activity peak (E oscillators). The dorsal group comprises approximately 50 neurons in each brain hemisphere, which can also be divided into subgroups (DN1, DN2, DN3). This complex organization indicates that specific neurons have distinct roles in the control of circadian rhythms. In particular, it has been suggested that, together with the lateral posterior neurons, the DN2 neurons play a prominent role in the temperature entrainment of the network (Picot et al., 2009).

Among the signaling molecules that have been identified in the fly circadian system, the neuropeptide pigment-dispersing factor (PDF) has been paid special attention. It is selectively expressed by the LNv clock neurons (except by the 5th s-LNv neuron) and is released in a circadian manner, propagating timing information