Neuroscience 247 (2013) 280–293

NEUROSCIENCE FOREFRONT REVIEW

THE CIRCADIAN SYSTEM: PLASTICITY AT MANY LEVELS

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Abstract—Over the years it has become crystal clear that a variety of processes encode time-of-day information, ranging from gene expression, protein stability, or subcellular localization of key proteins, to the fine tuning of network properties and modulation of input signals, ultimately ensuring that physiology and behavior are properly synchronized to a changing environment. The purpose of this review is to put forward examples (as opposed to generate a comprehensive revision of all the available literature) in which the circadian system displays a remarkable degree of plasticity, from cell autonomous to circuit-based levels. In the literature, the term circadian plasticity has been used to refer to different concepts. The obvious one, more literally, refers to any change that follows a circadian (*circa* = -around, *diem* = day) pattern, i.e. a daily change of a given parameter. The discovery of daily remodeling of neuronal structures will be referred herein as structural circadian plasticity, and represents an additional and novel phenomenon modified daily. Finally, any plasticity that has to do with a circadian parameter would represent a type of circadian plasticity; as an example, adjustments that allow organisms to adapt their daily behavior to the annual changes in photoperiod is a form of circadian plasticity at a higher organizational level, which is an emergent property of the whole circadian system. Throughout this work we will revisit these types of changes by reviewing recent literature delving around circadian control of clock outputs, from the most immediate ones within pacemaker neurons to the circadian modulation of rest–activity cycles.

Key words: circadian plasticity, circadian network, PDF, structural plasticity, clock neurons, rhythmic behavior.

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CIRCADIAN CIRCUITS

The behavioral and molecular characterization of numerous clock mutants, together with the unraveling of the molecular mechanisms underlying the circadian clock, have been the main focus of circadian research in the last decades (for a thorough review of the current understanding of the molecular clockworks, see Ozkaya and Rosato (2012)). Although by no means a closed topic, the challenge is now to understand how different clock neurons connect to each other and establish a network that is able to integrate environmental clues, culminating on a coherent and adaptive behavioral output. *Drosophila* provides an ideal model organism to study clock neuron connectivity because of its anatomically dispersed network, comprising defined clock neuron clusters that are becoming more and more molecularly distinct (Fig. 1, adapted from Peschel and Helfrich-Forster (2011) and Table 1). Compared to studying the connectivity of the densely packed clock neuronal network that the mammalian suprachiasmatic nuclei (SCN) represent, this task seems more feasible. It is this anatomical layout and its scarcity (150–200) of neurons (Kaneko et al., 1997; Helfrich-Forster, 2003) compared to 20,000 in the rat SCN (Van den Pol, 1980), together with the versatile genetic tools available in *Drosophila* (Venken et al., 2011), which makes this model organism an ideal choice to study this biological question.

Given that membrane properties are essential to neuronal function, it seems logical to begin by asking what kind of electrical signals clock neurons generate. In that regard early work on tissue islands containing rat SCN was pioneer showing that, under free-running conditions, electrical activity increased during the

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Abbreviations: AVP, arginine vasopressin; BRP, bruchpilot; CRY, CRYPTOCHROME; DD, constant darkness; DN, dorsal neuron; lLNvs, large ventral lateral neurons; LD, light–dark; LL, constant light; LN, lateral neuron; LNds, dorsal lateral neurons; LPNs, lateral posterior neurons; PDF, pigment dispersing factor; PDH, pigment dispersing hormone; PER, PERIOD; SCN, suprachiasmatic nuclei; sLNvs, small ventral lateral neurons; TIM, TIMELESS; VIP, vasoactive intestinal peptide.

0306-4522/13 $36.00
http://dx.doi.org/10.1016/j.neuroscience.2013.05.036

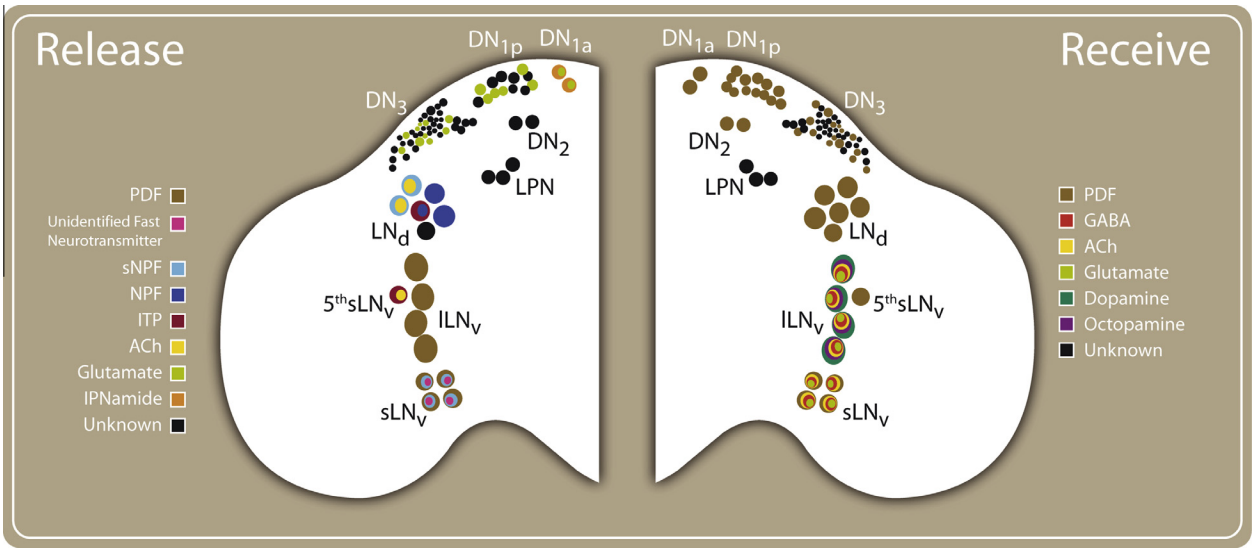

Fig. 1. Molecules released (pictured on the left hemisphere) or received (pictured on the right hemisphere) by clock neuron clusters of adult *Drosophila*. In several cases no physiological evidence exists on the biological function of these substances in the specific groups of cells; in those cases their release is implied by the fact that a specific vesicular transporter or a synthesizing enzyme is expressed there. The objective of the schematic diagram is to give an overview of the state of the art on the chemical substances putatively involved in neurotransmission in the *Drosophila* circadian network, for further information the reader should start by revising references included in Table 1.

Table 1. References to the chemical substances released or received by clock neuronal clusters of adult *Drosophila*

Cluster	Release	Receive
sLNvs	PDF[a,b]; sNPF[c]; Unidentified Fast Neurotransmitter[d,e]	PDF[i]; GABA[j]; ACh[j]; Glutamate[h]
lLNvs	PDF[a,b]	GABA[k]; ACh[k]; Glutamate[k]; Octopamine[l]; Dopamine[l]
5th sLNv	ITP[c]; ACh[c]	PDF[i]
LNds	Some cells NPF[c]	PDF[i]
	Some cells sNPF[c] and ACh[c]	
	One cell NPF[f] and ITP[c]	
LPNs	N/A	N/A
DN1as	IPNamide[g]; Glutamate[h]	PDF[i]
DN1 ps	Some cells Glutamate[h]	PDF[i]
DN2s	N/A	PDF[i]
DN3s	Some cells Glutamate[h]	Some cells PDF[i]

N/A: no information available about neurotransmitter and neuropeptides received or released by that particular cluster. Not included in the table but worth noting is the information relevant to neurotransmission in the larval circadian clusters, which includes the substances PDF (Renn et al., 1999), ACh (Wegener et al., 2004), GABA (Hamasaka et al., 2005), Serotonin (Hamasaka and Nassel, 2006), Glutamate (Hamasaka et al., 2007) and sNPF (Johard et al., 2009).

[a] Helfrich-Forster (1995).
[b] Renn et al., (1999).
[c] Johard et al. (2009).
[d] Yasuyama and Meinertzhagen (2010).
[e] Umezaki et al. (2011).
[f] Lee et al. (2006).
[g] Shafer et al. (2006).
[h] Hamasaka et al. (2007).
[i] Shafer et al. (2008).
[j] Lelito and Shafer (2012).
[k] McCarthy et al. (2011).
[l] Shang et al. (2011).

subjective day compared to the subjective night, therefore proving for the first time that electrical activity of clock neurons is circadianly regulated (Inouye and Kawamura, 1979). Moreover, thanks to the development of SCN slice preparations, mammalian models have been extremely useful in determining many electrophysiological characteristics of clock neurons (Kuhlman and McMahon, 2006; Ko et al., 2009; Colwell, 2011). Although very informative to study electrical activity and the properties of clock neurons under conditions that may render them synchronized/desynchronized, SCN preparations are not that practical, due to their complexity, in the unraveling of specific neuronal connectivity within a circadian neuronal network (Vansteensel et al., 2008; Welsh et al., 2010).

Anatomically, the circadian network of *Drosophila* has been thoroughly described (Helfrich-Forster et al., 2007), with each brain hemisphere containing three dorsal