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Review

Neuroanatomy of the extended circadian rhythm system

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ABSTRACT

The suprachiasmatic nucleus (SCN), site of the primary clock in the circadian rhythm system, has three major afferent connections. The most important consists of a retinohypothalamic projection through which photic information, received by classical rod/cone photoreceptors and intrinsically photoreceptive retinal ganglion cells, gains access to the clock. This information influences phase and period of circadian rhythms. The two other robust afferent projections are the median raphe serotonergic pathway and the geniculohypothalamic (GHT), NPY-containing pathway from the thalamic intergeniculate leaflet (IGL). Beyond this simple framework, the number of anatomical routes that could theoretically be involved in rhythm regulation is enormous, with the SCN projecting to 15 regions and being directly innervated by about 35. If multisynaptic afferents to the SCN are included, the number expands to approximately brain 85 areas providing input to the SCN. The IGL, a known contributor to circadian rhythm regulation, has a still greater level of complexity. This nucleus connects abundantly throughout the brain (to approximately 100 regions) by pathways that are largely bilateral and reciprocal. Few of these sites have been evaluated for their contributions to circadian rhythm regulation, although most have a theoretical possibility of doing so via the GHT. The anatomy of IGL connections suggests that one of its functions may be regulation of eye movements during sleep. Together, neural circuits of the SCN and IGL are complex and interconnected. As yet, few have been tested with respect to their involvement in rhythm regulation.

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Introduction

The suprachiasmatic nucleus (SCN), master clock of the circadian system (Green and Gillette, 1982; Inouye and Kawamura, 1979; Ralph et al., 1990; Stephan and Zucker, 1972), sits astride the supraoptic commissures, and well-positioned to receive photic input. This possibility became evident with the 1972 discovery of the retinohypothalamic tract (RHT) (Hendrickson et al., 1972; Moore and Lenn, 1972). Since that time, there has been progressive elaboration of the circadian visual system. Exploration of the intergeniculate leaflet (IGL) began in 1974 with the demonstration that it projects to the SCN (Swanson et al., 1974). Subsequent studies showed that the IGL is retinorecipient (Hickey and Spear, 1976), contains neuropeptide Y-IR cells (Card and Moore, 1982; Moore et al., 1984) and provides NPY terminals to the SCN (Card and Moore, 1982). The IGL became the first site distal to the SCN acknowledged as contributing to circadian system regulation with the 1984 demonstration that NPY infused into the SCN would elicit circadian rhythm phase shifts (Albers and Ferris, 1984; Albers et al., 1984).

With each experiment devoted to analysis of SCN or IGL efferent and afferent anatomy, the breadth of connections possibly contributing to the circadian rhythm system has grown. Presently, there are more than 100 brain regions that are *potential* contributors to circadian rhythm regulation. Eventually, each of these must be individually tested to determine whether it is a true member of the extended circadian rhythm system. The present reality is that very few brain regions are known to make such contributions because the rhythm-related functions of rather few regions have thus far been explored. Areas having or possibly having such functions include the SCN itself (Moore and Eichler, 1972), the IGL (Harrington and Rusak, 1986; Janik and Mrosovsky, 1994; Pickard et al., 1987), paraventricular thalamus (Moga and Moore, 2000), the subparaventricular (sPVz) zone (Schwartz et al., 2009), dorsomedial hypothalamus (DM) (Chou et al., 2003), the habenula (Paul et al., 2011), a poorly determined part of the pretectum and tectum (Marchant and Morin, 1999), and the dorsal (DR) and median (MnR) raphe nuclei (Meyer-Bernstein and Morin, 1999).

One intention of the present manuscript is to demonstrate the massive knowledge increase, both in breadth and depth, about the neuroanatomical substrate of the circadian system. Another is to demonstrate deficiencies in that knowledge. It is certainly true that not all brain regions identified here as projecting directly or indirectly to the SCN are necessarily part of an extended circadian rhythm system. But if such connections do exist, they may have a rhythm-related function. It is reasonable to expect that any route afferent to the circadian clock might alter its function in some fashion or other. The present anatomically-oriented discussion is necessarily open-ended precisely because, despite the large expansion in factual knowledge, there are few guiding principles that facilitate understanding of the routes by which the master SCN circadian clock is modified by various stimuli or the efferent routes through which it alters phase and function of various outputs.

The relationship between the sleep regulatory system and the circadian system exemplifies some of the difficulties. The sleep system functions on an oscillating foundation provided by the SCN, while also providing feedback to SCN function (Deboer et al., 2003, 2007a, 2007b; Houben et al., 2009; Schaap and Meijer, 2001). There are multiple candidate routes by which the SCN can influence the sleep system or, in turn, be influenced by it. These include connections with the ventrolateral preoptic area (VLPO) (Chou et al., 2002; Deurveilher and Semba, 2003; Novak and Nunez, 2000), possibly with lateral hypothalamic (LH) neurons of the orexin (OX) system (Abrahamson et al., 2001; Schwartz et al., 2011) or through IGL connections with brainstem sleep regulatory nuclei (Morin and Blanchard, 2005). Neither system can be fully understood without knowing the contribution of each.

A clearly incomplete aspect of the SCN afferent anatomy concerns which stimuli modify rhythmicity and what anatomical routes convey the stimulus information to the circadian clock. The route by which light alters rhythm function is well established (Hendrickson et al., 1972; Moore and Lenn, 1972) and is being refined regularly (Chen et al., 2011). In contrast, the exact nature of the stimulus by which locomotion modifies circadian clock function is not known, nor is the route by which the stimulus reaches the IGL through which it exerts its effect on the SCN (Mistlberger et al., 2003). In a few instances, as with the gonadotropin releasing hormone (GnRH) pathway to the SCN (Jennes and Stumpf, 1980; Merchenthaler et al., 1984), a general function can be inferred from the neuropeptide involved, but there are no data bearing on if, how or why a GnRH pathway alters rhythmicity although it is well known that a circadian clock controls GnRH release (Williams et al., 2011).

There is also a large amount of information available concerning SCN efferents and their targets. It is likely that all efferent projections carry circadian rhythm phase information to distal targets in other systems. The truth of this statement has not been demonstrated, nor has it been shown that different projections carry similarly phased timing information. Those sorts of studies await the research efforts of neurophysiologists. The neuroanatomists have provided a list of many brain regions and their related systems which receive SCN efferents. Those systems must be examined to determine the extent to which each receives and utilizes information about rhythm phase. And, the hope is that each such system will be studied to determine the extent to which it feeds back onto the circadian clock, influencing the very system that provides the baseline timing information.

Suprachiasmatic nucleus intrinsic anatomy

Distributions of cell phenotypes

Critical to the understanding of SCN intrinsic anatomy is the overall morphology of the nucleus and its species dependence. The SCN of hamster and mouse is an upright, roughly tear-drop shaped nucleus (somewhat more elliptical in the hamster), but in the rat, the shape is oblate. As a result, the robust retinorecipient region in the rat SCN, compared to that of mouse and hamster, has a larger medial–lateral axis than a dorsal–ventral one. This modification is associated with a change in the distribution of VP-IR neurons from a predominantly dorsomedial position to a position capping the more ventral, densely retinorecipient region (Morin et al., 2006).

Several different neuron classes that are positive for one or more neuropeptides have been identified in the SCN (Fig. 1), including vasopressin (VP), vasoactive intestinal polypeptide (VIP), gastrin releasing peptide (GRP), substance P (SP), neurotensin (NT), enkephalin (ENK), somatostatin (SS) and cholecystokinin (CCK). Presence of VP- and VIP-immunoreactive (IR) cells is a constant across most mammals (but possibly not in the mink or musk shrew Martinet et al., 1995; Tokunaga et al., 1992). In addition, all SCN neurons appear to contain GABA (Abrahamson and Moore, 2001; Moore and Speh, 1993; Morin and Blanchard, 2001). Presence and location of the other neuromodulator phenotypes vary across species or have not been studied sufficiently to allow generalizations (see Goel et al., 1999; Smale et al., 1991). A critical feature that appears common to rat, mouse and hamster is the presence of a central SCN subnucleus (SCNce) identifiable by a fairly circumscribed collection of GRP-IR neurons. This feature also appears in the SCN of a diurnal species, the Nile grass rat (Smale and Boverhof, 1999). The SCN of this species is very similar to those of the mouse, rat and hamster.

The hamster SCNce has cells identified as containing VIP, SP and GRP, and is easily identified by cells immunoreactive to calbindin (CALB) (LeSauter et al., 2002). The bulk of the VIP-IR cells lie ventral to the SCNce. This raises a functional question, that is, which is more important, the neuropeptide content or the location of the cell(s)?