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Neuroanatomy of the Extended Circadian Rhythm System

Lawrence P Morin

Department of Psychiatry, Stony Brook University Medical Center Stony Brook, NY 11794-8101

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.

Keywords

circadian; neuroanatomy; suprachiasmatic; intergeniculate leaflet; efferent; afferent; retrograde; anterograde; serotonin; connectivity; transneuronal

The suprachiasmatic nucleus (SCN), master clock of the circadian system (Stephan and Zucker, 1972; Inouye and Kawamura, 1979; Green and Gillette, 1982; Ralph, et al., 1990), 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

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Address Correspondence to: Dr. Lawrence P Morin, PhD, Department of Psychiatry, Stony Brook School of Medicine, Stony Brook University, Stony Brook, NY 11794-8101, phone 631-444-1613, fax 631-444-7534, lawrence.morin@stonybrook.edu.

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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; Pickard, et al., 1987; Janik and Mrosovsky, 1994), 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 (Schaap and Meijer, 2001; Deboer, et al., 2003; Deboer, et al., 2007; Deboer, et al., 2007; Houben, et al., 2009). 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) (Novak and Nunez, 2000; Chou, et al., 2002; Deurveilher and Semba, 2003), 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 gonadotrophin 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 (Tokunaga, et al., 1992; Martinet, et al., 1995)). In addition, all SCN neurons appear to contain GABA (Moore and Speh, 1993; Abrahamson and Moore, 2001; Morin and Blanchard, 2001). Presence and location of the other neuromodulator phenotypes varies across species or have not been studied sufficiently to allow generalizations (see (Smale, et al., 1991; Goel, et al., 1999). 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)? Likewise, VIP-IR and GRP-IR are co-localized in some hamster SCN neurons (Aioun, et al., 1998), but obviously this can only occur where the distributions of the two cell types overlap. Again, whether the location of the cells or their neuromodulator content is of primary functional importance is not known.

The region containing the GRP-IR cells is fairly discrete and centrally located in the rat, but substantially overlaps with and extends more caudally than the region containing VIP-IR

cells (Moore, et al., 2002). The evolving neuroanatomical work has been joined by more recent physiological and genetic studies of specific cell functions, especially as related to VIP (Cutler, et al., 2002; Harmar, et al., 2002; Aton, et al., 2005). This neuropeptide and its receptor, VPAC2, appear to be central to maintaining the cell-cell communication necessary for persistent SCN rhythmicity. The focus on neuropeptides capable of sustaining rhythmicity in an arrhythmic SCN has recently been expanded from VIP as the primary intrinsic neuropeptide synchronizer of SCN circadian rhythmicity to hierarchically include VP and GRP neurons as second and third order neuromodulators also capable of sustaining rhythmicity (Maywood, et al., 2011).

The topography of intrinsic SCN neuron phenotypes (Fig. 1) has been reviewed in detail (Morin and Allen, 2006; Morin, et al., 2006), and the appropriateness of various proposed organizational schemes has been questioned (e.g., core/shell; dorsomedial/ventrolateral). Contributing to the sense that such schemes are inadequate have been recent descriptions of cell distributions not consistent with the plan. In particular, the SCN of hamster, mouse and rat has a unique distribution of cells identified containing Fox-3 (formerly, NeuN) protein. These cells occupy a region that includes most of the lateral half of the SCN, including the SCNce (as seen in hamster and mouse) and the area lateral and dorsal to it (Geoghegan and Carter, 2008; Morin, et al., 2011). Similarly, the distributions of cells expressing the *Magel2* gene or containing neuroglobin-IR include both portions of both nominal “core” and “shell” portions of the SCN (Kozlov, et al., 2007; Hundahl, et al., 2010).

A unique distribution of calcitonin-gene-related peptide-(CGRP) IR neurons has been described in the ventrolateral part of the caudal two thirds of the mouse SCN (Park, et al., 1993). The distribution of the CGRP-IR cells would probably overlap medially and rostrally with the VIP cell distribution. Sparse cells are found near the midline, with more evident laterally in the SCN or on its border. The distribution appears continuous with a decreasing concentration of cells extending dorsally into anterior hypothalamus. These cells are not present in rat, guinea pig or rabbit (Park, et al., 1993).

The complexity of the SCN with respect to the anatomy of its fields of innervation and distributions of its constituent cell groups has been discussed previously (Morin, et al., 2006). The presence of novel cell distributions that transcend widely referenced SCN “divisions” emphasizes SCN complexity as a characteristic consistent with molecular, cellular and physiological analyses of intercellular communication across the whole nucleus. Recent studies emphasize the view that SCN rhythmic function is an emergent property of a cellular network capable of harnessing and organizing rhythmic activities of individual and groups of cells (Buhr, et al., 2010; Welsh, et al., 2010; Mohawk and Takahashi, 2011).

SCN Intrinsic Connections

Cell-cell communication by neuropeptides may be the primary contributor to normal rhythmicity, but the network properties of the whole SCN appear to provide rhythm stability in the absence of genes contributing to the molecular circadian clockworks (Liu, et al., 2007; Welsh, et al., 2010). This fact demands more attention to gathering fundamental neuroanatomical information concerning cell-cell connectivity within the SCN.

In his 1980 paper, van den Pol (van den Pol, 1980) described the existence of extensive gap junctions between glial cells. Subsequently, the presence of presumptive gap junctions between neurons has been observed and confirmed (Colwell, 2000; Shinohara, et al., 2000; Rash, et al., 2001; Jobst, et al., 2004; Long, et al., 2005).

The dendritic arbor of neurons of the hamster SCNce, whether or not they contain CALB, orient a few degrees medial from the vertical (Jobst, et al., 2004). A small percentage of

these cells apparently have gap junction contacts with adjacent neurons. The CALB cells in the hamster SCN contact neurons identifiably VIP-, GRP- or CCK-IR and each of those cell types project back onto the CALB-IR cells. In contrast, VP-IR neurons appear to have no connections with CALB-IR cells (LeSauter, et al., 2002).

A confocal laser scanning microscopic study (Romijn, et al., 1997) analyzed connections between cells representing the major phenotypes in rat SCN, including VP-, VIP-, GRP- and SS-IR neurons. The study showed abundant and reciprocal synaptic connections between VP and VIP cells, VP and GRP cells, VP and SS cells, VIP and SS cells, and between SS and GRP cells. Neurons immunoreactive to VIP, GRP or both VIP/GRP also reciprocally connect with each other. The widespread interconnectivity of cells in groups differentially located within the SCN may facilitate the rapid distribution of both intrinsic pacemaker and afferent information across the entire SCN. In addition, the complex features of the SCN cellular network have been suggested to be characteristic of an “oscillatory/reverberative activity generated by a non-linear self-organizing system” (Romijn, et al., 1997).

The term, “dynamic anatomy,” has been used in reference to the large apparent changes in the spatial distribution of certain neuropeptidergic cell groups according to circadian time (Morin, 2007). Thus, the SCN volume occupied by cells expressing VP mRNA appears to vary by a factor of 5-10 across the day. The number of actual intrinsic SCN connections with cells seemingly devoid of VP may be a function of circadian time rather than absence of VP. The same logic applies to the connections of all other classes of neuropeptidergic cells not yet tested for their dynamic anatomy.

A related phenomenon may be reflected in the ability of certain groups of SCN neurons to functionally reorganize according to past experience. Thus, an SCN “division” may emerge under the influence of photoperiod or gonadal hormone history (Watanabe, et al., 2006; Yan, et al., 2010; Karatsoreos, et al., 2011) (see above statement by Romijn et al. (1997). Collectively, the information concerning functional reorganization within the SCN reinforces the notion that the entire SCN achieves and maintains its status as the master circadian clock precisely because of its complexity (Buhr, et al., 2010; Welsh, et al., 2010; Maywood, et al., 2011; Mohawk and Takahashi, 2011).

In mice, GRP neurons identify an SCN region thought to be homologous to the hamster SCNce. Because of this, and because GRP is known to be a stabilizer and modulator of the circadian clock (Antle, et al., 2005; Brown, et al., 2005; Maywood, et al., 2011), mouse GRP neurons have been used as the basis for a thorough, systematic and very necessary anatomical analysis of intrinsic SCN connectivity in mouse (Drouyer, et al., 2010). These studies show that GRP cells are structurally different than similarly located non-GRP cells, having a dendritic tree with more branches, greater overall dendritic length and longer axons. Additionally, the non-GRP cells have a preferred axonal orientation about 10 degrees lateral to the vertical. With respect to cell-cell appositions, there are more from non-GRP cells on VP somas or fibers than from GRP cells. There are also smaller differences between the two cell types. Further, dye-coupled cells were more commonly seen adjacent to GRP cells (3.8/cell vs 1.3/non-GRP cell) with the vast majority found in the region containing the GRP cells and only 15% in the area of VP-IR neurons (Drouyer, et al., 2010).

An important result obtained by Drouyer and colleagues (2010), consistent with the Romijn et al (1997) studies, was the demonstration reciprocal connections between centrally located GRP or non-GRP neurons and VP or non-VP cells in the dorsomedial regions SCN. This result overturns a previous conclusion (Leak, et al., 1999), based on virus tract tracing methods, that SCN connectivity is one-way, with centrally or ventrally located cells generally projecting dorsomedially. This conclusion has also been disputed by Luo and

Aston-Jones (2009) who consistently observed a pattern of retrograde virus labeling opposite to that described by Leak et al. (1999) who used the same method. An unresolved issue related to the retrograde virus tracing studies concerns the extent to which the virus fills cells in the SCN. Studies from several labs (e.g., (Luo and Aston-Jones, 2009)) suggest that the Bartha strain of pseudorabies virus, whether injected into the brain or peripheral organs, may eventually fill all or nearly all SCN neurons. Accurate documentation of SCN cell filling would provide useful information regarding the extent to which SCN neurons are interconnected.

SCN Afferent Pathways

Retinohypothalamic Tract

Initial studies of the RHT demonstrated a simple projection from retina to the SCN (Hendrickson, et al., 1972; Moore and Lenn, 1972). With increasing investigation and newer methods, the RHT has been shown to be increasingly complex (Johnson, et al., 1988; Muscat, et al., 2003). The cells of origin are primarily melanopsin-containing, intrinsically photoreceptive retinal ganglion cells (ipRGCs) (Provencio, et al., 2000; Gooley, et al., 2001; Berson, et al., 2002; Hattar, et al., 2002; Provencio, et al., 2002; Morin, et al., 2003; Sollars, et al., 2003). These cells not only function as photoreceptors that pass phase-setting photic information to the SCN, they also function as conduits of photic information arriving from classical rod and cone photoreceptors (Goz, et al., 2008; Guler, et al., 2008; Hatori, et al., 2008).

Different types of ipRGCs have been observed in the mouse retina. Documentation exists for as many as five, currently designated M1-M5 (Ecker, et al., 2010; Chen, et al., 2011; Schmidt, et al., 2011). The dendritic stratification patterns allow division of the five types into three distinguishable classes with type M1 dendrites found exclusively in the OFF sublamina of the inner plexiform layer. The M3 type shows bilaminar dendritic stratification in the OFF and the ON sublamina of the inner plexiform layer. The M2, M4 and M5 types have dendrites exclusively in the ON sublamina. The M1 type is further divisible according to whether the cells express the transcription factor, *Brn3b*. The M2, M4 and M5 type are distinguishable according to quantitative morphological characteristics. Melanopsin has not been positively identified in the M4 or M5 types, but these cells show weak responses to light.

For the purposes of this review, the most important point is that functional differences related to the ipRGC axonal projection anatomy are emerging. The *Brn3b*-negative ipRGCs comprise about 10% of the melanopsin cell population, but the number is sufficient to allow normal rhythm entrainment (Badea, et al., 2009; Schmidt, et al., 2011; Schmidt, et al., 2011). In the absence of these cells, innervation of the SCN by the remaining ipRGCs remains robust and apparently normal. In contrast, ipRGC projections to the IGL are greatly reduced and those to the OPT are completely absent (Chen, et al., 2011). These anatomical alterations appear to account for the greatly reduced pupillary light reflex in mice lacking *Brn3b*-negative ipRGCs (absence of projection to the OPT), attenuation of the period lengthening effect of constant light (diminished projection to the IGL) and the maintenance of apparently normal entrainment (SCN innervation is apparently normal). This research represents the beginning of a process by which the RHT is being parsed into functional anatomical divisions (Badea, et al., 2009). Presumably, such efforts will eventually merge with existing reports that individual ipRGCs project to two or more retinorecipient nuclei (Pickard, 1985; Gooley and Saper, 2003; Muscat, et al., 2003). Bifurcating projections of ipRGCs are completely ipsilateral except those to the SCN which is innervated bilaterally.

It should be noted that the RHT projects to numerous hypothalamic regions in addition to the SCN (Johnson, et al., 1988; Morin and Blanchard, 1999; Major, et al., 2003). Some of these are sufficiently close to the SCN that most lesions directed at it are likely to destroy fibers of passage to neighboring or more caudal hypothalamic sites. Table 1 lists the brain nuclei, largely hypothalamic, receiving projections specifically from the RHT. For comparison purposes, Table 1 also indicates which of these nuclei have projections to or from the SCN and IGL.

The retina projects to approximately 30 brain regions, with ipRGCs projecting to most of them (Fig. 2). In addition to the large number retinorecipient nuclei, there are abundant connections between them, especially with respect to their relationships to the IGL. As indicated, the retinorecipient IGL projects to most of the subcortical visual nuclei which, in turn, project back to the IGL, creating a variety of theoretical loops through which photic information might indirectly influence function of the SCN.

Retinorecipient nuclei of the hypothalamus are also heavily interconnected. For example, the medial preoptic area (MPOA), subparaventricular zone (sPVz), DM and posterior hypothalamus (PH) each receive projections from, and provide reciprocal innervation to, the SCN, median preoptic nucleus (MnPO) and ventrolateral preoptic nucleus (VLPO) (Chou, et al., 2002; Deurveilher, et al., 2002; Deurveilher and Semba, 2003; Kriegsfeld, et al., 2004).

It should also be noted, that among the convoluted pathways of the broader circadian visual system there is a direct visual projection to the dorsal raphe nucleus (DR) in several species, including the gerbil, degus, cat and rat (Foote, et al., 1978; Shen and Semba, 1994; Fite, et al., 1999; Fite and Janusonis, 2001), but has not been seen in the hamster (Morin and Blanchard, unpub. data).

SCN Terminal Fields

There are three major terminal fields in the SCN, that of the RHT, of the median raphe projection and of the GHT from the IGL (Fig. 3). Each field has its most robust density in a different location, but upon close examination terminals from the three input pathways can be found in essentially all parts of the nucleus.

From the Retinohypothalamic Tract

There are species differences in the topography of RHT terminals in the SCN. Most obvious is the difference in ipsi- vs contralateral retinal contribution to SCN innervation which varies substantially. The predominant retinal input arrives from the contralateral retina. In the golden mantled ground squirrel, 100% of the terminals appear to be from the contralateral retina (Smale, et al., 1991), whereas in the mouse, each retina contributes 50% of SCN terminals (Morin, et al., 2006). The terminal field in the hamster SCN has been described, based on cholera toxin-HRP methods, to be approximately equal bilaterally (Johnson, et al., 1988), but more recently, a subtle ipsi-/contralateral difference in SCN innervation was noted (Fig. 3A). Cholera Toxin beta subunit (CTB) tract tracing revealed the ventral and medial SCN to be innervated predominately by the ipsilateral retina with the more centrally located region of densest retinal input arriving predominately from the contralateral eye (Muscat, et al., 2003). The pattern of hamster SCN innervation by the RHT places it between species (such as the ground squirrel mentioned above) receiving exclusively contralateral input and some primates with predominately ipsilateral input (Magnin, et al., 1989).

In the rat, there is virtually no retinal innervation of the dorsomedial SCN containing most of the VP-IR cells, although the retina provides terminals to the ventral 20-25% of the VP-

IR neuron distribution (Morin, et al., 2006). Both hamster and mouse SCN have substantially greater dorsomedial retinal terminals than the rat (Muscat, et al., 2003; Morin, et al., 2006).

The RHT terminal field in the SCN substantially fills the nucleus, at least for hamster and mouse (Muscat, et al., 2003; Hattar, et al., 2006; Morin, et al., 2006). The rat, with its oblate SCN, presents a somewhat different situation and may represent a true species difference. It is commonly stated that the RHT terminal plexus in the rat occupies the ventrolateral SCN with no dorsomedial SCN innervation (but see Fig. 4 in Moore et al. (2002) for an example of terminal “patches” within the dorsomedial rat SCN). In terms of generalities across species, the important points are, first, that there are regions of dense retinal innervation in all species which grade into regions of less dense or even sparse innervation and, second, there is a far from perfect match between the retinal terminal field (whether tightly or loosely defined) and a particular group of cells. For example, most of the VP cells are found dorsomedially where retinal innervation is sparse, but such cells are also plentiful, especially in mouse, more centrally where retinal innervation is dense. The actual relationship between the retinal terminal field and cell phenotype is known only for CALB-IR cells on which electron microscopy has demonstrated RHT terminals (Bryant, et al., 2000).

Indirect evidence for abundant innervation of the entire SCN comes from studies of light-induced FOS protein. Here also, initial reports from the hamster focused on FOS in nuclei of SCNce neurons (Rusak, et al., 1990), but subsequent studies have demonstrated light-induced FOS throughout the SCN, specifically including VP-IR neurons (Castel, et al., 1997), as well as in adjacent hypothalamus (Guido, et al., 1999; Mahoney, et al., 2001; Muscat and Morin, 2006; Vidal and Morin, 2007). The little appreciated paper by Guido et al. (1999) is noteworthy for several reasons. The authors show (a) that light-induced FOS is present throughout the entire SCN, but is denser in the SCNce region; (b) there is abundant FOS induced in peri-SCN hypothalamus; (c) the intensity of FOS staining in the nucleus of any particular SCN cell varies from pale gray to fully black (i.e., there is cell-specific differential induction, rather than an all-or-none response); (d) the level of FOS induction by light varies according to circadian time; and (e) the spatial distribution pattern of light-induced FOS in the SCN also varies according to time (see also (Romijn, et al., 1996)). These results clearly demonstrate consistency with the view that the SCN is broadly innervated by the retina, but that events at the cellular level must be hindering or facilitating FOS expression according to time of day and locus within the SCN. The incomplete induction of FOS (e.g., pale gray vs black staining) also appears to vary according to region and time of day (Guido, et al., 1999).

From the Geniculohypothalamic Tract

NPY-IR has been the most widely used marker of the GHT terminal field in the SCN. The rat GHT terminal field demarcated by NPY-IR reveals a fairly uniform distribution within the ventral two thirds of the nucleus (Morin, et al., 2006). The region with densest retinal terminals in the rat overlaps the ventral and lateral distribution of NPY terminals (Fig. 3B). In the mouse, NPY-IR terminals appear to be sparser than in either rat or hamster. As with RHT terminals, NPY-IR terminals are very scarce in periventricular SCN, in the region closely correspondent to that containing most of the VP-IR neurons (Card and Moore, 1989; Morin, et al., 2006). The hamster SCN also has few GHT terminals in the dorsomedial SCN region. In fact, there is a relative paucity of NPY-IR terminals around the entire terminal field in the SCN (Morin and Blanchard, 2001). In the mouse, NPY-IR terminals appear to more thoroughly occupy the SCN (especially the perimeter), although the distribution is otherwise similar to that of the hamster (Morin and Blanchard, 2001; Morin, et al., 2006). In all three species, NPY-IR terminals are densest ventro-centrally, grading to a sparse distribution laterally, dorsally and dorsomedially.

In the hamster SCN, three additional terminal fields have been identified as arising from the IGL. Double label retrograde tracing studies identify IGL cells containing ENK-, NT- and GABA-IR cells as projecting to the SCN (Morin and Blanchard, 2001). The distributions of ENK-IR terminals in the SCN are very similar to the NPY terminal distribution. Lesions of the IGL abolish immunoreactivity of terminals in the SCN to NPY, ENK and NT. GABA in the SCN after IGL lesions is confounded with the GABA remaining in all SCN neurons and processes (Moore and Speh, 1993; Morin and Blanchard, 2001).

The calcitonin-gene-related peptide (CGRP) terminals in the mouse SCN (Park, et al., 1993) tend to be ventrolaterally located, with most found on or adjacent to the lateral SCN boundary, extending dorsally and laterally into anterior hypothalamus. CGRP-IR cells are found in the SCN proper, in adjacent hypothalamus, and in the IGL. At the present time, it is not known whether the IGL neurons containing CGRP project to the SCN through the GHT, but the vastly different distribution of CGRP terminals suggests that they are not from the IGL.

From the Median Raphe Nucleus

The serotonergic terminal field in the SCN arises from median raphe neurons and has features common to mouse, hamster and rat. In all three, the serotonergic terminals are found throughout the SCN, but are densest ventrally and medially; density is greatest ventromedially (Fig. 3B). Innervation density gradually becomes sparse dorsally and dorsolaterally; centrally, the innervation is modest (Meyer-Bernstein and Morin, 1996). In the rat, the plexus appears as a medio-laterally oriented ellipse contained within the ventral two thirds of the nucleus and shifted to the medial side, substantially sharing the location with VIP-IR neurons (Morin, et al., 2006). The serotonergic terminals also overlap with the ventral part of the dorsomedial SCN region containing most of the VP-IR neurons. Further dorsally among the VP-IR cells, the serotonergic terminals are sparse. The distributions of the serotonin terminals, retinal terminals and VP-IR neurons, although overlapping, differ in density and distribution to such an extent that under certain evaluation conditions, the rat SCN can be imaged as a three-part layered structure (Fig. 4).

In mouse and hamster, the serotonergic terminal distributions in the SCN are quite similar. The most obvious similarities are the nearly complete innervation of the nucleus, albeit with substantial region-dependent density differences, and the crescent shape of the terminal field pattern (Figs. 3,4). In both hamster and mouse, terminals are quite dense in an arc extending from a dorsomedial point and curving ventrally, laterally and then slightly dorsolaterally. The greatest terminal density is along the medial and ventral SCN border, grading to sparse innervation centrally and very sparse dorsolaterally. There is substantial overlap between the retinal and serotonergic terminals and the dorsomedial region containing most VP-IR cells, but it is not 100%. Because the mouse SCN is upright (unlike the oblate rat SCN), it does not appear layered as in the rat, but does allow clear spatial distinctions between the same two terminal fields and the region of VP-IR neurons, at least with respect to their regions of greatest density.

The rhythm related functions of the serotonergic system have been thoroughly reviewed (Morin, 1999; Mistlberger, et al., 2000). The serotonergic system modulates both photic and non-photoc regulation of the circadian system.

From GnRH neurons

Release of GnRH is under the temporal control of the SCN and results in synthesis and release of luteinizing hormone from the anterior pituitary followed soon thereafter by ovulation (de la Iglesia and Schwartz, 2006; Tonsfeldt and Chappell, 2012). Robust

projections of the gonadotrophin releasing hormone (GnRH) cell system are present in rat and hamster, but descriptions are limited, especially as they relate to the SCN (Jennes and Stumpf, 1980; Merchenthaler, et al., 1984). The hamster GnRH projections are visible as modest innervation of the rostral half of the SCN (Fig. 5A, B). Further caudally, the region of the SCNce is fairly devoid of GnRH fibers and terminals which remain evident dorsomedially and in adjacent hypothalamus ventrally, laterally and dorsally (Fig. 5C,D).

In addition to the SCN afferent GnRH projections, there are SCN efferents that synapse on GnRH cells (De la Iglesia, et al., 1995; van der Beek, et al., 1997; Schwartz, et al., 2011). Thus, there is clear reciprocity between the gonadotropin regulatory and circadian rhythm systems, although it is not known whether the SCN cells contacting GnRH neurons also receive input from GnRH neurons.

From VIP neurons

The events in the foregoing paragraph occur prior to ovulation. If vaginocervical stimulation occurs in the female rat around the time of ovulation, one result is the appearance of two, accurately timed, daily peaks in prolactin secretion (Smith, et al., 1975). These events serve to transform a non-pregnant hypothalamo-hypophyseal-ovarian condition into one that can maintain pseudopregnancy or pregnancy until the corpus luteum becomes functional. The daily prolactin peaks require the presence of a functional SCN and which synchronizes their phase to the prevailing photoperiod (Poletini, et al., 2010).

Prolactin is under inhibitory control by tuberoinfundibular dopamine neurons (Freeman, et al., 2000; Gerhold, et al., 2002), but its release can be stimulated by the posterior pituitary hormone, oxytocin (Arey and Freeman, 1992). Both the infundibular dopamine and paraventricular oxytocin cells receive direct input from VIP neurons located in the SCN with the VIP acting on via VPAC2R receptors (Horvath, 1997; TeclemariamMesbah, et al., 1997; Gerhold, et al., 2001; Gerhold, et al., 2002; Mahoney, et al., 2007). Rhythmic output from the VIP cells is presumed to inhibit both the critical dopamine neurons and the oxytocin neurons with an unknown excitatory factor facilitating oxytocin release from the VIP-inhibited neurons (Egli, et al., 2004; Egli, et al., 2006). Readers are encouraged to explore the large body of work by M.E. Freeman that addresses multiple facets of the neuroendocrine system and its temporal coordination by the SCN.

From other brain regions

The SCN sends projections directly to about 15 regions (depending on the definition of “region”), primarily in the hypothalamus (Watts, et al., 1987; Kalsbeek, et al., 1993; Morin, et al., 1994). In contrast, the SCN receives input from approximately 35 areas revealed by standard retrograde tracing (Table 2). Injection of virus into the SCN to obtain transneuronal retrograde cell labeling reveals approximately 48 additional sites that appear to connect to the SCN via two or more synapses. See Table 1 of Krout et al. (2002) for a large list that identifies regions in which CTB and retrograde transneuronal virus tracer identify cells projecting to the SCN by mono- or multisynaptic pathways. Krout et al. summarize their abundant anatomical observations by categorizing the SCN afferent regions as relating to olfaction, corticoid-sensitive temporal lobe function, chemosensitive circumventricular organ function and autonomically-regulated visceral organ function. Note that many of the brain regions evaluated by Krout et al. (2002) show substantial between-case variability in virus labeling. Definitive judgments regarding whether or not such regions actually project to the SCN are not always possible.

The lateral habenula has recently been proposed as an extra-SCN rhythm regulatory site that primarily modulates the distribution of activity within a “window oscillator” controlled by

the SCN (Paul, et al., 2011). Severance of the fasciculus retroflexus, the primary output pathway of the habenula greatly disrupts the temporal locomotor structure without damaging the overt circadian rhythmicity of hamsters. The habenula is one of the distal structures that projects multisynaptically to the SCN (Krout, et al., 2002). It also receives direct input from the SCN (Kalsbeek, et al., 1993; Morin, et al., 1994). It is likely that the SCN is the target of information arriving directly or indirectly from more than 80 brain areas. Except for the obvious locations (IGL, retina, raphe nuclei) there is very little known about the individual or collective impact of these inputs on circadian rhythm function.

SCN Efferent Pathways

Kalsbeek et al. (1993) used a somewhat unusual method to study SCN efferent anatomy by making lesions in the SCN and determining which neuropeptidergic pathways were lost. The hamster SCN has dense efferent projections immunoreactive to VP, VIP and GRP (Table 3). When the SCN is completely lesioned, these projections are absent, supporting the view that the cells of origin are in the SCN. Projections to the VMH, identified by anterograde tracing with Phaseolus, do not contain any of the three neuropeptides evaluated. Both VP- and VIP-IR projections extend rostrally to contact GnRH cells directly (van der Beek, et al., 1993; Mahoney and Smale, 2005).

There is substantial agreement between the primary publications (Watts and Swanson, 1987; Watts, et al., 1987; Kalsbeek, et al., 1993; Morin, et al., 1994; Canteras, et al., 2011) providing information about rat and hamster SCN efferent projection patterns. Results from a more recent study of the California ground squirrel are consistent with prior results, but the authors have elected to emphasize innervation of a greater number of sub-regions, rather than a more limited number of primary regions (Canteras, et al., 2011). As initially described, there are three major projection patterns (Watts and Swanson, 1987; Watts, et al., 1987) (Fig. 6). Pattern 1, and the most robust, consists of input to the periventricular hypothalamic nuclei, including the several divisions of the preoptic region rostrally, the anterior parvocellular paraventricular nucleus, the subparaventricular zone and retrochiasmatic area, the dorsomedial and ventromedial nuclei and the premammillary area (Watts and Swanson, 1987). The hypothalamic innervation pattern in the rat suggests the presence of three projection zones, the rostral periventricular, the retrochiasmatic and a subparaventricular area that includes more caudal periventricular nuclei. Although the pattern is very similar in the hamster (Kalsbeek, et al., 1993; Morin, et al., 1994), equivalent zonal distinctions were not made because the hypothalamic radiation of efferent projections appears to be broad and non-specific with respect to proximal targets (Morin, et al., 1994). The point deserving emphasis is that hypothalamic nuclei caudal to the SCN are densely innervated by SCN projections in both rat and hamster.

SCN projection patterns 2 and 3 are to the septum and to the anterior paraventricular thalamus plus several divisions of the bed nucleus of the stria terminalis, respectively. In general, the septal innervation pattern is similar for rat and hamster, although the majority of the innervation is seen in the intermediate division of the rat lateral septum, but in the ventral division in the hamster (Watts, et al., 1987; Morin, et al., 1994). In both species, the entire anterior paraventricular thalamic nucleus receives SCN innervation. Innervation from the SCN has also been described for the adjacent parataenial nucleus (Watts and Swanson, 1987; Watts, et al., 1987; Morin, et al., 1994; Leak and Moore, 2001).

A projection to the amygdala has been described (Morin, et al., 1994), but it is more likely that amygdaloid innervation arrives from cells in the retrochiasmatic area. It should be noted that cells in the retrochiasmatic area project to many of the same targets as the SCN (Morin, et al., 1994).

A projection to the intergeniculate leaflet (IGL) has been reported in the rat (Card and Moore, 1989), the cells for which are located in the dorsomedial SCN with larger numbers found in adjacent anterior hypothalamus. The initial hamster report concurred, but was based on anterograde tracing of SCN efferents (Morin, et al., 1994) (see also (Kriegsfeld, et al., 2004)). It appears more likely that hamster SCN neurons do not project to the IGL. Retrograde tracer injected into the IGL labels sparse cells on or adjacent to the dorsal and lateral borders of the caudal SCN, with more in the retrochiasmatic area (Morin, et al., 1992; Morin and Blanchard, 1999), but not in the SCN proper. Retrogradely labeled neurons are seen in the same areas after tracer injection into the hamster IGL, ventrolateral geniculate (VLG), posterior limitans nucleus (PLi), olivary pretectal nucleus (OPT), medial pretectal nucleus (MPT) and commissural pretectal area (CPT) (Morin and Blanchard, 1998). Visualization of such a SCN-IGL projection by anterograde tracing methods may be a false positive resulting because of tracer spillage from the injection site into adjacent hypothalamus or, just as likely, from uptake by peri-SCN neurons which have dendrites extending into the nucleus. Some of these dendritic connections with the SCN are as long as 250 μm (Morin, et al., 1994). The technical difference relating to the exact location of SCN/peri-SCN cells projecting to the IGL may very well be moot with respect to whether or not they acquire information from the SCN convey it to the IGL.

Particular effort has been made to identify multisynaptic pathways from the SCN to the locus coeruleus (LC) and from the SCN to the ventral tegmental area (VTA) (Aston-Jones, et al., 2001; Luo and Aston-Jones, 2009). In each study, Bartha strain pseudorabies virus was injected into the nucleus of interest and the tracer was followed retrogradely to the SCN as neurons became sequentially infected over a 60 hr interval. Simultaneous injection of the tracer, cholera toxin B subunit, revealed the circuit to have a synapse in the DM. This circuit appears to rhythmically modulate LC neuronal activity according to circadian time (Aston-Jones, et al., 2001), possibly regulating rhythmic arousal (Berridge, 2008).

In the case of the VTA, it too receives indirect input from the SCN, but in a more round-about fashion via the medial preoptic nucleus (MPN). Lesions of this area eliminated most cell labeling in the SCN after virus injection in the VTA. As in the LC, neuronal activity is rhythmically regulated, with maximal activity during the activity phase. Thus, a multisynaptic pathway appears able to rhythmically modulate the VTA, a region known to be involved in the regulation of sleep/arousal and reward (Tsujino and Sakurai, 2009).

Organization of SCN cells with efferent projections

The locations of SCN neurons projecting to specific brain regions is the subject of some controversy in part because there have been insufficient studies of the issue. Watts and Swanson (1987) examined SCN innervation of 9 different brain regions and Leak and Moore (2001) explored innervation of 11 brain regions. Detailed comparisons of the two sets of are difficult for several reasons. The Watts and Swanson (1998) study was the first of its kind and, as such, simply documented the positions of cells retrogradely labeled from the various injections. Leak and Moore (2001) provide a more schematic perspective consistent with the basic core and shell model set forth earlier (Moore, 1996). The contrast between the perspectives of the two publications is stark, with Watts and Swanson stating, "At the present time, there is no conclusive evidence for a functional dichotomy between dorsal and ventral parts of the [SCN]." The essential word in that view is "dichotomy." It remains the focus of substantial research efforts directed toward demonstrating different "divisions" of the SCN and that they behave differently with respect to rhythm regulation, as suggested by Moore and colleagues (1996, 2001, 2002).

One technical point is worth emphasizing: no two tracer injections are ever made in the identical location, nor should there any expectation that the pattern of label uptake will be the same after two different injections. Given the small number of cases typically examined in tract tracing studies, the between-injection variability may overwhelm any consistency in the details of the results.

A second point concerns the locations to which groups of SCN neuropeptidergic cells project in the brain. The SCN lesion procedure used by Kalsbeek et al. (1993) specifically addressed this issue in the hamster. They showed that the DM and anterior paraventricular thalamus (PVA) receive moderately robust projections from both VP and VIP cells in the SCN. These cell types are found, in general, in the dorsomedial and ventral SCN, respectively, but retrograde tracer predominately labels cells in the SCN “shell” regardless of whether the injection was made in the DM or PVA (Leak and Moore, 2001). For a more thorough case by case comparison of the Watts and Swanson (1998) injection results with those of Leak and Moore (2001), see (Morin and Allen, 2006). The most important point seems to be that the exact distribution of SCN cells projecting to any target cannot be known at the present time because there are too few cases available for analysis.

Retrograde tracer injections have also been placed in targets of the hamster SCN (Kriegsfeld, et al., 2004). Microscopy images show numerous labeled cells scattered fairly homogeneously across the SCN following an injection in the DMH or ventral LS; and after a VLPO injection, small numbers of labeled cells are seen both in the SCNce and in a dorsal area containing VP-IR neurons. However, insufficient detail is available to support any conclusion about the relationship between tracer injection site and location of retrogradely labeled cells in the SCN of this species.

The above studies agree that the distributions of labeled cells following retrograde label injection are not uniform across the SCN. This result should not be surprising given the clustering of specific neuropeptide-containing cell types in the SCN and their moderately target-specific efferent, neuropeptidergic projections (Kalsbeek, et al., 1993). For example, anterograde Phaseolus tracing of SCN projections reveals a pattern of parataenial thalamic innervation that is closely mimicked by the distributions of VP- and VIP-IR fibers which are eliminated by SCN lesions. Immunohistochemical analysis indicates that VP and VIP neurons have virtually non-overlapping distributions in the SCN. This means that spatially distinct sets of SCN cells project to the same target region.

In their pioneering studies of rat IGL and SCN connections, Card and Moore (1989) injected each IGL with a different retrograde tracer. The results not only demonstrated retrogradely labeled cells in the SCN and peri-SCN region, they provided a unique demonstration that individual SCN neurons project bilaterally to each IGL. This result may be important because it speaks directly to the possibility that individual SCN neurons provide identical phase information to many targets. There has not been a similar study since the Card and Moore effort. Thus, there is presently no information concerning the extent to which individual SCN cells project to multiple targets.

Transneuronal retrograde viral tracer has been injected into the vitreous of the eye (Pickard, et al., 2002; Smeraski, et al., 2004), DM and sPVz (Leak, et al., 1999) and a variety of sympathetic or parasympathetic targets (reviewed in (Bartness, et al., 2001)). Each of these procedures yields cell labeling in the SCN. In the case of retinal injections, the virus appears to infect the SCN via a peripheral route from the eye to the nucleus of Edinger-Westphal, to the olivary pretectal nucleus and IGL, and ultimately to the SCN (Pickard, et al., 2002). An important technical note concerns the fact that the virus does not provide anterograde infection of the SCN via the RHT after an intravitreal eye injection.

To the extent that it is possible to discern from published photomicrographs, virtually all SCN cells eventually appear to be infected with virus (e.g., 60-67 hr after a VTA or paraventricular hypothalamus (Pa) injection (Aston-Jones, et al., 2001; Luo and Aston-Jones, 2009)). There has not been a systematic investigation of the percentage of SCN neurons ultimately infected by transneuronal virus or if there are cell types or regions in the SCN that do not become infected. Such studies would provide useful information regarding the extent to which SCN neurons are interconnected.

Intergeniculate Leaflet Intrinsic Anatomy

The IGL is homologous with the medial division of the cat VLG (Pu and Pickard, 1996; Van der Gucht, et al., 2003; Nakamura and Itoh, 2004) and with the primate pregeniculate nucleus (Moore, 1989; Van der Gucht, et al., 2003). The IGL is a nucleus of relatively large volume despite its typical presentation as a small laminar structure intercalated between the DLG and VLG. The overall length of the IGL is evident by embryonic day 14, well before the final adult shape of the lateral geniculate complex is completed (Botchkina and Morin, 1995).

The hamster IGL contains NPY-, ENK-, NT- and GABA-IR cells that project to the SCN. There does not appear to be any topographical order to the cell types, but there is co-localization of neuromodulators (Morin and Blanchard, 2001). The extent of co-localization varies substantially. About 100% of NT-IR cells contain NPY-IR and 50% of NPY-IR cells also contain NT-IR. About 50% of cells positive for NPY are also positive for ENK-IR, and the opposite is also true. In the rat, the anatomical details for ENK differ from those in the hamster with ENK-IR cells of the IGL projecting to the contralateral IGL and not to the SCN (Card and Moore, 1989; Takatsuji and Tohyama, 1989). All IGL neurons of the rat may contain GABA-IR (Moore and Speh, 1993), but this is not readily apparent in the hamster (Morin and Blanchard, 2001). Abundant CGRP-IR neurons have been demonstrated in the rat IGL, but not reported in other species. (Park, et al., 1993). At least some of these cells project to the contralateral IGL.

The IGL of the mouse, Siberian hamster, golden hamster and rat each contain a robust terminal plexus of SP-IR fibers (Morin, et al., 1992; Moore and Card, 1994; Piggins, et al., 2001). The origin of the SP projection is not known, although it may be from the laterodorsal tegmentum (LDTg) or the pedunculopontine tegmentum (PPTg) both of which have numerous SP-IR neurons (Kohlmeier, et al., 2002) and cells that project to the IGL (Horowitz, et al., 2004).

There is ample literature describing rhythm-related functions of the IGL and the innervation of the SCN by NPY projections through the GHT. Most of the functional studies have been with hamsters. In the rat, one study indicates a role of the IGL in entrainment (Edelstein and Amir, 1999). In the mouse, IGL lesions do not yield responses to constant light that are equivalent to what has been reported after similar lesions in hamsters (Pickard, 1994; Morin and Pace, 2002). However, other mouse studies have indicated that an intact IGL is necessary for rhythm regulation by certain non-photoc stimuli (Marchant and Mistlberger, 1996; Marchant, et al., 1997).

Caution should be observed with respect to attributing all IGL functions exclusively to rhythm regulation or to NPY. It is apparent on anatomical grounds that the IGL has multiple functions (in particular, those related to eye movements during sleep; see below). In addition, NPY cells in the IGL project to pretectal nuclei (Morin and Blanchard, 2001) and could contribute to rhythm regulation via an indirect influence on the SCN. Note, for example, that there do not appear to be direct retinal connections to NPY cells in the IGL (Thankachan and Rusak, 2005), but see (Takatsuji, et al., 1991)). Although light

induces FOS protein in IGL neurons, including some that contain NPY (Janik, et al., 1995; Muscat and Morin, 2006), light-induced FOS is seldom found in cells projecting to the SCN (Peters, et al., 1996; Muscat and Morin, 2006). An explanation for the observation of light-induced FOS in NPY-IR IGL cells may lie with the fact that such cells also project to the pretectum. Retrograde tracer injected into the pretectum co-localizes with light-induced FOS-IR in IGL cells (Muscat and Morin, 2006) and there are abundant NPY- and ENK-IR projections from the IGL to the pretectum (Morin and Blanchard, 1997). The two results (Thankachan and Rusak, 2005; Muscat and Morin, 2006), suggest the presence of interneurons or other intervening cells between the retinal terminals and cells of origin of the GHT.

It should also be noted that novel wheel access induces FOS in both NPY and non-NPY neurons in the IGL (Janik and Mrosovsky, 1992; Janik, et al., 1995), but not in cells projecting directly to the SCN (Muscat and Morin, 2006). While the behavioral data strongly support the view that NPY released by GHT terminals in the SCN regulates circadian phase in response to certain non-photic stimuli (Johnson, et al., 1988; Biello, et al., 1994), the pathway by which those stimuli gain access to and influence the activity of IGL neurons is obscure.

The pretectum and/or deep superior colliculus are implicated in the regulation of triazolam-, but not novel wheel-induced, circadian rhythm phase control (Marchant and Morin, 1998). Electrical stimulation of the same region greatly attenuates light-induced phase shifts. These subcortical visual areas have substantial interconnections with the IGL (Morin and Blanchard, 1998), possibly accounting for the ability of pretectal/tectal and IGL lesions to block the response to triazolam. In the rat, the phenomenon of dark-induced REM sleep is also prevented by lesions of the pretectum/superior colliculus (Miller, et al., 1998; Miller, et al., 1999), but there is no information as to whether the IGL is a part of the sleep-regulatory circuitry.

IGL Efferent and Afferent Connections

Tracing studies have elaborated on the degree of IGL connectivity to the point of demonstrating projections to over 100 brain regions (Mikkelsen, 1990; Morin and Blanchard, 1998; Morin and Blanchard, 1999; Moore, et al., 2000; Morin and Blanchard, 2001; Vrang, et al., 2003). Three principles of IGL connectivity have emerged: 1) Abundance - the projections include many targets; 2) Bilaterality - most IGL projections are bilateral, a feature that is particularly evident in the subcortical visual shell; and 3) Reciprocity - about half the regions receiving IGL projections send efferents back to the IGL (Fig. 2; see (Morin and Blanchard, 2005) and (Morin and Blanchard, 1998) for a discussion). These attributes are not exclusive to the IGL, but are also characteristic of adjacent ventral thalamic nuclei, including the VLG, subthalamic nucleus and zona incerta (Harrington, 1997; Morin and Blanchard, 1998; Morin and Blanchard, 1999; Power and Mitrofanis, 2001; Horowitz, et al., 2004; Morin and Blanchard, 2005). Notably, the IGL projects to most regions innervated by the SCN (Fig. 6).

There is very little known about the function of the vast majority of IGL efferent and afferent pathways. The GHT is the exception to that rule. Nevertheless, clues to function reside in the anatomy. One such is the fact that the IGL is innervated by orexin (hypocretin) neurons residing in the lateral hypothalamus and zona incerta (McGranaghan and Piggins, 2001; Mintz, et al., 2001; Nixon and Smale, 2004; Vidal, et al., 2005). A primary function of the OX system is sleep regulation (Sakurai, 2007; Burt, et al., 2011). The circadian basis of sleep can theoretically be influenced via direct SCN projections to OX-IR neurons (Abrahamson, et al., 2001; Schwartz, et al., 2011), but other studies suggest that there is

little if any direct innervation of OX neurons by the SCN (Sakurai, et al., 2005; Yoshida, et al., 2006). The sleep-regulatory cells in the VLPO receive direct and indirect SCN input (Novak and Nunez, 2000; Chou, et al., 2002; Deurveilher and Semba, 2003) and sleep may be regulated through multisynaptic routes to brain stem sleep regulatory nuclei via OX projections to the IGL (Morin and Blanchard, 2005) or through the locus coeruleus or the ventral tegmental area (Aston-Jones, et al., 2001; Luo and Aston-Jones, 2009).

The IGL, because of its particular distribution of efferents, could conceivably act as a funnel through which rhythmically governed sleep regulatory information is distributed. Of potentially great, but unexplored importance, are the IGL projections to brain nuclei known to be involved with visuomotor, sleep functions, or the orexin system (Table 4). The IGL projects to 38 of 45 nuclei (84.4%) concerned with visuomotor function; to 14 of 16 nuclei (87.5%) concerned with sleep; and 57 of 65 areas (87.6%) bearing OX terminals. In addition, the IGL receives input from the medial vestibular nucleus (MVe), a region involved in maintaining equilibrium and coordination of head and eye movements (Leigh and Zee, 1999; Leigh and Zee, 1999) and possibly circadian rhythm regulation (Fuller, et al., 2002; Fuller and Fuller, 2006). The IGL also projects to many (36) regions innervated by MVe cells. A more thorough presented of the relationship between the several systems, the IGL connections and areas with MVe connections is provided elsewhere (see Table 1 in Morin and Blanchard, 2005). The MVe also projects to 12 out of 16 sleep-related nuclei and to 25 of 45 visuomotor nuclei, providing an anatomical rationale for the MVe being a regulator of eye movements during sleep as suggested earlier by lesion studies (Pompeiano and Morrison, 1965; Pompeiano and Morrison, 1966). The abundant connectivity of the IGL to sleep, equilibrium, and visuomotor control areas (Fig. 7) supports the view that, in addition to its role in circadian rhythm regulation, a second major function of the IGL concerns the control of eye movements during sleep.

Dozens of brain regions project to the IGL with the theoretical possibility that each could influence SCN function via the GHT. This is not likely, as demonstrated by studies involving injection of transneuronal virus tract tracer into the SCN. One clear result from this procedure is the absence of labeled neurons in the superior colliculus or lateral pretecal nuclei (Krout, et al., 2002; Horowitz, et al., 2004). This contrasts with the many retrogradely labeled cells present in those areas following CTB tracer injection in the IGL (Morin and Blanchard, 1998; Horowitz, et al., 2004). These observations demonstrate the existence of at least two functional sets of IGL cells, those that receive inputs from the visual midbrain, but do not project to the SCN, and those that project to the SCN, but do not receive input from visual midbrain. The former are likely to be concerned with visuomotor functions of the midbrain, and the latter with circadian rhythm regulation (Horowitz, et al., 2004).

The serotonergic system contributes to circadian rhythm regulation either through its direct projection from the MnR to the SCN or via an indirect DR projection to the IGL. There is evidence supporting function of both routes to the extent that electrical stimulation of DR or MR elicit similar behavioral and physiological responses-related pathways are involved in circadian rhythm function (Meyer-Bernstein and Morin, 1999; Glass, et al., 2003). In fact, under normal conditions, both DR and MR projections may participate in rhythm regulation because of their reciprocal connections (Tischler and Morin, 2003). See Fig. 5 in Morin and Allen (2006) for a diagrammatic representation of redundant routes for achieving serotonergic regulation of the circadian system by either the DR or the MnR.

Anatomy of the Human Circadian System

The literature concerning the intrinsic anatomy of the human SCN is sparse, as are studies of SCN connectivity. Readers are referred to the body of work by J.P. Dai, D.F. Swaab,

R.M.Buijs and colleagues describing RHT in relationship to VP, VIP and neurotensin cell distributions (Dai, et al., 1998), co-localization of VIP and VP in SCN cells (Romijn, et al., 1999), SCN-efferent VP and VIP projections (Dai, et al., 1997), anterogradely labeled SCN efferent projections (Dai, et al., 1998), and afferent connections with the DMH (Dai, et al., 1998). There are several noteworthy differences reported between the human data and results from rodents such as unexpected co-localization of VIP and VP and the sparse, limited distribution of retinal fibers in the hypothalamus. Also of note is an earlier publication (Moore, 1989) describing the presence of an IGL in monkey and human, as indicated by NPY cell and fiber labeling. This study also noted a monkey-rodent difference with the human SCN to the extent that the human SCN contains NPY-IR neurons whereas the other species do not.

Summary

On the one hand, there is a large degree of complexity in the retina with respect to how the three photoreceptor classes provide visual information to the circadian system. On the other hand, the product of complex photoreception appears to be simplified in the process of being funneled through ipRGCs to the SCN where it acts on individual circadian clock cells (first order oscillators) to modulate overall SCN circadian rhythm phase and period. Although the cell groups in the SCN have been well described, there is still little information regarding how the cells connect together or what each phenotype contributes to circadian rhythm regulation. The generation and maintenance of stable SCN rhythmicity appears to be the interactive product of rhythmic gene expression in SCN neurons and the complex interaction of many rhythmic cells (second order oscillation). The SCN, as master circadian clock, provides phase-regulatory information to a relatively modest number of brain regions, but receives input from many additional locations. Thus, there is another layer of complexity, one by which the SCN efferent and afferent anatomy creates potential third order oscillatory circuits feeding back on the SCN to modify the baseline rhythmicity. It is even conceivable that expression of molecular clockworks in brain regions having input to the SCN may contribute to a greater circadian system than has been described here (see (Guilding and Piggins, 2007) for a review).

Single and multisynaptic connections provide communication between the SCN and other systems, especially the hypocretin and sleep systems. Such communication is two-way, there being clear anatomical routes by which oscillatory behavioral systems can modify circadian rhythmicity. One such pathway is the GHT through which the IGL and a great many brain areas have real or theoretical direct access to the SCN. In addition to the GHT, the IGL projects to many brain regions with both SCN efferents and afferents. The broad, reciprocal connections between the IGL and the SCN add a third layer of theoretical circuitry that may contribute to rhythm regulation. Further, the anatomical relationships between the sleep/vestibular/visuomotor systems create the strong possibility that the IGL regulates eye movements during sleep. The simple fact about the circadian system anatomy is that there are a great many possible circuits that may be involved in rhythm regulation, but only a small fraction have thus far been evaluated for possible inclusion as part an extended circadian rhythm system.

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ABBREVIATIONS

3	Oculomotor N
4	Trochlear N
AAA	Anterior amygdaloid area
AD	Anterodorsal thalamic N
AH	Anterior hypothalamic N
AHi	Amygdalohippocampal zone
APT	Anterior pretectal N
APTd	Anterior pretectal N, dorsal
APV	Anteroventral periventricular hypothalamic N
Bar	Barrington's N
BNST	Bed N. stria terminalis
BNSTpm	Bed N. stria terminalis, posteromedial
CGM	Central gray, medial part
CGPn	Central gray, pontine
Cl	Clastrum
CL	Centrolateral thalamic N
CLi	Caudal linear raphe N
CM	Centromedian thalamic N
CnF	Cuneiform N
CPT	Commissural pretectal N
DA	Dorsal hypothalamic area
Dk	N darkschewitsch
DLG	Dorsal lateral geniculate N
DLPAG	Dorsolateral periaqueductal gray
DM	Dorsomedial hypothalamic N
DMPAG	Dorsomedial periaqueductal gray
DpG	Superior colliculus, deep gray layer
DPGi	Paragigantocellular N, dorsal
DpMe	Deep mesencephalic, N
DpWh	Superior colliculus, deep white layer
DR	Dorsal raphe N
DT	Dorsal terminal N
EW	N Edinger-Westphal
GHT	Geniculohypothalamic tract
GiA	Gigantocellular reticular N, alpha part
GiV	Gigantocellular reticular N ventral part
IGL	Intergeniculate leaflet
IMLF ²	Interstitial N, medial longitudinal fasciculus
InG	Superior colliculus, intermediate gray layer

Int	Interposed cerebellar N
InWh	Superior colliculus, intermediate white layer
IOM	Inferior olive, medial N
IOPr	Inferior olive, principal N
IRt	Intermediate reticular N
KF	Kölliker-Fuse N
LC	Locus coeruleus
LD	Laterodorsal thalamic N
LDTg	Lateral dorsal tegmental N
LDTgV	Lateral dorsal tegmental N, ventral part
LH	Lateral hypothalamic N
LOT	N Lateral olfactory tract
LP	Lateral posterior N
LPAG	Lateral periaqueductal gray
LPBC	Lateral parabrachial N, central part
LPBE	Lateral parabrachial N, external part
LPBS	Lateral parabrachial N, superior part
LPGi	Lateral paragigantocellular N
LPO	Lateral preoptic N
LS	Lateral septum
LSV	Lateral septum, ventral
LT	Lateral terminal N
LVe	Lateral vestibular N
MA3	Medial accessory oculomotor N
MeA	Medial amygdala
Med ³	Medial (fastigial) cerebellar N
MnR	Median raphe N
MPAG	Medial periaqueductal gray
MPN	Medial preoptic N
MPO	Medial preoptic area
MPT	Medial pretectal N
MT	Medial terminal N
MTu	Medial tuberal N
MVe	Medial vestibular N
NOT	N optic tract
Op	Superior colliculus, optic nerve layer
OPT	Olivary pretectal N
ot	Optic tract
ox	Optic chiasm
Pa	Paraventricular hypothalamic N

PAG	Periaqueductal gray
PaPA	Paraventricular hypothalamic N, anterior parvicellular
PaR	Pararubral N
PCRt	Parvicellular reticular N
PH	Posterior hypothalamus
Pir	Piriform cortex
PLi	Posterior limitans N
PM	Premammillary N
PMnR	Paramedian raphe N
PnC	Pontine reticular N, caudal part
PnO	Pontine reticular N, oral part
PnV	Pontine reticular N, ventral part
POA	Preoptic area
PP	Peripeduncular N
PPT	Posterior pretectal N
PPTg	Pedunculopontine tegmental N
Pr	Prepositus N
PrC	Precommissural N
PT	Parataenial thalamic N
PVA	Paraventricular thalamic N, anterior
PVP	Paraventricular thalamic N, posterior
RCh	Retrochiasmatic area
Re	N Reuniens, thalamus
RHT	Retinohypothalamic tract
RIP	Raphe interpositus N
RLi	Rostral linear raphe N
RMg	Raphe magnus N
RPa	Raphe pallidus N
RRF	Retrorubral field
RtTg	Reticulotegmental N, pons
S	Subiculum
SC	Superior colliculus
SCN	Suprachiasmatic N
SON	Supraoptic N
sox	Supraoptic commissures
SPTg	Subpeduncular tegmental N
SpVe	Spinal vestibular N
sPVz	sub-Paraventricular hypothalamic zone
SU3	Supraoculomotor periaqueductal gray
SubCA	Subcoeruleus N, alpha part

SubG	Subgeniculate N
SuM	Supramammillary N
SuVe	Superior vestibular N
Tu	Olfactory tubercle
VLG	Ventral lateral geniculate N
VLPO	Ventrolateral Preoptic N
VLtg	Ventrolateral tegmental area
VMH	Ventromedial hypothalamic N
VTa	Ventral tegmental area
ZI	Zona incerta
Zo	Superior colliculus, zonal layer

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Figure 1.

Schematic showing the approximate locations of cell phenotypes in the hamster SCN. The regional boundaries are “fuzzy” and should not be rigidly applied. Also, the schematic applies only to the mid-caudal part of the SCN where the SCNce is evident. For example, both VP and CCK cells occupy most of the rostral third of the nucleus. The black dots ventrolaterally signify the presence of a few CCK neurons at that location. VP – vasopressin; SS – somatostatin; CCK – cholecystokinin; SP – substance P; CALB – calbindin; CALR – calretinin; GRP – gastrin releasing peptide; VIP – vasoactive intestinal polypeptide. The figure is modified after Fig. 1 in Morin and Allen (2006).

Figure 2.

Diagrammatic representation of brain regions receiving retinal input from melanopsin-containing ipRGCs (blue lines; red fill) in the mouse (data from (Hattar, et al., 2006; Ecker, et al., 2010)). The figure also identifies retinorecipient regions not innervated by ipRGCs (unfilled). Connections of the IGL with nuclei of the subcortical visual shell are also shown (green lines). The reciprocal connections between the DR and MnR, and the MnR to SCN projections are identified by yellow fill and yellow lines. The figure is modified after Fig. 21.3 in (Morin, 2012).

Figure 3.

SCN schematic showing the relative positions of (A) retinal terminal fields, and (B) geniculohypothalamic tract terminal field (left side) containing terminals from four IGL neuron classes (NT – neurotensin; NPY – neuropeptide Y; ENK – enkephalin; GABA – gamma amino butyric acid) and (right side) the variably dense serotonergic (5-HT – serotonin) terminal field. In (A), the red area indicates the region of densest retinal input which arrives predominately from the contralateral retina. The green region indicates the area receiving input predominately from the ipsilateral retina. Note that the density is not uniform for any terminal distribution. As for Fig. 1, the boundaries should not be rigidly applied. The figure is modified after Fig. 1 in Morin and Allen (2006).

Figure 4.

Triple label images of SCN anatomy in (A) the rat and (B) mouse stained for vasopressin (blue), serotonin (green) and retinal projections (red). The yellow color does not indicate co-localization. Rather, it results from merging information from adjacent red and green pixels or because green and red items are superimposed in the original tissue. The oblate rat SCN enables the triple stain procedure to give the tissue a laminar appearance not visible in the more upright SCN of the mouse. The figure is modified after Figs. 5 and 8 in Morin et al. (2006).

Figure 5.

(A) Parasagittal section through the hamster SCN showing GnRH fibers and terminals in rostral part of the nucleus and surrounding hypothalamus, but absent from the caudal SCN (arrow). (B-D) Coronal images of the SCN showing GnRH fibers and terminals in the SCN and adjacent hypothalamus, but also showing their absence from the SCNce (arrow). ox – optic chiasm; sox – supraoptic commissure. Bar = 100 μ m.

Figure 6.

Schematic showing diencephalic and basal forebrain areas receiving projections from the SCN (black pathways) and IGL (red pathways). Blue fill identifies regions receiving input from both SCN and IGL; those receiving only IGL input have red fill. One region (PM) has yellow fill and is the only target of SCN projections that does not also receive input from the IGL. Line thickness indicates relative size of the projection. See the list of Abbreviations for anatomical names.

Figure 7.

Schematic presentation emphasizing the relationship between the IGL and sleep-regulatory nuclei (red fill), nuclei of the orexin system (blue fill and blue projections), nuclei of the visuomotor system (green fill or green outline) and the vestibular system (purple fill and purple projections). The dotted line between the MVe and superior colliculus indicates that only the deep gray later is connected reciprocally with the MVe, although there is also an intermediate gray projection to MVe. The GHT is indicated by the thick dashed line from IGL to SCN and the putative reciprocal connection by thinner dotted line.

Brain nuclei with retinal terminals received via the retinohypothalamic tract and connections of those nuclei with the IGL and SCN.^{a b}

Table 1

Retinorecipient Nuclei	From IGL	To IGL	From Retina	From SCN	To SCN
AH	++	+/-	+++	+	+
DA	+	--	+	+	+
DM	+	--	+	+	+++
LH		--		--	++
LPO, ventral	+	--	+	--	--
Pa		--	+/-	+	+
Re	+++	--	+/-	+	--
sPVz	+	+	++		+++
SCN	++++	c	+++++	d	d
MTu	+	+/-	+	+	**
VLPO	++	--		+	++
VMH	++	--	+	--	+++

^abased on data from (Morin, et al., 1994; Moga and Moore, 1997; Morin and Blanchard, 1999; Moore, et al., 2000; Krout, et al., 2002)

^b-- no evident connection; +/- very sparse; +sparse; ++ moderate; +++ dense; ++++ very dense

^cin the rat, SCN cells may project to the IGL as determined by retrograde tracer(Card and Moore, 1989), but in the hamster, the such labeled cells lie on the border or just outside the SCN as do cells projecting to other parts of the subcortical visual shell(Morin, et al., 1992; Morin and Blanchard, 1998; Morin and Blanchard, 1999)

^dcells project to the contralateral SCN

Table 2Brain regions projecting directly to the rat SCN^a

Amydalohippocampal zone	Lateral septum	Parastriatal N
Anterior Hth N	Laterodorsal tegmental N	Paraventricular thalamic N
Anterodorsal preoptic N	Locus coeruleus	Piriform cortex
Anteroventral periventricular Hth N	Medial amygdala	Posterior Hth N
Anteroventral preoptic N	Medial preoptic area	Precommissural N
Arcuate N	Medial preoptic N	Subfornical organ
BNST, principal N	Medial pretectal N	Subparaventricular zone
Clastrum	Median preoptic N	Tuberomammillary N
Dorsal Hth area	Median raphe N	Ventral subiculum
Dorsomedial Hth N	N incertus	Ventromedial Hth N
Infralimbic cortex	Olivary pretectal N	Zona incerta
Intergeniculate leaflet	Parabrachial N	

^abased on data from (Moga and Moore, 1997; Krout, et al., 2002), using the nomenclature of Krout et al.

Neuropeptide projections in the hamster brain that originate from cells in the SCN (after Kalsbeek et al., 1993).

Table 3

Structure & SCN input ^a	VP		VIP		GRP	
	present	from SCN	present	from SCN	present	from SCN
BST	+	no	yes	no	yes	no
LSv	+	no	yes	no		
POA	+	partly	sparse	yes		
MPN	+	partly	sparse	yes		
PVA	+	yes	yes	yes	yes	yes
PVP	+	no			yes	no
APV	+	yes			yes	no
PVN	+	yes	yes	yes	yes	yes
subPVN ^c	+	no	yes	yes	yes	yes
DMH	+	yes	yes	yes	yes	yes
VMH	+	no	no	no	no	no
SON	+	no	no	no	yes	yes
Ce	–	no	yes	no	yes	no
LHb	+	no				
IGL	–	no	no	no	yes	no

^aSCN input to the various nuclei is from PHAL tracing in hamster (Morin et al., 1994) except for the updated IGL information (see text);

^byes, in mouse and rat;

^cequivalent to the upper retrochiasmatic region in Morin et al. (1994)

Table 4

Relationship between brain regions with direct IGL efferent or afferent connections and visuomotor, sleep, or orexin systems

	Functional Systems			Projections	
	Visuomotor	Sleep	Orexin	From IGL (PHAL)	To IGL (CTB)
<i>Hypothalamus</i>					
DM	+	+	+	+	-
MTu	+	+	+	+	+
VLPO	+	+	+	+	-
subPVz	+		+	+	+
<i>Thalamus</i>					
IGL	+		+	+	+
PP	+		+	+	+
VLG	+		+	+	+
ZI	+		+	+	+
<i>Pretectum</i>					
APT	+			+	+
CPT	+		+	+	+
NOT	+	I_{+}		+	-
OPT	+	I_{+}	+	+	+
PLi	+		+	+	+
<i>Superior colliculus</i>					
DpG	+		+	+	+
DpWh	+		+	+	-
SuG	+		+	+	+
InG	+		+	+	+
InWh	+		+	+	+
Op	+		+	+	+
Zo	+		+	+	-
<i>Accessory optic nuclei</i>					

	Functional Systems			Projections	
	Visuomotor	Sleep	Orexin	From IGL (PHAL)	To IGL (CTB)
DT	+		+	+	+
LT	+		+	+	+
MT	+		+	+	+
<i>Periaqueductal gray</i>					
DLPAG		+	+	+	+
DMPAG			+	+	+
LPAG		+	+	+	+
MPAG		+	+	+	+
<i>Oculomotor complex</i>					
3	+			+	-
4	+			+	-
Dk	+			+	+
EW	+		+	+	-
IMLF ²	+			+	-
MA3	+			+	-
SU3	+		+	+	+
<i>Additional midbrain nuclei</i>					
ChF			+	+	+
DpMe			+	+	+
LDT _g		+	+	+	+
LDT _g V		+	+	+	+
PaR	+		-	+	+
PPT _g	+	+	+	+	+
PR			-	+	-
RRF			+	+	+
VLT _g			+	+	-
<i>Raphe nuclei</i>					
CLi		+	+	+	-

	Functional Systems			Projections	
	Visuomotor	Sleep	Orexin	From IGL (PHAL)	To IGL (CTB)
DR	+		+	+	+
MnR			+	-	-
PMnR			-	+	-
RIP	+		-	+	-
RLi			+	+	-
RMg			+	+	-
RPa			+	+	-
<i>Pontine Region</i>					
Bar			+	-	+
CGM			+	+	-
CGPh			+	+	-
KF			+	+	-
LC	+	+	+	-	+
LPBC			+	+	-
LPBE			+	+	-
LPBS			+	+	-
PnC			+	+	+
PhO		+	+	+	+
PnV			+	+	-
RtTg	+		+	+	-
SPTg			+	+	+
SubCA		+	+	-	-
<i>Medullary Region</i>					
DPGi	+	+	+	-	-
GiA			+	+	-
GiV			+	+	-
IOM	+			+	-
IOPr	+			+	-

	Functional Systems			Projections	
	Visuomotor	Sleep	Orexin	From IGL (PHAL)	To IGL (CTB)
IRt			+	+	-
LPGi	+		+	+	-
LVe	+			-	+
MVe	+		+	-	+
PCRt	+		+	+	-
Pr	+		+	-	B
SpVe	+		+	-	+
SuVe	+		-	-	+
<i>Cerebellum</i>					
Int	+		+	+	-
Med ³	+		+	-	-

See Morin & Blanchard (2002) for references regarding the functional systems.

¹ OPT and/or NOT

² IMLF, same as interstitial nucleus of Cajal

³ Med, same as fastigial nucleus