Ann. Ist. Super. Sanità, vol. 29, n. 4 (1993), pp. 501-510

Chronobiology: neural pacemakers of biological rhythms *

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Summary. - Biological rhythms are ubiquitous being demonstrable of any level of organization in living matter. However, the myriad of biological oscillators in peripheral organs are organized and synchronized by special structrure, i.e., biological clocks, mostly located in central nervous system. Neural pacemakers show intrinsic properties which are illustrated and discussed. Understanding the meaning and function of neural oscillators is fundamental for those who wants to know how the biological structure of time is processed in living systems.

Key words: biological rhythms, endogenus oscillators, oscillatory structures, pacemakers.

Riassunto (*Cronobiologia: gli oscillatori biologici neurali dei ritmi biologici*). - I ritmi biologici sono ubiquitari nella natura vivente, essendo ritrovabili ad ogni livello della organizzazione biologica. La miriade di siti biologici degli organi periferici è organizzata e sincronizzata da speciali strutture centrali, i cosiddetti orologi biologici, locati principalmente nel sistema nervoso centrale. I pacemakers neurali mostrano proprietà specifiche che qui sono illustrate e discusse. Capire il significato e la funzione degli oscillatori biologici neurali significa comprendere come la struttura biologica del tempo è organizzata nei sistemi viventi.

Parole chiave: ritmi biologici, oscillatori endogeni, strutture oscillatorie, pacemakers.

Introduction

A host of experiments involving mainly rats and hamsters have led to the recognition of the suprachiasmatic nuclei (SCN) of the hypothalamus as the site of an endogenous circadian oscillator in mammals [1, 2]. Using an autoradiographic tracing method, Moore [3] demonstrated a direct neuronal connection between the retina and the SCN in the rat, the retino-hypothalamic projection (RHP). In addition to this anatomical finding there is other empirical support for the assumption that the SCN are a major pacemaker. Many behavioural circadian rhythms are abolished by complete bilateral SCN lesions or surgical isolation [4]. Electrical stimulation of the SCN alters the phase of circadian rhythms in locomotor activity in rodents [5]. With the aid of the 2 DG-method, Schwartz *et al.*, [6] demonstrated a circadian rhythm in metabolic activity in the SCN, glucose utilization being high during the light period. No other brain area exhibit a similar rhythm. In accordance with this are electrophysiological studies [7], showing that *in vivo* and *in vitro* the multiunit activity within the SCN is high during the light period, low during darkness.

From the anatomical point of view the SCN are two small nuclei lying immediately above the optic chiasm. Each nucleus contains about 10.000 neurones. There is also anatomical evidence that the SCN in the rat has at least three subdivisions. A rostral part, about one-fourth of the total nucleus, that contains small neurons with a scant cytoplasm and relatively few organelles. The few dendrites have a limited arborization [8]. The caudal part consists of a dorsomedial part, quite similar to the rostral part. The neurones of the ventrolateral part are larger with more cytoplasm and a more extensive dendritic arborization. This latter region is characterized by the presence of the terminals of the RHP. Using classical neuro anatomical techniques van den Poll [9] described that SCN neurones have relatively simple dendritic arbors. He identified simple bipolar, curly bipolar, radial, monopolar and spinous multipolar cells. At the ultrastructural level Gueldner [10] described two types Gray I type synapses and three types Gray II types. The compartimentalization of the SCN is further supported by histochemical studies. Three groups of neuropeptide containing cells are found within the nucleus. Vasopressin-containing neurones are located exclusively in the rostral and dorsomedial part. Vasoactive intestinal peptide is present in neurones of the ventrolateral part, whereas neurons containing somatostatin, substance-P or avian pancreatic polypeptide are present throughout the whole SCN. In addition, a number of other peptides is found in terminals. Serotonin and moluscan cardioexcitatory peptide containing fibres are found in the ventral portion of the SCN, whereas fibres containing leu-enkephalin and cholecystokinin are found in the area immediately surrounding the border of the SCN. Terminals in this region prob-

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ably innervate dendrites extending outside the cellular area of the SCN. It is an intriguing but as yet unsolved problem why so many neuropeptides are localized within the SCN.

The SCN as an endogenous oscillator

A pacemaker function of the SCN has been suggested in many studies in which complete bilateral lesions or surgical isolation of the SCN abolished various circadian rhythms in rodents [4]. These experiments, however, are not conclusive in addressing the question whether the SCN is a pacemaker of circadian rhythmicity. First, the SCN may function as a relay station for those particular rhythms that are abolished after SCN lesions. The demonstration that disruption of several afferent connections (e.g. from the eyes, the ventral lateral geniculate nucleus and the raphe nuclei) fails to abolish freerunning activity patterns does not solve this problem since other, undisrupted, inputs may be responsible for maintaining the activity rhythm. Second, physical injury that causes neurons to die will bring about permanent changes in the structure of the nervous system and this structural change is usually accompanied by long-lasting alterations in the functions of the affected areas [11]. Such secondary effects of SCN lesions may not be restricted to the SCN.

In several studies, a non-destructive technique was used to investigate the pacemaker function of the SCN [5, 12-17]. Electrical stimulation of the SCN in hamsters and rats resulted in phase-dependent phase shifts of the freerunning activity cycle [5]. Phase shifting effects are also observed after local stimulation of the SCN with neuropeptide Y [13], with the cholinergic agonist carbachol [16] and with glutamate [15]. Local application of the protein synthesis inhibitor anisomysin also induces phase dependent phase shifts [17]. In all these cases the demonstration that stimulation of the SCN phase shifts circadian rhythms implies that the SCN drives rhythmicity by imposing its oscillation on structures located elsewhere in the animal.

When suprachiasmatic tissue of young embryos is transplanted into the anterior chamber of the eye or in the lateral, third or fourth ventricle, differentiation and growth occurs [18-20]. Implantation of suprachiasmatic tissue of rat fetuses in the third ventricle results in a number of efferent connections. Vasopressinergic connections have been observed to the medial preoptic area, the periventricular and dorsomedial hypothalamic nuclei, the paraventricular nucleus of the thalamus and hypothalamus, the retrochiasmatic area, the arcuate nucleus and to the SCN of the host brain, four to six weeks after the implantation [20]. Iontophoretic application of the orthograde tracer *Phaseolus vulgaris* leucoagglutinin in the graft (after at least 14 weeks following the transplantation) resulted only in a few labeled fibers in the adjacent host hypothalamus [21]. These results show that transplanted SCN tissue grows with (few) efferents into the surrounding brain areas.

Fetal or neonatal suprachiasmatic tissue has also been transplanted in host animals that had previously received a SCN lesion. Such transplantations could restore rhythmicity of the behavioral activity and drinking rhythm [22-25]. Rhythmicity was restored in blinded host animals as well as in rats that were exposed to a light-dark cycle or constant darkness. In one of these studies [21] extensive histological inspection afterwards revealed that unsuccessful grafts were characterized by an incomplete immunostaining for several neuropeptides (vasoactive intestinal polypeptide, neuropeptide Y, somatostatin and neurophysin or vasopressin). This may suggest that the organization of peptides within the SCN is critical for locomotor rhythmicity [21]. On the other hand, a well organized peptidergic structure of the transplanted SCN may reflect an overall well developed structure of this tissue.

In summary, it can tentatively be concluded that the SCN is not merely a circadian oscillator but also functions as a circadian pacemaker. As yet, we lack criteria by which SCN neurons that are part of the rhythm generating mechanism can be recognized. As a result, the distinction between the afferents of the circadian pacemaker and the pacemaker of the SCN itself is arbitrary. For instance, visual responsive cells of the mammalian SCN can be considered as input to the pacemaker. However, they could just as well be part of the rhythm generating mechanism. The same is true for the neurotransmitters that are present within the SCN. The phase shifting effects of these transmitters may indicate that they are of importance for photic entrainment (or entrainment to other physiological processes). Alternatively the induced phase shifts could also reflect that these substances are involved in mutual entrainment of groups of pacemakers (or pacemaker cells) inside the SCN. This latter possibility holds especially for transmitters that are implicated in suprachiasmatic inter-neurons (such as GABA).

On the other hand, the properties of suprachiasmatic cells, as they are determined by electrophysiological experiments, may be primarily of importance for entrainment of the pacemaker and may not be relevant for the generation of rhythms.

Are single neurons or a network involved?

According to Moore [26] the SCN neurones are initially produced as a set of genetically determined, independent oscillators that become interconnected during development so that individual neuronal function now becomes a network function. Firstly, each SCN is interconnected with the contralateral SCN by a highly topographically ordered fibre system. Neurones of a individual SCN subsequently differentiate probably into at least two neuronal networks within the SCN, a ventrolateral and a dorsomedial group including a rostral component. This fits with the results of experiments described by Rietveld [27]. Electrolytic lesions of the rostral part of both SCN in blinded rats alter the period of

their freerunning behaviour. After such partial lesions the rhythms in locomotor activity, food and water intake, in body temperature as well as in urine corticosterone return within a period of 30-60 days but now with a shorter freerunning period than before the lesion. Complete lesions of the whole SCN as well as lesions of the caudal part completely disrupt all circadian rhythmicity (suggesting a dual oscillator system). As for the generation of circadian rhythms synaptic interactions between SCN cells are important. Infusion of tetrodotoxin (TTX) into the SCN of unanesthetized and unrestrained rats blocks the function of input and output pathways without affecting the actual oscillatory mechanism of the nuclei itselves [28]. Drinking activity disappeared during infusion of TTX during 14 days, but reappeared with a phase that could be predicted by extrapolation of the period length before infusion. This suggests that intercellular communication plays a role in the synthesis of the oscillation. Ca-dependent spike activity or graded Ca-dependent release of neurotransmitters playing a role more than by firing all-or-none spikes. Also glia-neuronal inetractions may play a role in circadian rhythm generation. Morin *et al.*, [29] describe a dense GFAP-like immunoreactivity in the SCN suggesting that astrocytes are involved, either by producing a specific trophic substance required for maintenance of the clock function or by enhancing the neuronal communication. SCN astrocytes have extensive gap junctions which could facilitate intranuclear communication. In addition it is noteworthy that astrocytes contain numerous specific receptors [30]. So neuropharmacological effects might be due to an effect on the glial-neuron interaction.

For most of the neuropeptides present in the SCN cells it is still unknown in how far they are involved in circadian timekeeping. Local injection of alpha-bungarotoxin, an irreversible cholinergic antagonist, into the SCN does not affect circadian rhythmicity in pineal activity [16]. Brattleboro rats that lack vasopressin in the SCN show undisturbed circadian rhythms. Injection of vasopressin in the rat SCN does not change the period of freerunning activity rhythms. The serotonin (5-HT) in the SCN is located in terminals, the perikarya of which are located in the midbrain raphe nuclei. 5-HT may act as a transmitter between these nuclei and the SCN. Electrophysiological studies reveal a response of SCN neurons to iontophoretical application of serotonin (5-HT). In spite of this there is no effect on free running period after local application of 5-HT into the SCN.

One of the first agents known to affect circadian rhythms is lithium. In most of the earlier experiments on plants, on insects, on mammals including man, it has been described that it lengthens the period of free running rhythms, [31-37]. Others like Delius *et al.* [38] studying locomotor activity of hamsters could not find any consistent effect of lithium added to the drinking water. Infusion of lithium into rats using Alzet miniosmic pumps did not show a difference in period length between the lithium group and control rats. So any consistent effect on the pacemaker is not easy to understand. Delius *et al.* [38] therefore propose a model in which lithium alters the coupling between circadian oscillators equivalent to the model developed by Kronauer *et al.* [39]. The fact that gene-dependancy has been shown in mice by a differential lengthening in different strains, [40, 41] supports the view of a more complicated action of lithium on the central control of behaviour.

Similar rather inconsistent data have been obtained from experiments with chronic application of the MAO-A inhibitor clorgyline. Administration of the drug by means of miniosmic pumps increases the circadian period of locomotor activity of female hamsters. Similar experiments done in rats do not show any effect [42]. Clorgyline applied for two weeks by means of osmotic minipumps reduces significantly 5-HT and 5-HIAA levels of brain tissue as compared to control rats. The amplitude of free running food intake is reduced for about three weeks after implantation. In none of the animals there was any change in period value. However, in case of local inplantation of clorgyline near the SCN there is some evidence of an increase in period length [31].

Another antidepressant drug, imipramine, seems to have an effect on the period length [43]. These authors claim that in rats as well as in hamsters free running rhythms in behaviour are slowed down after continuous infusion of the drug. A similar slowing of the pacemaker has been described after application of deuterium oxide and lithium [44].

Entrainment of the oscillator to the environment

In addition to the freerunning period, the phase dependent phase shifts of a rhythm exposed to stimuli at various time points, is another parameter of an oscillator that can be measured. However, little is known about the physiological mechanisms that mediate the entrainment of SCN neurons to the L/D cycle or communicate circadian information to other physiological systems. Recent studies have provided information on the morphology and neurochemistry of afferent projections to the SCN. Although the RHP is the main pathway mediating the effects of light on circadian rhythms, it does not imply that it is the only one. Later anatomical data proved the existence of a secundary projection from the ventral geniculate to the SCN. The terminal distribution of both tracts overlap. Cells of the SCN that are light-responsive change their firing rate tonically either by an increase or by a decrease when the ambient luminance level is changed [45]. Similar cell types are found in the VLGN. Photic entrainment may involve acetylcholine and its nicotinic cholinergic receptor in the SCN. Injections of the cholinergic agonist carbachol into the SCN

phase-shifts locomotor activity in rodents [46]. It is, however, unknown whether acetylcholine is a transmitter between RHP terminals and SCN cells or between intrinsic cells of the SCN itself. Recent experiments described by Liou *et al.* [47] suggest a role of glutamate and of aspartate in the transmission of signals from the RHP into the SCN. There is evidence that the ventral part of the lateral geniculate nucleus (VLGN) projects to the SCN with avian pancreatic polypeptide (APP) containing fibres [48]. Recent experiments [49] have demonstrated that this is probably neuropeptide Y, (NPY), another 36 amino acid peptide which has 20 amino acids homologous with APP. Microinjections of APP into the SCN shift hamster circadian activity rhythms in a similar way like dark pulses during constant light [12]. However, lesions of the VLGN have no effect on the rate of reentrainment after a phase shift. So the function of this afferent connexion remains unclear for the rat. Unilateral lesions of the SCN shorten the period of locomotor activity in the hamster in constant light. In the rat no change in period can be observed, there is a slight increase in reentrainment after a phase shift in this animal. Unilateral blinding however, retards the rate of phase shifting by two days and decreases the period of free running in constant light suggesting an effect of asymmetrical innervation of the two SCN by the RHP. This view is supported by the fact that this phenomenon is not present in the hamster in which the RHP innervates the SCN symmetrically [50].

Slowing down a circadian pacemaker will delay the phase position of entrained rhythms [51]. This is the case for lithium, clorgyline and pargyline in rats and in hamsters [52, 53]. This does not hold for all rhythms. McEachron *et al.* [54, 55] showed that in lithium fed rats that were synchronized to a light-dark cycle the plasma prolactin rhythm was phase delayed, whereas the pineal serotonin rhythm was not. A similar delay was described for locomotor activity. It is note worthy that the C14-2-deoxyglucose rhythm of the SCN was undisturbed [55]. Aschoff [56] described that adding imipramine to the drinking water over one month did not affect the circadian activity rhythm of hamsters. There were no changes in phase position nor differences in re-entrainment after a 6 hour phase shift. Similar negative results of effect of imipramine on entrained rhythms are described by Fowler *et al.* [57]. After oral administration for 21 days there was no effect on the pineal melatonin rhythm in the rat. Haeusler *et al.* [58] describe a lack of effect on rat urinary corticosterone rhythm after repeated intraperitoneal injections of imipramine.

In addition to an effect of species differences, these results suggest a selective effect on different pacemakers of the circadian oscillator network. In man Kripke *et al.* [59] described a slight delay of the phase of midpoint sleep.

Not only the phase position of a rhythm in respect to the entrainment signal, but also the shape of the phase response curve itself seems to be affected. Han [60] demonstrated an effect of lithium on the phase response curve of hamster locomotor activity, reducing the phase advance area and whereas the phase delay area increased. This might explain the finding of Reinhard [61, 62] that during application of lithium hamsters show an increase of the upper range of entrainment.

Control of subordinate structures

The SCN drive a great number of behavioral and physiological rhythms. SCN lesions affect the rhythmicity in locomotor activity [63], food intake [64, 65], water intake [64], sexual behavior [66, 67] as well as deep body temperature [68-70] and sleep wakefulness cycle [7, 68, 71]. In addition, several hormone levels are under the influence of the SCN. This holds in particular for the synthesis and/or secretion of adrenocorticotropic hormone [72], adrenal corticosterone [73], pituitary prolactin [74, 75], pineal melatonin [76] and gonadotropin [77].

The involvement of neuronal pathways in the control of these functions becomes evident as effects of SCN lesions can be mimicked by surgical isolation of the SCN [78]. Moreover, TTX infusion in the SCN, which blocks sodium-dependent spikes produces arhythmicity in activity and food intake during the infusion [28]. This result also indicates neuronal control of these rhythms. Transplantation of the SCN into an arhythmic animal can restore circadian rhythmicity in activity and drinking. In these experiments only a few efferents of the graft were detected [21]. The transplantation experiments therefore contradict the importance of neuronal efferents for rhythmicity outside the SCN. Instead these results suggest humoral control of circadian rhythms [21]. Although this matter remains as yet unresolved, it is conceivable that a small number of efferent projections is sufficient to impose rhythmicity on other functions.

Evidence on the distribution of projections from the SCN is based on numerous studies, using anterograde as well as retrograde labelling techniques. Autoradiographic experiments using [^{3}H]-amino acids [79-81] as well as experiments using *Phaseolus vulgaris* Leucoagglutin (PHA-L) [82] reveal six main efferent pathways to areas in which fibre terminals can be identified (see [82]).

A dense plexus of fibers originate in the SCN just dorsal and caudal to the nucleus between the periventricular nucleus and the anterior hypothalamic area. Fiber endings are mostly ipsilateral in a region ventral to the posterior part of the paraventricular nucleus, the subparaventricular zone. A few fibers continue dorsally from this zone, pass through the parvocellular parts of the paraventricular nucleus and midline thalamic nuclei, to end in the midrostral parts of the paraventricular nucleus of the thalamus, the dorsomedial nucleus and the

area around the ventromedial nucleus as well as the posterior hypothalamic area.

The other pathways consist of relatively smaller amounts of fibers. A second bundle runs rostrally and ends in the ventral parts of the medial preoptic area and anteroventral periventricular nucleus. Anterodorsally fibers pass through the medial preoptic nucleus to end in the intermediate lateral septal nucleus. Caudally to this group, fibers have been traced that end in the preoptic continuation of the bed nucleus of the stria terminalis, in the parataenial nucleus, in the rostral part of the paraventricular nucleus of the thalamus as well as into the midbrain central grey and the raphe nuclei [80-84].

Laterally directed fibers end in the ventral lateral geniculate nucleus. Finally, descending fibers connect the SCN with the zone between the arcuate nucleus, the ventral part of the ventromedial nucleus as well as in parts of the lateral hypothalamic area. All these pathways have been confirmed by retrograde labelling with fluorescent dyes [85].

A striking observation from these studies is the finding that retrograde labelling was never restricted to the SCN, but was always accompanied by a marked labelling of the area around the SCN as well as of the subparaventricular zone [82]. Implants of the dye True Blue in the zona incerta, the dorsomedial nucleus and the ventromedial nucleus labelled even more neurons in the area immediately surrounding the SCN than within the nucleus [82]. Two efferent projections of the SCN terminate in areas from which in turn afferents to the SCN arise. One is the IGL [82] which projects with neuropeptide Y containing fibers to the SCN. The second is the raphe [83] from which serotonergic fibers arise. Both feedback loops could allow the SCN to modulate its own input.

Several attempts have been made to identify transmitter substances of these efferent systems [85-89]. Neurochemically, cells are organized in several subfields within the SCN in a heterogeneous way [82, 90, 91]. Immunocytochemistry has been used to trace the efferent fibres from the SCN. However, as the origin of immunoreactive fibres is difficult to ascertain, other tracing techniques are required.

Fibres from the SCN to the paraventricular nucleus have been described containing vasopressin, neurophysin and VIP [92, 93]. Combining immunohistochemistry and retrograde transport of fluorescent dyes [82] shows that projections from the SCN to the midline thalamus, the subparaventricular zone and the dorsomedial nucleus contain vasopressin, VIP and neurotensin stained fibers. These fibers follow separate pathways. Vasopressin axons run laterally around the lateral edge of the paraventricular nucleus into the dorsomedial nucleus, whereas VIP neurons do not project as far laterally but terminate caudally to the paraventricular zone [82]. For a detailed study and review on the neuropharmacology of SCN efferents we refer to Watts and Swanson, 1987.

An important finding is that the efferent fiber system of the SCN projects to the same area that receives an input from the peri-SCN as well as from the supraventricular area. This suggests some integrative or amplifying function of the latter [85]. However, the question still remains to be solved whether this only involves the transmission of the timing signal from the SCN pacemaker already controlled by the photic signal that is presented via the RHT [94].

The question arises to what degree different homeostatic control systems are affected by the efferents of the SCN. The rostral fibres end diffusely in the medial preoptic area. This connection allows the SCN to control the intake of water, the deep body temperature as well as the reproductive behavior. In the female rat the cyclic control of gonadotropins is exerted by the anteroventral periventricular nucleus, which also contains endings of the SCN [77, 95]. However, the control of neuroendocrine rhythms probably takes place by way of multisynaptic pathways as there are no endings at the level of the median eminence [82]. This is in contrast with earlier reports [79, 80]. In these studies probably neurons in the neighborhood of the SCN have been labelled [81, 82]. This widespread distribution might explain why knife cuts posterior to the SCN abolish adrenal corticosterone and pineal N-transferase rhythms as well as the estrous cycle, whereas food intake and drinking are abolished only by larger semicircular knife cuts around the SCN [77, 96-101].

The caudal fibers reach the anterior hypothalamus including the retrochiasmatic zone, diverge and end in zones immediately surrounding the arcuate nucleus, the ventromedial nucleus as well as the dorsomedial nucleus. Luiten and Room [102] have shown that neuronal connections between the ventromedial and the lateral hypothalamic area all pass through the dorsomedial nucleus. This explains the finding that selective lesioning of the dorsomedial nucleus interrupts the circadian control of food intake without affecting the rhythm in body temperature, drinking and locomotor activity [103].

An important pathway is the one involved in the generation by the SCN of the circadian rhythm in pineal N-acetyltransferase. This rhythm is controlled by a release of norepinephrine from postganglionic fibres of the superior cervical ganglion. Preganglionic fibres originate in the intermediolateral cell column of the spinal cord. Monosynaptic projections to the spinal cord have been described from the dorsal and medial parvocellular area of the paraventricular hypothalamic nucleus as well as from the retrochiasmaic area [104, 105]. Both areas receive efferents from the SCN.

Although the present studies provide some evidence that different circadian rhythms are controlled by separate neuronal pathways, it remains to be solved whether or not there is any interaction between these pathways. Such interactions could

explain complex behavior in which several functions are mutually integrated.

Dissociation of a rhythm can be considered as a modification of the coupling between the driving oscillator and subordinate control centers. Sometimes this can be induced by constant light as well as by administration of drugs. A similar effect has been described after continuous infusion of clorgyline and imipramine by means of osmic mini-pumps during 4-28 days [43]. This is specific drug effect, as in case of application of deuterium oxide or lithium, drugs that lengthen the free running period too, such an effect has never been seen.

The most dramatic internal desynchronization has been observed after application of methamphetamine, a stimulant with a mild antidepressive action [106-109]. Oral application of the drug in blinded rats while recording free running food intake, water intake as well as wheel running activity results in a delay of part of the activity sometimes in the range of circabidian days. Other components free run with the same period length as before the drug suggesting an uncoupling of the SCN from other lower order control centres. This is supported by the fact that similar circabidian activity can be induced by methamphetamine in rats the have received a bilateral lesion of the SCN [107]. Administration of methamphetamine by means of osmotic minipumps seems to be ineffective as was described by Kraeuchi *et al.* [110].

Finally a last question to ask is whether there are other circadian oscillators outside the SCN. There are conflicting data about the presence of body temperature rhythms in SCN lesioned animals. Stephan *et al.* describe anticipatory response in animals that have received complete lesioning of both SCN, however both location and nature of such an oscillator still remains to be illucidated.

Submitted on invitation.
Accepted on 18 February 1993.

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