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Slow oscillation circuit of the intergeniculate leaflet

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Mini review

Abstract. The slow oscillation circuit of the intergeniculate leaflet seems to constitute a natural basic rhythm of the neuronal mechanism of mammalian biological clock. The results of studies conducted so far indicate that photic information flowing from ganglion cells of the retina is necessary for its generation. On the other hand, this circuit is maintained thanks to the oscillatory activity of GABAergic interneurons, the majority of which build up this structure, mainly in combination with neuropeptide Y and enkephalins. The activity of non-specific projections of the brain, whose terminals are present in the intergeniculate leaflet, modulates the slow oscillation circuit of the leaflet neurons, without changing its oscillatory pattern, though. Our hypothesis predicts a role of the oscillatory activity of intergeniculate leaflet neurons in facilitation the secretion of neuropeptides and neurohormones present in the very elements making up the mechanism of mammalian biological clock and structures linked to it. This constitutes a kind of functional junction between the central mechanism of mammalian biological clock with an ultradian rhythm and its peripheral clocks whose rhythm is circadian.

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Key words: oscillation, intergeniculate leaflet, biological clock

INTRODUCTION

The intergeniculate leaflet (IGL) belongs to the lateral geniculate nucleus (LGN) of the thalamus and is localized between its dorsal part (dorsal lateral geniculate; DLG) and ventral one (ventral lateral geniculate; VLG) (Fig. 1). For a long time this structure had not been distinguished from the remainder of the lateral geniculate body and had been ascribed to its ventral part. Only immunohistochemical and autoradiographic methods demonstrated its entirely different anatomical character and determined the limits of its occurrence and its links with other brain structures (Hickey and Spear 1976, Moore and Card 1994). The IGL is composed of small and medium-size multipolar interneurons whose dendritic zone is limited to the area occupied by the IGL, a feature that distinguishes it from the remainder of the lateral geniculate body. A homologue of this structure in monkeys and man is the pregeniculate nucleus (Moore 1989).

The IGL is an extremely important structural and functional element of the neuronal mechanism of mammalian biological clock (Fig. 2). It receives photic information from ganglion cells of the retina, i.e., the same cells that project their fibers to the suprachiasmatic nuclei (SCN), the main generator of biological clock. Above all, however, the IGL is responsible for the receipt of non-photic information which, besides photic information, is regarded as a pivotal external synchronizer of biological rhythms. These non-photic informations are of particular importance to higher organisms including man, for

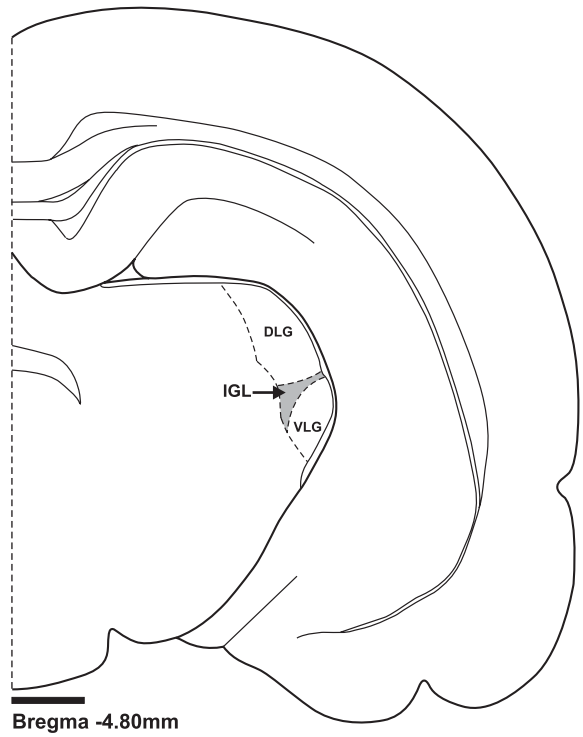

Fig. 1. Schematic drawing of the coronal section through the rat brain illustrating the localization of the intergeniculate leaflet (IGL): (DLG) dorsal lateral geniculate nucleus; (VLG) ventral lateral geniculate nucleus; (IGL) intergeniculate leaflet. Scale bar = 500 μm

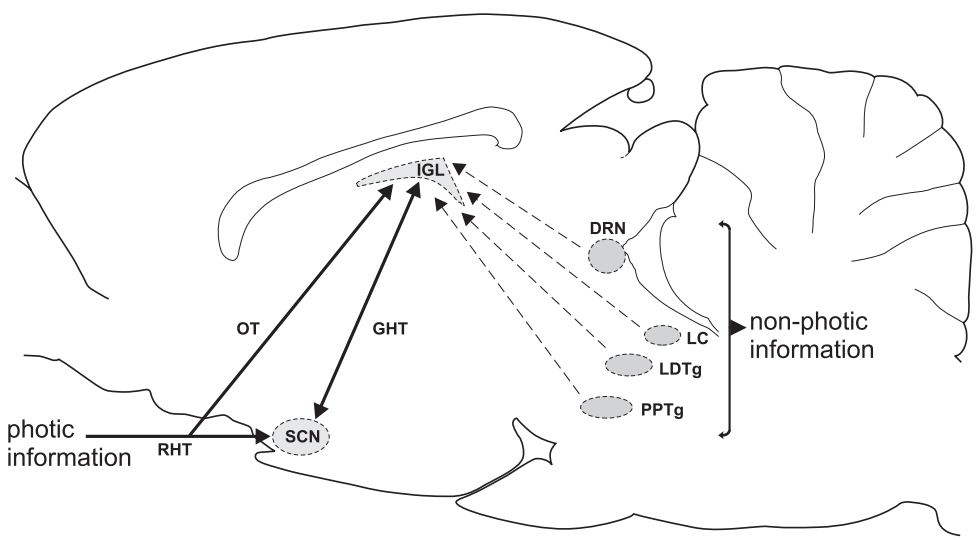

Fig. 2. Schematic drawing of the sagittal section through the rat brain illustrating the rough wiring between the main neuronal elements of the mammalian biological clock and the sources of the modulatory input to the IGL. (SCN) suprachiasmatic nucleus, (IGL) intergeniculate leaflet; (RHT) retinohypothalamic tract; (OT) optic tract; (GHT) geniculohypothalamic tract; (DRN) dorsal raphe nucleus; (LC) locus coeruleus; (LDTg) laterodorsal tegmental nuclei; (PPTg) pentuculopontine tegmental nuclei

whom light and darkness, the availability of food or ambient temperature are not the only factors affecting his work. The equally important stimuli that synchronize our rhythmic processes are all non-photic effects. Under certain conditions, their influence on the organism and thus also on rhythmic processes may be stronger than that of light. Such non-photic stimuli as behavioral arousal (which induces both hyperactivity and sleep deprivation), food shortage and social interactions (e.g., mating-oriented behaviors) do not have their specific projections in the brain, hence *via* activation of non-specific systems they affect the whole brain evoking its arousal (Hastings et al. 1998). There exists some anatomical evidence for a close connection between sources of non-specific projections in the brain stem and the IGL (Vrang et al. 2003). Thanks to them, the whole neuronal mechanism of mammalian biological clock receives information about the organism's arousal. The role of IGL consists in integrating the photic effects transmitted by the optic tract (OT) with non-photic ones and in analyzing them. The outcome of this analysis reaches – *via* the geniculate-hypothalamic tract (GHT) – the main generator of mammalian biological clock, i.e., the suprachiasmatic nuclei. *Via* the SCN, this signal stringently regulates – through other brain structures, mainly the pituitary-hypothalamic axis – rhythmic behavioral and physiological processes of the whole organism. Recently there have been discovered additional efferent projections from rat IGL to regions situated beyond the circadian system (Moore et al. 2000, Morin and Blanchard 2001). However, numerous authors agree that the tract to the SCN is of basic and utmost importance.

The role of the reciprocal connection between leaflets of both lateral geniculate bodies through the supraoptic and posterior commissures is extremely interesting and still remains to be fully elucidated (Mikkelsen 1992). It is noteworthy that none of the two remaining parts of the LGN (dorsal and ventral) has such a connection. The two main oscillators of the biological clock, SCN and IGL (and in practice four, as each of them has its contralateral neighbor), form through their reciprocal anatomical connections a closed system of the neuronal mechanism synchronizing mammalian biological rhythms (Fig. 2). These reciprocal connections between the IGL and the SCN constitute anatomical evidence for the involvement of the IGL in the regulation of rhythmic processes.

This anatomical evidence for the relationship between the IGL and the mechanism of mammalian biological clock is confirmed by the results of physiological and behavioral studies which directly demonstrated IGL involvement in the synchronization of circadian rhythms. Electric stimulation of the IGL produces a shift in the rhythm phase – different from that evoked by a light impulse, though. Electric lesion of both IGL always results in desynchronization of the locomotor activity rhythm in the mouse (Lewandowski and Usarek 2002). The results of the latter experiment corroborated some earlier observations on the pivotal role of the IGL in synchronizing rhythmic phenomena, especially in animals kept under constant conditions (constant darkness or constant light). In that experiment, however, we were the first to demonstrate – using a specially designed program for the analysis of chronobiological data (Domosławski et al. 1991) – a statistically significant decrease (by 68%) in locomotor activity, and prolongation of the rhythm length by 45 min after IGL lesion. These findings point to a lack of non-photic synchronization in the circadian system after IGL lesion (Wickland and Turek 1994), which is probably due to the absence of inhibitory effect stemming from the IGL. The activity of as many as 70% of SCN neurons is inhibited after IGL stimulation (Roig et al., 1997). Also behavioral activity, being one of non-photic factors, induces a decrease in the firing rate of SCN neurons (Schaap and Meijer 2001). Of crucial importance is the observation that under standard laboratory conditions and at a constant light regimen (12 h light/12 h darkness), IGL lesion does not hinder the course of circadian rhythms. Light or darkness, which is a strong stimulus, delivered always at the same time intervals at a limited access to other (non-photic) stimuli, is a dominating signal and the only synchronizer of rhythmic processes. However, it should be borne in mind that laboratory conditions are far from the real situation in which the majority of organisms, including man above all, live. Therefore the presence and significance of the structure that receives and integrates non-photic information with photic one is extremely important. This pivotal role is played by the IGL itself.

SLOW OSCILLATION OF IGL NEURONS

There are only few papers concerning electrophysiological studies into the activity of neurons making up the IGL (Harrington 1997). Using a method of extracellular recording of the spontaneously generated

action potentials, we found – completely by accident – an extremely interesting isoperiodic oscillatory activity of neurons making up the IGL (Lewandowski et al. 2000). These neurons generate action potentials in rhythmically repeating burst firing episodes at constant interburst intervals (Fig. 3). The mean time in which IGL cells change their activity level amounts to 124 ± 7 s. Interestingly, such an activity pattern is displayed by leaflet neurons only and is absent within the dorsal and ventral parts of the LGN. On the other hand, the pattern in question can be seen in suprachiasmatic nuclei of the hypothalamus (Aggelopoulos and Meissl 2000, Miller and Fuller 1992), and in the activity of cells of the pineal gland (Reuss 1987) to which the IGL has an additional projection in rats (Mikkelsen and Moller 1990) and Mongolian gerbils (Mikkelsen et al. 1991). The same pattern of cellular activity in two main structures (SCN and IGL) of the neuronal mechanism of mammalian biological clock permits an assumption that it constitutes a very important, natural, basic rhythm which is characteristic of the work of not only these two structures, but also of the whole mechanism of mammalian biological clock. However, a crucial, most important question is bound to occur regarding the physiological significance and functional relationship of this short-lasting ultradian rhythmic activity of neurons with a long-lasting, commonly observed circadian rhythm. To formulate a hypothesis which would draw us closer to answering this question, we should examine the source of oscillations of IGL cells, their pharmacology, and the impact of non-specific projections on these oscillations.

THE ORIGIN OF OSCILLATIONS OF IGL NEURONS

The oscillatory activity of neurons most frequently stems from the rhythmic activity of the neuronal network itself which makes up a particular structure, or is the sum of activities of individual neurons, induced by external factors. Thalamic cells, to which the IGL belongs, fire in two distinct modes: burst or tonic. It is commonly believed that relay cell bursting can be seen only during certain phases of sleep, deep anesthesia, or absence of seizures when the bursting is rhythmic (Steriade et al. 1993). This may suggest that also the oscillatory activity of IGL neurons of rats under urethane anesthesia, recorded in our experiment, stems from it. However, some bursting has been observed in lightly anaesthetized and behaving animals (for reviews see Massaux and Edeline 2004, Ramcharan et al. 2000). It is suggested that general anesthesia may suppress the photoentrainment of the circadian system; this, however, does not concern urethane anesthesia (Colwell et al. 1993). The very distinct territorial occurrence of oscillations (limited only to the area occupied by the IGL) and its disappearance after switching the light off and

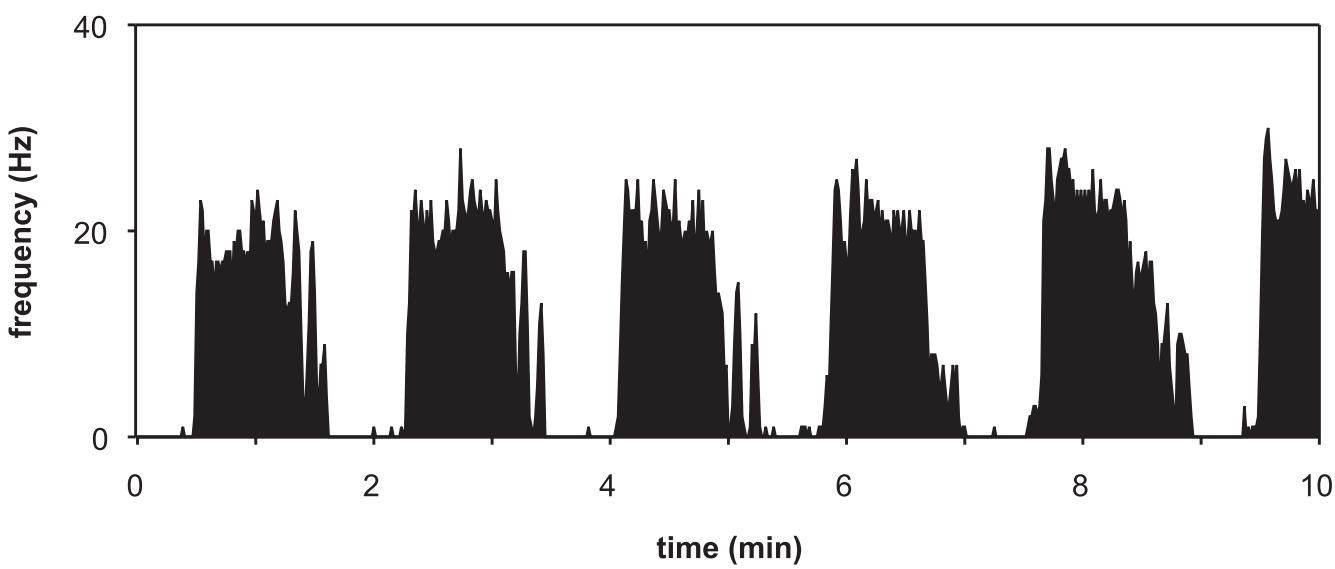

Fig. 3. Firing rate histogram showing rhythmic slow bursting activity (isoperiodic, ultradian oscillation) of intergeniculate leaflet (IGL) neurons. Bin size = 1 second

reappearance after switching it on also point to its occurrence irrespective of anesthesia. However, the above assumption will be fully corroborated only by the results of the recording conducted on behaving animals. A high degree of correlation between the activity of neurons of the dorsal part of lateral geniculate nucleus and that of visual cortex neurons testifies to a functional relationship between these two extremely important structures and their participation in the process of seeing. The lack of such correlation in the case of the IGL further corroborates the involvement of this structure in a mechanism different from the latter process (Lewandowski et al. 2000).

The reciprocal connection between both leaflets of the LGN may suggest that the activity of either of them, and thus also of the recorded oscillations, depends on the presence and activity of the other leaflet, especially as the population of neurons participating in this reciprocal connection differs from that projecting to the SCN, and since electric stimulation of one leaflet causes inhibition of the neuronal activity of the other (Harrington 1997, Zhang and Rusak 1989). It has turned out, however, that electric lesion or pharmacological blockade of the activity of one leaflet has no effect on the oscillations recorded in the contralateral leaflet (Lewandowski et al. 2002). These findings prove that the neuronal population generating oscillations differs from that connecting both leaflets of the LGN, which may indicate their endogenous origin, irrespective of other influences. However, our latest experiments with antidromic responses to the stimulation of the contralateral IGL have indicated that some bursting cells form a reciprocal connection between both these structures (unpublished observation). All the same, the significance of the reciprocal connection between both IGL still remains an open question. The hypotheses about the endogenous origin of oscillations have not been confirmed by the results of our *in vitro* studies (Błasiak and Lewandowski, in press). In all our experiments we observed three patterns of the activity of neurons whose largest percentage were cells working in both an irregular and a regular way, i.e. tonically. A distinct, statistically significant group of cells with an oscillatory activity pattern was lacking, though. Three similar types of the firing pattern (regular, irregular and bursting) were also described in SCN neurons (Zhang et al. 1995). Like in the SCN (Shibata et al. 1984, Thomson et al. 1984), in the IGL those three types of neuronal activity occurred spontaneously, but at the same time without any noticeable or explicable regularity. In an *in vitro* preparation, not only connections with other brain structures are eliminated, but also local interactions between cells are reduced, which in the case of oscillating cells is of utmost importance. Similar disproportions in the cell activity recorded *in vitro* and *in vivo* have been found in the SCN and are discussed in a paper by Meijer et al. (1998). The disappearance of oscillations of IGL neurons in an *in vivo* preparation after turning the light off during measurement and their reappearance after turning it on again (Lewandowski et al. 2000) suggests a role of light in generating this type of activity pattern of IGL neurons (Fig. 4). The latter assumption was amply confirmed by our latest experiments in which blockade of the sodium conduction of ganglion cells of the retina by means of tetrodoxin (TTX) administration to the eyeball of tested animals, always caused the disappearance of oscillations in the IGL (Błasiak and Lewandowski, in press).

The latter results are particularly interesting, as the disappearance of oscillations was observed only when TTX was administered to the eyeball contralateral to the recording site. The latter electrophysiological effect fully corroborated the anatomical studies which demonstrated the prevalence of contralateral retina ganglion cells axons in the IGL (Hickey and Spear 1976, Moore et al. 1995). Also other nuclei involved in the circadian system receive innervation largely, but not solely, from the contralateral retina (Muscat et al. 2003). However, the significance of this interesting phenomenon for the functioning of the clock mechanism still remains unclear. All the same, we may definitely propose that light is a trigger for oscillations in the IGL. So far, we have not been able to unequivocally ascertain, though, whether they are generated already at the level of ganglion cells themselves, or only in the IGL.

PHARMACOLOGY OF OSCILLATIONS OF IGL NEURONS

The vast majority of neurons that build up the mechanism of mammalian biological clock are inhibitory GABAergic nerve cells (Moore and Speh 1993). Approximately 60% of the SCN neurons in culture are immunoreactive to glutamic acid decarboxylase (GAD), a GABA-synthesizing enzyme. Also in cells building up the IGL, GABA is present in combination with neuropeptide Y in a projection to the SCN, and in combination with enkephalins in a projection to the

contralateral IGL. The Nissl staining, combined with GAD immunohistochemistry have revealed that all IGL neurons produce this neurotransmitter. The pharmacological results of our studies have unequivocally shown that the GABAergic projection participates in generating isoperiodic oscillations of IGL neurons. In our experiment (Błasiak and Lewandowski, in press), intraventricular administration of a $GABA_A$ receptor antagonist (bicuculline, picrotoxin) always blocked the observed oscillations in a statistically significant manner time-wise (Fig. 5).

That effect was dose-dependent, which additionally points to the involvement of a GABAergic projection in the observed phenomenon. However, on the basis of intraventricular administration we are not absolutely sure whether the observed disappearance of oscillations

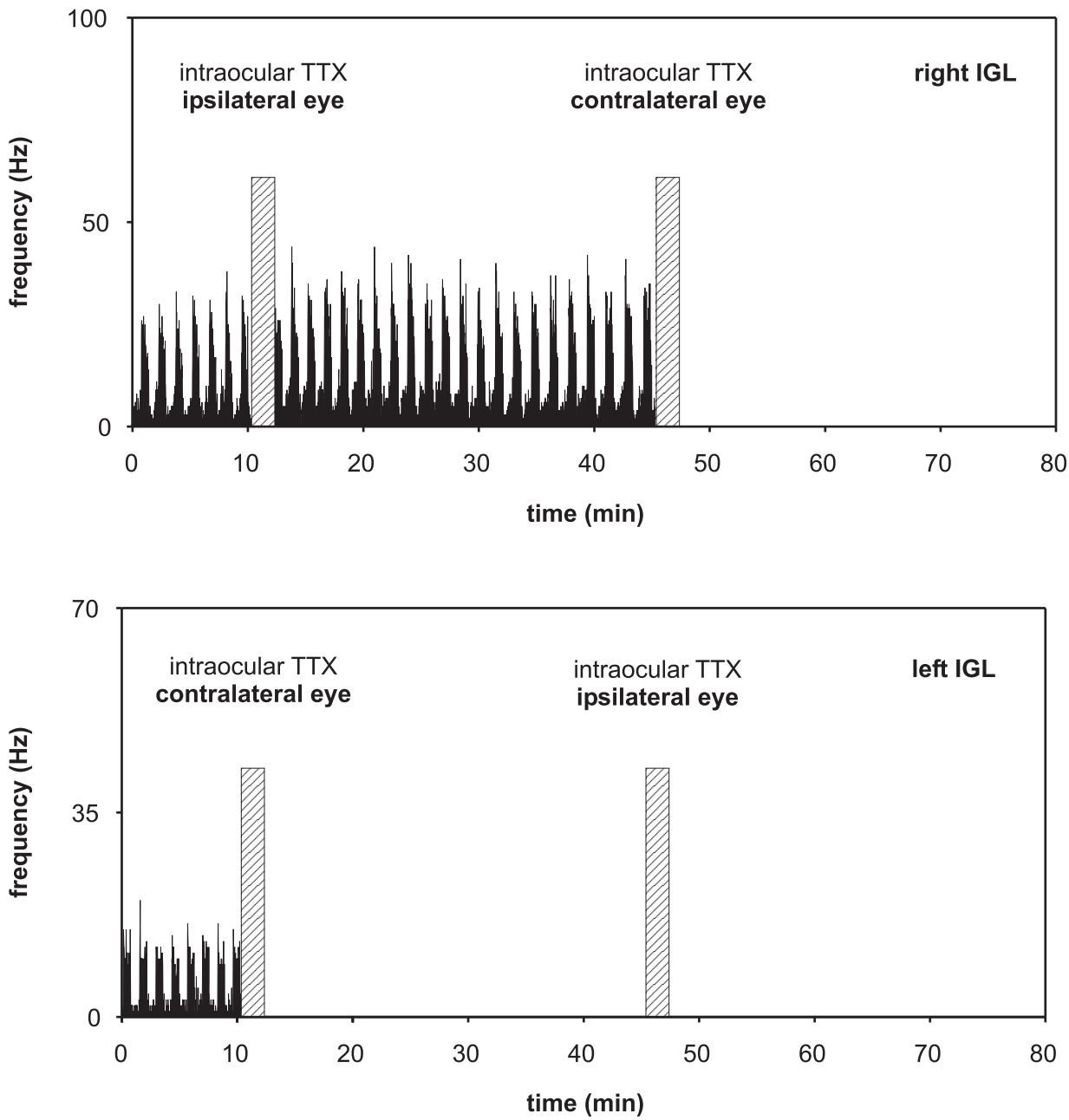

Fig. 4. Firing rate histograms of simultaneously recorded neuronal activity of both right (top) and left (bottom) IGLs. Chemical blockade of the right eye retina (TTX injection; first vertical bar – both histograms) causes total disappearances of the neuronal activity in the left IGL and induces no change in the activity of neurons in right IGL at the same time. Shut down of neuronal firing of right IGL was caused just after the TTX has been injected (second vertical bar – both histograms) into the left eye. Bin size = 1 second

stems from the blockade of inhibitory connections at a level of the leaflet itself, or other external structures with projections to it, in which GABA is also present. The disappearance of oscillations after turning off the light, as observed in our first experiments (Lewandowski et al. 2000), may indicate a decrease in GABA level in the entire circadian system, above all, however, in ganglion cells of the retina. It so happens that GABA, apart from the distinct circadian rhythm of its activity (Aguilar--Roblero et al. 1993), shows a visible decrease in its level under constant darkness conditions, at least as observed in the SCN (Ralph and Menaker 1989). There may be, however, another explanation of the disappearance of oscillations after the blockade of GABA receptors, which is connected with dual GABA activity, dependent on the time of day or night. It exerts an inhibitory effect during the night, and a excitatory one in the daytime (Wagner et al. 1997). This dual activity is linked to oscillatory alterations in intracellular chloride concentration: from high levels during a subjective day to low levels during a subjective night (Wagner et al. 2001). Both the stimulatory and the inhibitory effect is blocked by bicuculline or picrotoxin administration, which suggests that either response is mediated by $GABA_A$ receptors connected with chloride channels. GABA has also been shown to act as either an inhibitory or an excitatory transmitter in the synchronization mechanism of circadian firing rhythms in cultures of rat suprachiasmatic neurons (Shirakawa et al. 2000). It may therefore be assumed that the oscillatory activity of IGL neurons stems from the stimulatory action of GABA, while their disappearance after turning the light off is due to the inhibitory action of GABA; however, this hypothesis needs to be experimentally verified.

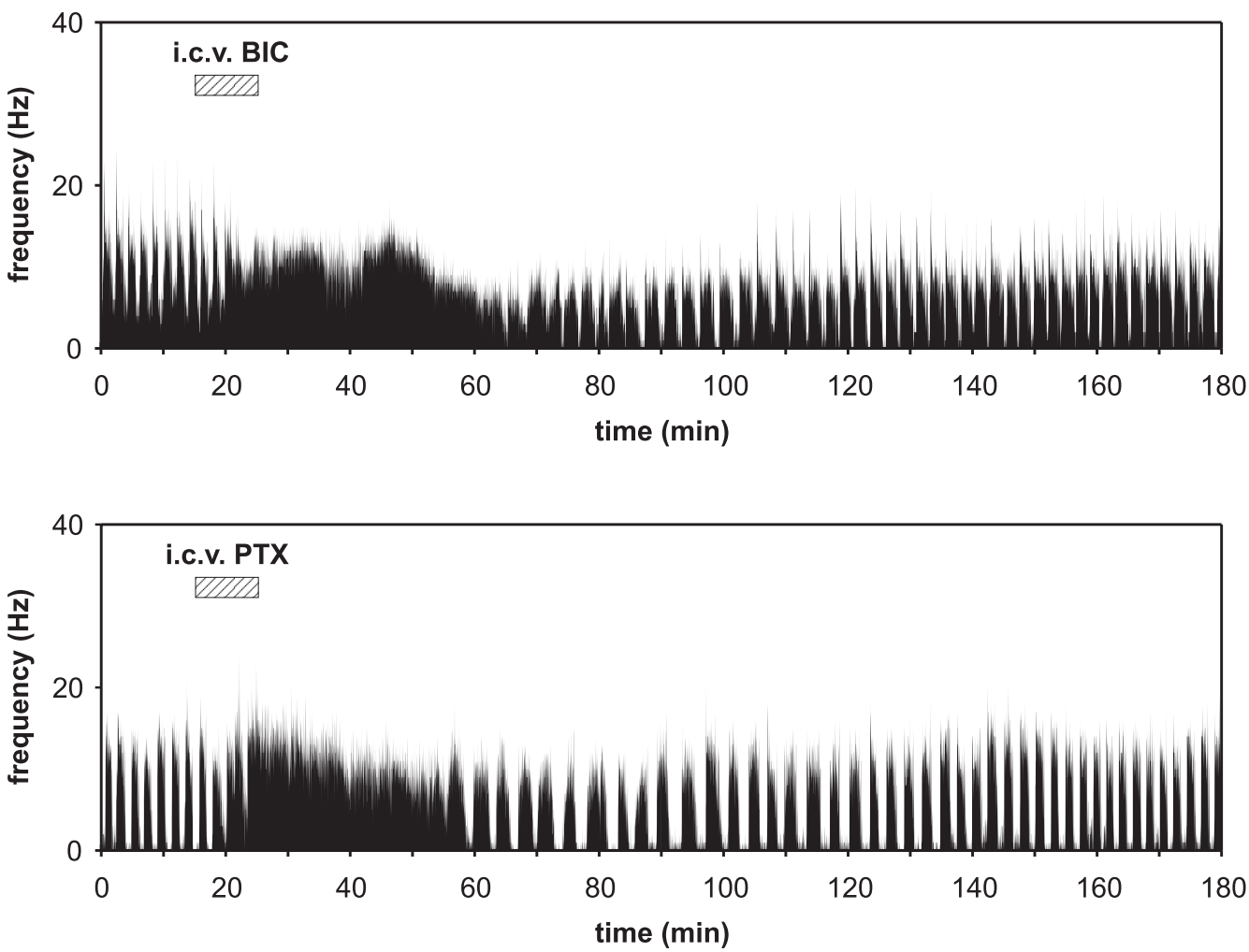

Fig. 5. The firing rate histogram of IGL neuronal activity before and after i.c.v. application of bicuculline (top) and picrotoxin (bottom). Bin size = 1 second. A horizontal, dashed bar indicates the time of drug application (1.6 μg, BIC and 0.8 μg, PTX).

INFLUENCE OF NON-SPECIFIC SYSTEMS ON OSCILLATIONS IN THE IGL

One of the most pivotal non-specific projections of the brain, which is of crucial significance to the regulation of circadian rhythmic processes including above all the most important one: the sleep and waking rhythm, is the serotonergic system of midbrain raphe nuclei (Mistlberger et al. 2000). The median part of raphe nuclei (MnRN) has its terminals in the suprachiasmatic nuclei of the hypothalamus, while the dorsal part of raphe nuclei (DRN) – in the IGL (Fig. 2). Electric stimulation of the DRN always produced a statistically significant decrease in the amplitude of isoperiodic oscillations in the IGL, whereas its lesion caused a distinct increase in that parameter (Fig. 6) (Błasiak and Lewandowski 2003a).

On the other hand, intraperitoneal and intraventricular administration of a serotonin receptor agonist (8-OH-DPAT) evoked a statistically significant (reversible) increase in the level of oscillatory activity of IGL neurons (Fig. 7) (Błasiak and Lewandowski 2003b). That unexpected result, seemingly opposed to the expected one, was probably caused by a process of the so-called desensitization of serotonergic neurons to the administered compound, due to which their activity – and thus also the amount of serotonin released by them – was inhibited.

We do not have sufficient evidence, however, to unequivocally ascertain whether the observed effect stems directly or indirectly from the impact of a serotonergic projection on IGL activity, especially as reciprocal serotonergic connections have recently been found between the median and the dorsal raphe nuclei in the hamster (Tischler and Morin 2003). Hence the observed modulatory effect of the serotonergic projection on IGL activity may be mediated by the SCN.

Undoubtedly, the distinct inhibition of the oscillatory activity of IGL neurons after activation of the serotonergic system is an example of the modulatory effect of non-specific projections of the brainstem on the clock mechanism. Possibly, the character of this modulation depends on the state of brain arousal and the impact of both the specific stimulus, i.e., light, and unspecific, i.e., the non-photic ones on the circadian mechanism of mammalian biological clock. In some states, the modulation that originates in the brainstem may facilitate transmission of the information reaching the IGL, and inhibit it in others. We do not know, however, whether and when inhibition or facilitation is always connected with synchronization only, or whether it may also cause desynchronization of the entire circadian system. A modulatory effect on the IGL is also exerted by a cholinergic projection of the brainstem. Electrical or pharmacological activation of the main sources of that projection affected in a statistically significant manner the field potential evoked in IGL by

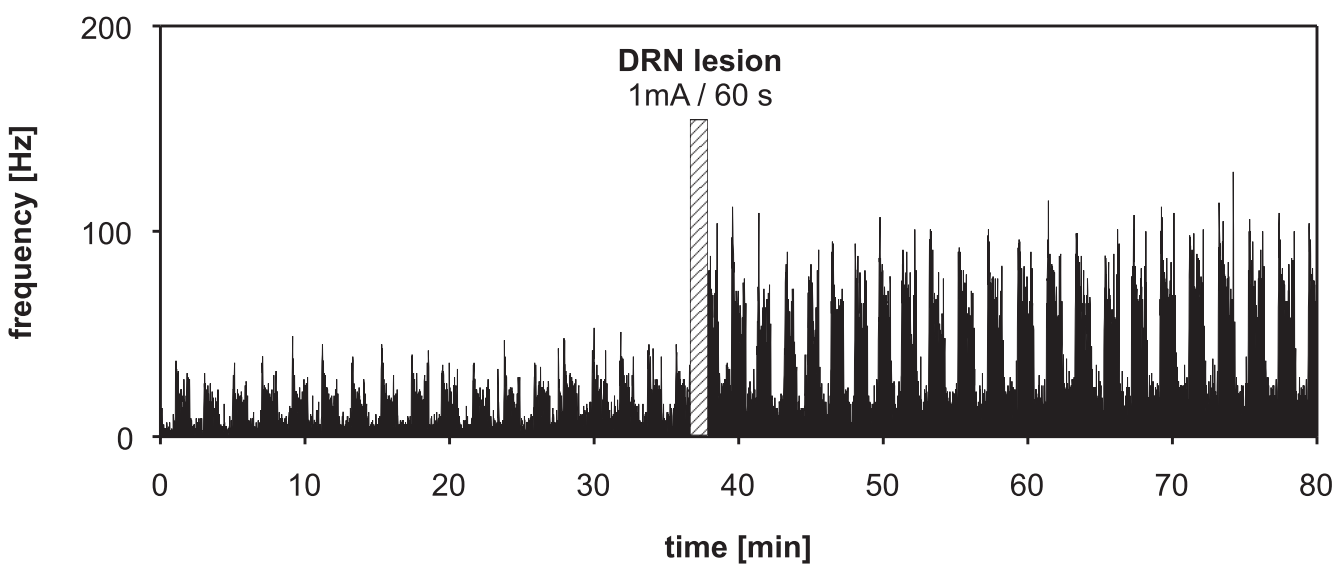

Fig. 6. A firing rate histogram of IGL neuronal activity before and after an electrolytic lesion of the dorsal raphe nucleus (DRN). The vertical bar indicates a DRN lesion. Bin size = 1 second

stimulation of the SCN (Lewandowski and Błasiak 1999). Taking account of the fact that GABA is a dominating neurotransmitter of both the IGL and the entire circadian system, the effect observed in our experiment may be due to stimulation of the cholinergic receptors localized on these neurons. Possibly, prolongation of the rhythm of locomotor activity by IGL lesion, described in behavioral studies, stems from the lack of modulatory inhibition originating in the IGL.

SENSE OF A SLOW OSCILLATION CIRCUIT IN THE IGL HYPOTHESIS

One of the frequently asked questions concerning the observed neuronal oscillations in the IGL is that about their role in the functioning of the mechanism of biological clock and the whole organism (Lewandowski and Błasiak 2002). In comparison with the commonly recorded oscillations of high frequency, whose significance has been well documented (Singer 1998), this activity is very slow. On the other hand, however, it is fairly fast compared to the commonly recorded circadian rhythm. In an attempt to put forward a hypothesis drawing us closer to an answer to this key question, a few basic facts should be considered: (i) the circadian rhythm, often termed "clock hands", is a final, external effect of work of the internal ultradian mechanism of mammalian biological clock; (ii) the two main structural elements (SCN and IGL) that make up the neuronal mechanism of mammalian biological clock are closely linked anatomically and functionally with each other;

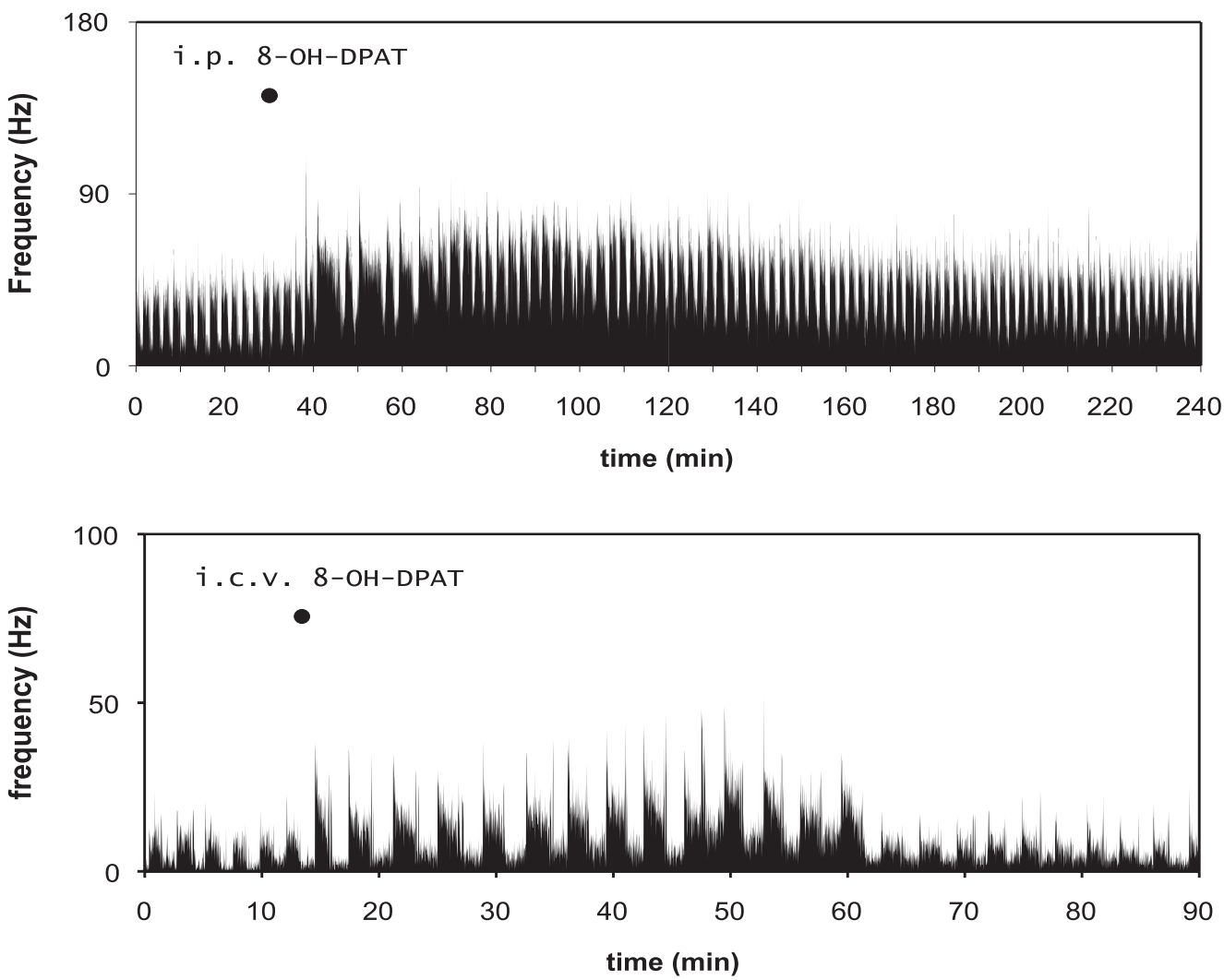

Fig. 7. A firing rate histogram of IGL neuronal activity before and after 8-OH-DPAT intraperitoneal (i.p. – top) and intracerebroventricular (i.c.v. – bottom) injection. The white-filled dot indicates time of the injection/infusion. Bin size = 1 second

(iii) SCN and IGL show the same oscillatory pattern of neuronal activity; (iv) SCN is situated in the very close vicinity of the hypothalamic nuclei and the hypothalamus-pituitary axis; (v) SCN has a direct nerve connection with a number of hypothalamic nuclei: the dorsomedial nucleus (DMN), paraventricular nucleus (PVN), subparaventricular zone (sPVz), supraoptic nucleus (SON), or the lateral and dorsal hypothalamic areas (LDH) (Leak et al. 1999, van Esseveldt et al. 2000); (vi) there has also been demonstrated oscillatory (eruptive) activity of neurons making up the following nuclei: paraventricular nucleus, supraoptic nucleus, lateral hypothalamic area (LH) (Haller and Wakerley 1980, Hatton 1982, Poulain and Wakerley 1982); (vii) there has been shown pulsatory (eruptive) secretion of some neurohormones, e.g., the antidiuretic hormone – vasopressin (ADH), growth hormone (GH), luteinizing hormone (LH), follicle-stimulating hormone (FSH), adrenocorticotropin hormone (ACTH), or gonadotropin-releasing hormone (GnRH) (for reviews see Silverman and Zimmerman 1983, Vollrath 2002).

It may thus be hypothesized that the oscillatory (eruptive)-ultradian activity of neurons forming the mechanism of mammalian biological clock regulates the pulsatory secretion of hormones (Ahmad et al. 2001, Pitts et al. 2001). It facilitates the release of these macromolecular compounds from the SCN, IGL and structures directly linked to them (van Esseveldt et al. 2000). This activity may constitute a functional link between the activity of neurons making up the clock mechanism and the secretion of neuropeptides and neurohormones. Hermes et al. (1996) demonstrated the presence of GABA and glutamate in monosynaptic transmission from the SCN to defined specific neurons in the paraventricular nucleus, and their involvement in the regulation of neuroendocrine processes and autonomous functions. The oscillatory isoperiodic activity of structures of the mammalian biological clock mechanism possibly constitutes a functional junction between the central clock situated in the brain and its "hands", i.e., peripheral clocks whose circadian activity is commonly perceived and recorded, in contrast to the hardly perceptible activity of the mechanism itself.

CONCLUSIONS

On the basis of studies conducted so far we may most certainly conclude that the isoperiodic oscillatory activity of IGL neurons is engaged in the mechanism of mammalian biological clock. Nevertheless, a full understanding of the mechanism of generation of these oscillations at a cellular level requires further electrophysiological *in vivo* and *in vitro* studies, above all, however, an attempt at their recording in behaving animals. On the other hand, the knowledge of their role in the functioning of the mechanism of mammalian biological clock should involve combining electrophysiology with pharmacology and endocrinology. All the same, a conclusion can be propounded that, in contrast to the rapid oscillations recorded mainly in the cerebral cortex, which constitute a kind of "a link between the outside world and the interior of our organism" and are necessary for its normal perception, the slow oscillations combine changes occurring inside our organism with the world that surrounds us. They are an indispensable substrate for the synchronization of our behaviors and physiological processes in the changing circadian rhythm of day and night.

It should, however, be borne in mind – especially in the case of interference in rhythmic processes – that the internal clock mechanism works in a rhythm that is considerably shorter than that commonly perceived and recorded by us.

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