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Review

A review on the effect of the photoperiod and melatonin on interactions between ghrelin and serotonin

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ABSTRACT

Ghrelin and serotonin, which exhibit rhythmic secretion profiles under feeding/fasting conditions, are sensitive to increases and decreases in the day length and form a close web of interrelationships in the regulation of energy homeostasis. Ghrelin and serotonin are biochemically and functionally linked to the suprachiasmatic nucleus, which is a circadian pacemaker, and melatonin, which is an internal transducer of photic environmental changes. Ghrelin and serotonin might be candidates for integrating photic and nonphotic signals, such as light and food availability in the central nervous system. The mechanisms that convert a light signal into a variety of physiological and behavioral rhythms remain unknown. However, we know that the conversion of light signals is necessary to maximize an animal's chances of survival and reproduction.

1. Introduction

In the course of evolution, animals have developed a number of mechanisms for survival under the adverse conditions of a changing environment, such as the ability to respond to stimuli associated with changes in day-length, seasons of the year or circannual rhythms of temperature, and the ability of an organism to adequately adapt to its own physiological changes and energy demands. In terms of endocrinology, these adaptations are manifested via circadian and circannual fluctuations in the concentration and activity of a number of hormones and neurotransmitter-like compounds. Ghrelin is an important hormone that was initially shown to play a role in the secretion of growth hormone (GH). Subsequent studies have revealed an entire spectrum of ghrelin effects, including the stimulation of hunger processes in response to energy deficits and the regulation of the sleep-wake cycle and reproductive functions. Immunocytological analyses have shown that ghrelin is highly concentrated in brain centers that regulate energy homeostasis and shape the endogenous rhythms of physiological processes [27]. These actions are mediated through the release of neurotransmitters, such as serotonin, which are subject to regulation via the current metabolic status of the organism and are affected by the photoperiod through direct or indirect interactions with melatonin. Although light controls the activities of serotonin and ghrelin, these two factors can also impact changes in rhythm phases and synchronization under various environmental conditions that are independent of light.

2. Interactions between selected photic and nonphotic factors in the central nervous system

The results of intensive studies have shown that other brain areas and peripheral tissues can act as SCN-independent circadian and circannual oscillators [56] that are stimulated through nonphotic factors, such as food availability and ambient temperature. Information from peripheral tissues is conveyed to the central nervous system (CNS) via two channels: the sympathetic and parasympathetic autonomic nervous system; and hormones and nutritive substances that overcome the blood–brain barrier or get directly routed to the brain via circumventricular organs. In the first case, nerve signals initially reach the paraventricular nucleus (PVN), where they are modified, enhanced and released into the SCN. In the second case, compounds from peripheral tissues bind to specific receptors on neurons in the arcuate nucleus (ARC) and are subsequently directed to the SCN (Fig. 1).

Abbreviations: BBB, blood-brain-barrier; CNS, central nervous system; CVO, circumventricular organs; DRN, dorsal raphe nucleus; DMH, dorsomedial hypothalamus; GHSR-1a, growth hormone secretagogue receptor; MRN, median raphe nucleus; MT1, receptor of melatonin type 1; RHT, retino hypothalamic tract; GHT, geniculohypothalamic tract; IGL, intergeniculate leaflet; LH, lateral hypothalamus; PVN, paraventricular nucleus; SCN, suprachiasmatic nucleus; SPZ, subparaventricular *zone*; vmARC, ventral-medial part of arcuate nucleus; VMH, ventromedial hypothalamus.

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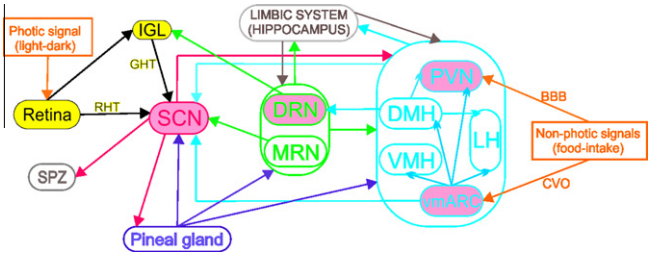

Fig. 1. Schematic representation of photic and non-photic 1 input in the CNS. The SCN can be entrained through light (via RHT, GHT) and circulating hormones (such as ghrelin) and nutrients, which access the ARC through the BBB or are routed directly to the PVN via CVO (*orange lines*). The ARC and PVN communicate with other hypothalamic nuclei, such as VMH, DMH, LH, which are important for the metabolic integration of feeding signals (*blue lines*). These nuclei send their references into the SCN, where light and metabolic information are enhanced, synchronized and sent to various CNS areas, including the SPZ and the pineal gland (*blue lines*). The pineal gland produces melatonin, which communicates with the DRN, PVN, and ARC directly via MT1 (*purple lines*) to influence the activity of ghrelin and serotonin neurons (*pink circles*). The non-photic serotonergic projections originate in the MNR and extend into the SCN, whereas serotonergic terminals that exist in the IGL are derived from the DRN with NPY neurons projections from the DMH (*green lines*). Serotonin and ghrelin receptors are expressed in the PVN, DMH, VMH and hippocampus where they exchange metabolic information. Peripheral and centrally synthesized ghrelin transmit nonphotic information to the SCN via vmARC or directly via GHS-R1a, which is expressed in the SCN.

Thus, a network of functional connections between selected brain areas is formed, and previous studies have suggested important roles for the dorsomedial nucleus (DMH), PVN and ARC in the regulation of energy homeostasis and physiological rhythms. These hypothalamic nuclei send their outputs to the SCN, which also receives light information via two paths: the so-called retinohypothalamic tract (RHT) and the geniculohypothalamic tract (GHT) [23,30]. In the SCN, light information is enhanced and synchronized and eventually sent via multiple pathways to various CNS areas, including the PVN, ARC, lateral hypothalamus, medial preoptic area (POA), subparaventricular zone and pineal gland (Fig. 1) [21].

In higher vertebrates, the pineal gland, retina and SCN regulate daily physiological processes. In the pineal gland, a light impulse is transformed into a biochemical signal that inhibits or stimulates the secretion of a neurohormone-like compound (i.e., melatonin) [12]. This indoleamine is enzymatically synthesized from serotonin (5-hydroxytryptamine, 5-HT) through the sequential actions of tryptophan hydroxylase 1 (TPH1), arylalkylamine-N-acetyl-transferase (AA-NAT) and hydroxyindole-O-methyltransferase (HIOMT). The circadian activity rhythms of AA-NAT have been proposed to reduce the amount of melatonin that is constitutively secreted from the pineal gland during the dark phase [31].

Because melatonin is a lipophilic molecule, it can easily penetrate the cerebrospinal fluid (CSF). Thus, melatonin can directly influence the hypothalamus and pituitary to modulate the activity and secretion of hormones [44,50]. In sheep, a particularly high number of melatonin receptors are located in the area of the third brain chamber, in the vicinity of the SCN and other hypothalamic structures, including the PVN, DMH and the ventromedial hypothalamus (VMH) (Fig. 1) [37]. A number of neurohormones and neurotransmitters that regulate food intake and appetite are active in these hypothalamic areas. In particular, there is a population of neurons that secrete molecules with orexigenic [e.g., NPY and agouti-related peptide (AgRP)] and anorexic properties [e.g., cocaine and amphetamine-regulated transcript (CART) and pro-opiomelanocortin (POMC)]. The administration of exogenous melatonin in rats has been reported to induce the expression of the POMC gene in the ARC [57]. However, in zebra danio (*Danio rerio*) exogenous melatonin stimulates the expression of compounds with anorectic properties, such as leptin and the melanin receptor (MC4R) and reduces the expression of ghrelin, NPY and the cannabinoid type 1 receptor, whose synergistic action intensifies food consumption [42].

3. The biological role of serotonin in the CNS

The pineal gland in mammals is a part of the CNS and is particularly rich in 5-HT. In the cytosol of pinealocytes, the concentration of serotonin is 3140 ng/g of tissue. For comparison, the entire human hypothalamus contains 61 ng/g, the hippocampus contains 56 ng/g, and the grey matter of the midbrain contains 482 ng/g [26,27]. *In vitro* experiment have demonstrated that the concentration of serotonin that is secreted from pinealocytes into the medium increases rhythmically during the day, reaches its peak value at the beginning of the night and then drops significantly. One study revealed that the secretion of 5-HT and melatonin from the pineal gland, which was monitored by microdialysis, was increased in the 1st and 4th hour prior to the increased synthesis of melatonin in rats and Syrian hamsters [41]. Other studies have confirmed that the highest average value of secreted 5-HT corresponds to the highest average activity of TPH1 [32], which is an enzyme involved in serotonin biosynthesis.

Apart from its role as a melatonin precursor, serotonin is also an important neurotransmitter that mediates the regulation of appetite, circulatory system function, breathing, reproduction, thermoregulation and higher mental functions, such as learning and memory [35]. Information for the modulation of SCN activity is sent via serotonergic pathways either directly from the medial raphe nucleus or indirectly from the dorsal raphe nucleus with NPY neuron projections from the DHN and intergeniculate leaflet (IGL) (Fig. 1) [17]. The serotonin receptors 5-HT1B, 5-HT7, and 5-HT2C and the serotonin reuptake transporter (SERT) are found in the SCN, and clock genes are expressed on serotonergic neurons [4,11,29]. Serotonin has a presynaptic effect on afferent endings in the retina and a postsynaptic effect on SCN neurons, which blocks inputs sent from the retina to the SCN [11,43]. Recent studies have confirmed that the mRNA expression of *tph2* in the raphe nuclei of the brain stem is subject to rhythmic regulation similar to the secretion of 5-HT from SCN neurons. In addition, the level of the *tph2* transcript also changes during the circannual cycle, displaying a clear declining tendency in the winter months [6,36]. The concentration of 5-HT metabolites and monoamines in blood plasma is also markedly lower in the winter, and the introduction of light impulses at that time of year increases the concentration of these compounds in the peripheral circulation [11,33]. Studies have shown that a deficiency of serotonin in the winter months causes the so-called seasonal affective disorder (SAD) [11]. The rhythm of the activity of serotonin neurons is also shown as circadian changes, with a clear downward trend during the dark phase and an increase during the light phase. The changes were revealed in the dorsal raphe nucleus (DRN), hypothalamus and striatum; and these changes are likely the result of interactions between melatonin and serotonin. Anatomic proof of the existence of direct dependence between these two hormones is demonstrated through the proximity of their receptors in the DRN. The inhibitive impact of exogenous melatonin on the immunoreactivity of serotonin neurons in the DRN was observed, and the receptor of melatonin type 1 (MT1) acted as an agent in this effect. However, removal of the pineal gland increased immunoreactivity and the serotonin content in DRN during the dark phase. Moreover, the suppressive effect of exogenous melatonin on serotonin secretion from the synaptosomes of the anterior and preoptic hypothalamus was observed *in vitro*, which indicates that, although the interaction between serotonin and melatonin in the context of circadian changes primarily occurs in the DRN, other areas of the CNS also