REVIEW

MELATONIN AND MONOAMINERGIC SYSTEM – BEHAVIOURAL ASPECTS

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ABSTRACT

Melatonin, the hormone synthesized mainly by the pineal gland, is a key member of the complex monoaminergic signaling system, and a circadian regulator with pleiotropic functions. This ubiquitary lipophilic and hydrophilic molecule acts both at cellular and subcellular level, exerting anti-inflammatory, anti-oxidative and anti-apoptotic activities, extremely important in the nervous system, given its high vulnerability to oxidative injury. Melatonin deprivation and the consecutive chronodisruption are associated with multiple behavioural abnormalities, psychiatric disorders and neurodegenerative diseases. The present review summarizes the available information concerning the link between melatonin, monoaminergic neurotransmission and the pathophysiological bases of these conditions.

Keywords: melatonin, serotonin, norepinephrine, dopamine, neuroprotection, anxiety, depression, memory, aggression

INTRODUCTION

Melatonin is an endogenous indoleamine mainly produced by the pineal gland with a circadian rhythmicity. In the past years, this hormone has been found in the highlight of medical research, due to its multiple roles in human and animal physiology: circadian regulator (1-6), antioxidant (7-17), sleep inducer (18-24), anti-carcinogenic (25-27), immune-modulator (28-36), neuroprotection (37-40).

Melatonin has an extensive role in the physiology and physiopathology of the nervous system, both by its remarkable antioxidant properties and functional networking with the monoaminergic neurotransmission system.

Most of melatonin is of pineal origin, but there seem to be also other central nervous system sources. These sources are not known, but mRNA for arylalkylamine N-acetyltransferase (AANAT) and hydroxyindole-O-methyltransferase (HIOMT), key enzymes in the melatonin synthesis, have been identified in the brain tissue of rats (41). The astrocytes of rats and the human glioma C6 cell line have been found to produce melatonin under *in vitro* conditions (42). Melatonin level in the cerebrospinal fluid is much higher than its maximum plasmatic one, and studies in sheep sustain a direct release of melatonin in the cerebrospinal fluid of the third ventricle (43). Several studies point the role of melatonin in different behaviours such as learning, anxiety behaviour, depression, stress response (41-52), memory (53) and pain perception (55-57). Abnormalities of melatonin secretion are associated with different psychiatric disorders in humans (bipolar disorder, depression, bulimia, an-

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orexia, schizophrenia, panic attack, and obsessive compulsive disorder), but its involvement in the pathophysiology of these diseases has not being clearly established (54).

Melatonin was shown to be neuroprotective to both fetal and adult brain (70-77), especially by its powerful antioxidant action. By this effect, melatonin seems to be involved in aging, aging-related nervous system pathology, neurodegenerative disorders and neuropsychiatric diseases.

Melatonin and neuroprotection

A common pathophysiological mechanism of neuropsychiatric diseases is increased brain inflammatory response caused by exposure to proinflammatory agents and accumulation of degenerated neurons, oxidized proteins, lipid peroxidation or glycated products in the adult brain (58). These oxidative stress processes are also involved in the pathophysiology of neurodegenerative diseases (Alzheimer's disease, Parkinson's disease, multiple sclerosis, lateral amyotrophic sclerosis, Huntington corea and tardive dyskinesia) (59). Nervous system cells produce a high quantity of free radicals mainly due to the biochemical composition of the neurons that contain unsaturated lipids, with a very intense sensitivity to peroxidation and other oxidative processes (60). Recent research has shown a particular sensitivity of nervous system cells to oxidative stress, free ROS triggering apoptosis in both glial cells and neurons (61).

Melatonin, by melatonin radicals, exerts its antioxidant properties by direct scavenge of hydroxyl radical (HO.), superoxide anion radical (O_2.-), hydrogen peroxide (H_2O_2), nitric oxide (NO.) and peroxynitrite anion (ONOO-) (62). Moreover, melatonin metabolites which result during ROS neutralisation processes are even more powerful antioxidant agents (63,64). Except for this direct role, melatonin exerts an indirect one through enhancing antioxidant enzymes activity (glutathione peroxidase, superoxide dismutase, catalase) and glutathione synthesis in the cells (65,66). Melatonin also contributes to mitochondrial homeostasis, lowers free radicals generation at this level and enhances ATP production, by direct stimulation of I and IV enzymatic complexes. This is referred as the free radical avoidance effect of melatonin (67).

A comprehensive body of evidence suggests the neuroprotective effect of melatonin, by virtue of its anti-inflammatory, anti-oxidant and anti-apoptotic effects. Fetal and neonatal brain neuroprotection efficacy of melatonin has been reported in several studies conducted in animals. Its administration after 10 minutes following a hypoxic-acidemic episode, lowered apoptosis, inflammation and gliosis in the brain of sheep fetuses (70). Melatonin treatment before and during temporary fetal asphyxia stabilized blood-brain barrier and reduced free hydroxyl radicals, lipid peroxidation and apoptosis in the fetal brain (71).

Maternal melatonin administration reduced fetal asphyxia, enhanced neurodevelopment and lowered cerebral damage and oxidative stress in an animal model of intrauterine growth restriction in newborn lambs (72). Melatonin was also proven to augment neuroprotection, when combined with therapeutic hypothermia against transient hypoxic-ischemic brain injury in a piglet model of perinatal asphyxia (73). Systemic melatonin administration in newborn rats with intracerebral haemorrhage showed a positive effect on the consecutive cerebral atrophy, cognitive and sensorimotor dysfunctions (74). In asphyxiated human newborns melatonin showed a significant decrease in plasma levels of nitric oxide metabolism end products (nitrate/nitrite) and lipid peroxidation (75).

As an effective antioxidant and neuroprotective molecule, melatonin synthesis may be induced by a negative feedback loop triggered by high oxidative stress or other stresses. Stress-induced melatonin production has been observed in rat pancreas (76) and in human cerebrospinal fluid after brain trauma (77).

Functional relationship between melatonin and central monoaminergic system

Melatonin influences normal function of the central nervous system, through a fine interaction with central neurotransmitters, especially the monoaminergic ones: serotonin, norepinephrine and dopamine.

Melatonin and serotonin

First, serotonin has a biosynthetic relationship with melatonin, as the latter is a tryptophan derivative (N-acetyl-5-methoxytryptamine), in a pathway that has serotonin as an intermediate product. Melatonin synthesis is regulated by the suprachiasmatic nucleus (SCN) of the hypothalamus that receives serotonergic afferent fibers from the median nucleus of the mesencephalon (78,79). It appears that serotonin modulates the manner in which light influences the suprachiasmatic nucleus, by controlling glutamate release at the level of the retinohypothalamic tract (80). The administration of a serotonin agonist determines variations in the su-

prachiasmatic nucleus rhythm (81). The molecular mechanism by which serotonin influences SCN is not known, but an interesting theory points that serotonin raises K+ influx at postsynaptic level in a population of neurons in the nucleus (82). Another study shows a presynaptic influence of serotonin (83).

It seems that serotonin synchronises circadian rhythms, as similarly the light does, but it works only under light conditions, in the dark/night its administration having no action on Clock genes expression (84). This effect may be explained by a circadian manner of expression of the serotonergic receptors (85). Interestingly, melatonin has an inhibitory role on the serotonin secreting raphe nuclei, via the melatonin type 1 receptor (MT_1) (86).

Melatonin and norepinephrine

SCN is regulating melatonin secretion via a multisynaptic pathway. First of all, it sends fibers to the superior thoracic segments of the spinal cord that in turn sends fibers to the C_1 ganglion of the paravertebral sympathetic chain. Postganglionic fibers reach the pinealocytes and influence them through a noradrenergic synapse (87). In darkness, noradrenaline release in the synaptic cleft is enhanced and determines a raise in intracellular cAMP levels by acting on beta1 receptors, leading to AANAT synthesis and melatonin secretion (88,89). Melatonin pineal synthesis depends on this rate-limited enzyme that catalyses serotonin N-acetylation (90).

There are other mechanisms by which noradrenaline controls melatonin secretion: insulin enhances melatonin synthesis and AANAT expression, whilst substance P (for which pinealocytes have receptors) inhibits AANAT synthesis (91,92).

Melatonin and dopamine

Dopamine is the precursor of norepinephrine. Secretory cells of the pineal gland have a high expression of D_4 dopaminergic receptors, and their expression seems to be modulated by light (93).

Melatonin controls dopamine synthesis in certain brain regions like the hypothalamus, tuberoinfundibular region and the ventral hippocampus (94). Some studies show that melatonin might have a direct effect on dopaminergic receptors producing a raise in D_2 receptor expression in the striated nucleus of the rat (95). Localisation of the MT_1 and MT_2 receptors at the level of the SCN overlaps with dopaminergic receptors in the hippocampus, cortex and hypothalamus (96-98). It has been demonstrated that dopaminergic receptors have a circadian manner of expression, being low during light conditions (99). Melatonin shows a protective role in medication induced dopaminergic motor dysfunctions in rats (100,101).

Monoaminergic system involvement in neurodegenerative diseases

There are several studies pointing the involvement of the monoaminergic system and associated areas (raphe nuclei, hippocampus and locus coeruleus) in the pathophysiology of neurodegenerative diseases, including Alzheimer's disease (AD) (102,103), supporting the association of depression in these diseases (104,111,112).

A low melatonin level in the cerebrospinal fluid has been found in AD patients (68), correlated negatively with the disease severity (69). Also, brain and cerebrospinal levels of norepinephrine and its metabolite (3-metoxy-4-hydroxyphenylglycol) have been found low in patients with AD compared to healthy controls (105,106).

Post-mortem determinations of serotonin in Alzheimer's patients have shown its low levels in both cerebral tissue and cerebrospinal fluid (107, 108), negatively correlated with the severity of the disease (109). A significant loss of 5-HT neurons in the raphe nuclei has been found (113,114) and 5-HT is decreased in the brain of depressed AD patients (115). Extrapyramidal symptoms are present in up to 30% of AD patients, and also when Parkinson's and Alzheimer's diseases overlap (110), sustaining the coexistence of dopaminergic dysfunction.

Parkinson's disease degeneration targets the nigrostriatal dopaminergic system (116), but serotonin and noradrenaline systems have also been shown to be involved (117). Thus, Parkinsonian tremor is accompanied with serotonergic impairment (118) and the Parkinson's disease associated psychiatric disorders (dementia and depression) have a direct relationship to the monoaminergic dysfunction, supported by the therapeutic use of monoamine oxidase inhibitors (MAOI) in Parkinson's associated depression (119).

Melatonin and the pathophysiological basis of depressive disorders

Pathophysiological mechanisms of depressive disorders are not entirely known but there is enough evidence that points the contribution of genetic, environmental, anatomic and functional dysregulations of the central nervous system. There are two

neuroanatomical pathways involved: the first one includes the amygdala, mediodorsal nucleus of the thalamus, and prefrontal cortex, and the second one includes strium and globus pallidus (120).

The neurobiological hypothesis of depression shows an abnormal interaction between the three monoaminergic systems (serotonin, norepinephrine and dopamine). The noradrenergic neurons have a functional intermediate position between the serotonergic and dopaminergic ones, controlling the amplitude and rate of action potentials of the dopaminergic neurons in the ventral tegmental area, an area crucially involved in mood (120).

Serotonin deficiency seems to be the most important pathophysiological mechanism, this idea being supported by the intensive use of selective serotonin reuptake inhibitors (SSRI) in depression treatment. There are 14 subtypes of serotonin receptors (121), from which 5-HT1a, highly expressed in the cortex, limbic system and hippocampus, being the most important one in depression pathogenesis (122).

Nocturnal melatonin levels are low in subjects with major depressive disorder (123,124) and also in people with seasonal (125) and melancholic depression (126). Major depressive disorder is associated with circadian rhythm abnormalities. Li et al. have shown dysregulations in the synchronisation activity of the internal biological clocks, day/light succession and abnormal clock genes expression in major depressive disorder (MDD) (127).

MT_1 receptors knock-out mice show a low mobility in forced swim and tail suspension despair tests that in depressive behaviour test in lab animals. These results may be related to neurobiological and behavioural abnormalities, corresponding to human melancholic depression (128). Melatonin's involvement in depression is supported by the fact that agomelatin, a non-selective MT_1 and MT_2 receptors agonist and 5-HT2c serotonin receptors selective agonist, has a high efficacy in depressive disorders treatment, measured by clinical psychiatric scores (129-132).

Shahnaz et al. (2012) monitored morning and nocturnal levels of melatonin in patients with MDD. Their data showed that nocturnal serum melatonin levels in depressed patients were lower than in controls. Also, the peak melatonin phase in the depressed patients was reached with a delay, compared with controls. All these data sustain that melatonin deficiency may be among the factors involved in depression incidence in patients with MDD (133). Also, a study on acute multiple sclerosis patients with concomitant MDD showed that the nocturnal melatonin peak occurred 77 minutes later than in patients without depression (134).

The relation between serotonergic neurotransmission and melatonin, other than the biosynthetic pathway connection, is shown by the rise in cerebral serotonin levels after melatonin administration (135).

Regarding the genetic factors involved in depression, it is hard to point one specific gene but some studies have identified 5-HTT and brain-derived neurotrophic factor (BDNF) as candidates. 5-HTT gene codes the serotonin reuptake inhibition at presynaptic level. Caspi et al. have identified the presence of a mutated allele of this gene to have a higher risk of depression following stressful events (136).

BDNF is mainly expressed in the nervous system, especially in the cortex and hippocampus. Egan et al. (2003) identify a single nucleotide polymorphism of the BDNF gene in which a valine-methionine substitution at codon 66 leads to depression in stressful circumstances (137). There are also studies in rats that associate depression with low BDNF expression in the hippocampus, and anti-depressive medication determines normalization of BDNF levels (138). BDNF expression in the adult brain is highest at the level of the hippocampus, amygdala and hypothalamus (139), areas involved in depression and anxiety disorders.

Kaufman et al. (2006) identify an interaction between three factors concurring to depression pathophysiology, the same short allele of 5-HTT gene as in the previously mentioned study, BDNF gene polymorphism and a stressful event (140). Melatonin positively modulates BDNF expression in the hippocampus and the cerebellum. This effect was investigated in a chronic sleep deprivation model in rats that follows the level of cognitive deficit (139). There are no studies showing the direct connection between melatonin levels and 5-HTT gene expression, but investigations in this direction are surely needed, considering the important functional link between melatonin and serotonin.

Melatonin deprivation in pregnant rats, in the second part of their pregnancy leads to depressive-like behaviour when assessed by the forced swim test, but with a normal appearance of the tail suspension test in adult male offspring (141). Because forced swim test is dependent on dopamine signaling solely, while tail suspesion test on both dopamine and serotonin, the authors concluded that melatonin deprivation in dams leads to abnormalities in serotonin secretion and/or signaling in adult offspring. This study points a probable prenatal

cause for depression, that may concur with the previousely mentioned pathophysiological cues.

Increasing amounts of data suggest that chronic inflammation is an important factor in the pathogenesis of depression (142). Proinflammatory cytokines activate indolamine 2, 3-dioxygenase (IDO), an enzyme that catabolizes tryptophan, the precursor of serotonin, impairing peripheral and cerebral serotonin synthesis (143) and producing neurotoxic metabolites. 3-hydroxykynurenine (3-OH-KYN) is one of these neurotoxic metabolites that initiate neuronal apoptosis by inducing reactive oxygen species production (144).

Melatonin and memory

Areas of the central nervous system involved in memory are the prefrontal cortex and amygdala for the long-term memory and hipoccampus, enthorhinal and parietal cortex for both of them (146). Short-term and long-term memories have different physiological mechanisms, involving specific monoaminergic neurotransmitters. Rat studies developed by Vianna et al. (2015) show that an infusion of a D_1 receptor antagonist substance stimulates short-term memory. Administration of a D_1 receptor agonist or a 5-HT1A one inhibits short-term memory without affecting long-term memory. Noradrenaline facilitates long-term memory, having no influence on the short-term one (145).

Clock gene expression seems to be important in memory. Distruction of the SCN or induced abnormalities of the circadian system by inappropriate light exposure, determine long-term memory impairment (147). Mice with clock genes mutations have abnormal hippocampus-dependent memory function (148,149). Melatonin itself has been shown to have a role in short-term memory. Argyrou et al. have investigated rats response to social olfaction memory, before and after intraventricular melatonin administration. Recognition time was shorter in the melatonin treated group than in the luzindol (selective MT_1 receptor antagonist) treated one (53). However,studies regarding melatonin involvement in memory are contradictory, as one shows that intra-amygdalian injection of melatonin in rats leads to alterations in spatial memory (150). Amir et al. (1999) have used c-Fos gene product determination for cellular activity measurment, showing that cortical areas involved in olfaction express the protein in a circadian manner. Also, olfactory stimulation leads to an enhanced c-Fos expression in the SCN (151). Granados-Fuentes et al. (2006) identified an intrinsec regulation system at olfactory bulb level and showed that circadian responsivity depends on circadian rhythm, being higher at night and lower during daytime in mice, rats and humans (152).

Melatonin and anxiety behaviour

Anxiety disorders represent the most common pshychiatric pathology in adults. This group is very heterogenous, but all subtypes encounter serotonergic and noradrenergic abnormalities and also disregulations of the hypothalamic-hypophyseal-corticosuprarenal and hypothalamic-hypophyseal-thyroid axes. There is also a documented genetic predisposition of anxiety disorders, based on studies involving twins. If one twin has an anxiety disorder, the other one has 50% higher risk to develop one in the future, compared with the general population (153).

Serotonergic pathways involved in anxiety (dorsal raphe nucleus) innervate the amygdala and prefrontal cortex, leading to an enhancement of the avoiding and run behaviour when facing a stress. Noradrenergic system (locus coeruleus) and dopaminergicone sensitize autonomic activation and vigilence as threat responses (154).

Melatonin has an anxiolytic effect (155). Anxious behaviour has been linked with melatonin deprivation in adult Wistar rats. El Mrabet et al. (2012) point that pinealectomy in adult rats leads to both anxious and depressive behaviour, and that melatonin administration cancels these effects (156). Melatonin enhances the anxiolytic effect of diazepam, when symultaneously administered (157) and modifies anxiety behavioral tests response (forced swim test) under long-term administration (158). Apparently, the effect of melatonin on anxiety is modulated by GABA central release. A positive correlation between brain melatonin levels and GABA transmission has been identified in vivo and in vitro (159,160).

Clock circadian genes malexpression has been linked with anxiety. Mutant Clock gene mice show a higher anxiety level, when behaviourally assesed using open field test and elevated plus maze test (161). There is only one study regarding anxiety disorders in humans, in which 13 genes mutations were investigated. The study included 321 patients and 653 healthy controls and identified 3 possible anxiety- related genes: BCL-2, DRD-2 and PAWR (162). BCL-2 (B-cell CLL/Lymphoma 2) codes for a protein that has key functions in the central nervous system, its most important one being apoptosis regulation. Melatonin modulates BCL-2 expression in different organs (liver, B cells), but there are no studies using nervous system cells (163,164).

BCL-2 expression is low in anxiety disorders (165). DRD2 gene (dopamine receptor gene 2) has been shown to be induced by light in the retina and its mutations are strongly associated with anxiety disorders. There is no study showing a direct relationship between melatonin and DRD2 gene expression, but signaling mediated by the dopamine D2 receptor potentiates circadian regulation by CLOCK/BMAL1 (166). Clock protein is the central molecule of the circadian system, a transcription activator regulated by melatonin (167). Clock gene abnormalities have been associated with mood disorders and anxiety in several studies (168,169).

Melatonin and aggressive behaviour

Aggressive behaviour is primitive, but highly conserved on phylogenetic scale, including humans. It can be regulated by nervous and humoral mechanisms. Humoral regulation has been studied intensively, and there are several possible involved molecules: testosterone (170), progesterone (171), estrogens (172), melatonin (173), vasopressin (174), cortisol (175) and ghrelin (176).

Aggression is abolished in castrated males, this pointing a higher importance of sex hormones in its physiology (177). There are also studies showing that both central serotonin depletion (170) and high melatonin level enhances aggression (178,179). It was recently suggested that melatonin could mediate adrenal gland regulation of aggressive behaviour, by increasing adrenal dehydroepiandrosterone release (180)

CONCLUSIONS

Melatonin is an important neuromodulator in central nervous system, which acts on any of the three monoaminergic systems and on complex intricated pathways by which it depends upon eachother. Regulation of the melatonin secretion is rather simple, being enhanced by darkness and lowered by light, blue light having the most powerful inhibitory effect. This makes it very sensitive to external environment conditions in the era of blue light emitting electronic devices, depression and anxiety.

The hormone is involved in many types of behaviours such as depression, aggression, memory and anxiety. Its importance is crucial for the normal functioning of the central nervous system. The association of melatonin deprivation with behavioral abnormalities might be caused by the direct lack of modulation and abnormal functioning of the central monoaminergic circuits, but also by the resulted oxidative stress, confusing circadian inputs and gene expression abnormalities in the brain. Melatonin provides important antioxidant activity, inhibition of apoptotic processes and immunomodulatory effect. The effects of circadian system disruption have not been studied enough compared with their outcome in central nervous system physiology and pathology. Melatonin seems to be involved in the pathophysiology of both neuropsychiatric and neurodegenerative diseases, and the prevalence and/or severity of these diseases may have a direct link with unhealthy general chronodisrupting behaviours that modern society adopts.

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