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The pattern of melatonin receptor expression in the brain may influence antidepressant treatment

Eric Hirsch-Rodriguez, **Marta Imbesi**, **Radmila Manev**, **Tolga Uz**, and **Hari Manev**
Department of Psychiatry and the Psychiatric Institute, University of Illinois at Chicago, Chicago, IL 60612, USA

Summary

The pineal hormone melatonin produces most of its biological effects via G protein-coupled receptors MT1 and MT2. In mammals, these receptors are expressed in various tissues and organs including in the brain. Recent research points to a putative role of MT1/MT2 dimerization as a mechanism that could determine the receptor-mediated biological effects of melatonin. Brain content and the ratios between MT1 and MT2 receptors are affected by illness, e.g., Alzheimer's disease, and by prolonged drug treatment, e.g., antidepressants. New drugs with antidepressant properties that bind and activate melatonin receptors have been discovered. We hypothesize that endogenous, i.e., low, levels of melatonin could contribute to antidepressant effects depending on the expression pattern of melatonin receptors in the brain. Hence, we propose that a prolonged treatment with classical antidepressant drugs alters the brain ratio of MT1/MT2 receptors to enable the endogenous melatonin, which is secreted during the night, to further improve the antidepressant effects. A corollary of this hypothesis is that antidepressants would be less effective in conditions of pathologically altered brain melatonin receptors, e.g., in Alzheimer's patients or due to genetic polymorphisms. If our hypothesis is confirmed, supplementing classical antidepressant treatment with an appropriate dose of a melatonin receptor agonist might be used to improve antidepressant effects in subjects with a susceptible pattern of brain melatonin receptor expression.

Keywords

melatonin; G protein-coupled receptors (GPCR); MT1; MT2; GPR50; dimerization; depression; circadian

Introduction

Melatonin, *N*-acetyl-5-methoxytryptamine, is a tryptophan-derived molecule widely distributed in nature. Its functional role has been demonstrated in a wide range of organisms, from unicellular to plants, animals, and humans. In humans, melatonin is synthesized primarily in the pineal gland but is also produced by other organs such as the retina and the gut. Melatonin is an important regulator of physiologic functions; its chronobiotic properties are the most studied [1].

Correspondence: Hari Manev, M.D., Ph.D., Professor of Pharmacology in Psychiatry, Department of Psychiatry, University of Illinois at Chicago, 1601 West Taylor St., M/C912, Chicago, IL 60612, USA, Phone: 312-413-4558; fax: 312-413-4569; e-mail: E-mail: HManev@psych.uic.edu.

It is believed that the majority of physiological effects of melatonin in mammals are mediated by specific G protein-coupled receptors (GPCRs) MT1 and MT2 [2,3]. In addition to their expression in the suprachiasmatic nucleus (SCN), these receptors are expressed in the mammalian central nervous system (CNS) including in humans [4-7].

Two additional proteins appear to act as melatonin receptors or melatonin receptor modulators. Thus, a third melatonin binding site, MT3, was recently identified as the enzyme NRH:quinone oxydoreductase 2 (QR2) [8]. Another protein, GPR50 (also termed H9 and ML1X), is an orphan GPCR that is about 45% identical overall to human MT1 and MT2. Althoug structurally related to MT1 and MT2 receptors, GPR50 does not directly bind melatonin [9,10] but it influences the binding of melatonin to MT1 [11]. It was reported that a deletion mutant of GPR50 is genetically associated with psychiatric disorders such as bipolar disorder and major depression [12].

CNS expression of melatonin receptors in the human brain appears to be affected by pathological conditions such as Alzheimer's disease. In this pathology, it was noted that distribution of MT1 and MT2 immunoreactivities is altered in postmortem brain from Alzheimer's patients compared to age-matched controls. Hence, in the hippocampus of Alzheimer's patients, MT1 immunoreactivity was significantly increased whereas MT2 immunoreactivity was decreased [13,14]. On the other hand, MT1 expression is decreased in the SCN of Alzheimer's patients [15].

Although melatonin has been considered for its therapeutic potential for a relatively long period of time, for example as a neuroprotective hormone with antioxidant activity [16], only recently have melatonin receptors been considered as the mediators of melatonergic therapeutic treatments [17].

Melatonin receptor dimerization

It is becoming increasingly evident that GPCR proteins frequently form homodimers or that they hetrodimerize with other members of the same receptor family [3]. The ongoing research in this field is directed towards better understanding of functional implications of GPCRs dimerization. These implications include effects on ligand binding, receptor signaling, and receptor trafficking. Melatonin receptors appear to be a good example of dimerizing GPCRs.

Ayoub et al. [18] have used a bioluminescence resonance energy transfer (BRET) assay to study MT1/MT2 dimerization in transfected HEK 293 cells. They found that the relative propensities for MT1 homodimer and MT1/MT2 heterodimer formation was similar, whereas the propensity for MT2 homodimer formation was 3- to 4-fold lower. With the addition of radioligand binding studies, these authors found that heterodimers contain two functional ligand binding sites that maintain their respective selectivity for MT1 and MT2 ligands and that occupation of either binding site induces a conformational change within the heterodimer. BRET methodology was also applied to monitoring the melatonin receptor dimerization in living cells transfected with melatonin receptors [19].

Recently, it was shown that GPR50 heterodimerizes constitutively and specifically with MT1 and MT2 receptors [11]. These authors found that GPR50 dimerization with MT2 did not modify MT2 function, but GPR50 dimerization with MT1 abolished high-affinity agonist binding and G protein coupling to the MT1 receptor. These results suggest that in spite of the fact that GPR50 does not bind melatonin, the dimerization of this protein with MT1 might be functionally important because it could modulate the balance of melatonin signaling between MT1 and MT2 pathways.

It appears that melatonin receptor dimerization may be particularly important in cells that in their native state co-express MT1 and MT2 receptors, for example, in certain types of CNS neurons [20].

Effects of classical antidepressants on brain MT1 and MT2 mRNA

Imbesi et al. [21] found evidence that the CNS content of melatonin receptor mRNA is significantly modified by prolonged treatment with antidepressants whereas a single drug injection did not alter MT1 and MT2 mRNA content. The effects of fluoxetine, desipramine, and clomipramine on mouse MT1/MT2 mRNAs were brain region-specific. In the hippocampus, protracted treatment with these antidepressants increased the amount of MT1 mRNA (with the exception of fluoxetine) but decreased MT2 mRNA conten. In the striatum, antidepressants produced the opposite effect on MT1 mRNA content; they decreased it. They did not significantly alter striatal MT2 mRNA. The similar effect of all three antidepressants on melatonin receptor expression is rather surprising because these drugs operate via different primary mechanisms of action. It was proposed that a common second or third messenger intracellular mechanism, which is triggered by protracted but not by a single drug application that may be responsible for the common therapeutic, i.e., antidepressant, activity of these drugs, also regulates the expression of melatonin receptors.

Here, we hypothesize that endogenous levels of melatonin could contribute to antidepressant effects depending on the expression pattern of melatonin receptors in the brain. Hence, we propose that a prolonged treatment with classical antidepressants alters the brain ratio of MT1/MT2 receptors to enable the endogenous melatonin, which is secreted during the night, to further improve the antidepressant effects.

Melatonin receptor ligands with putative antidepressant/anxiolytic activity

Agomelatine was recently introduced as the first melatonergic antidepressant [22]. This drug is a potent agonist of melatonin receptors MT1 and MT2 with antagonistic activity at the serotonergic receptor 5-HT2C. It was reported that 25 mg/day agomelatine was efficacious in treating major depressive disorder. Furthermore, agomelatine also produces a significant decrease of anxiety compared to placebo, according to Hamilton Rating Scale for Anxiety scores [22].

There is an ongoing search for novel melatonin receptor ligands [23]. One of the new compounds, termed UCM 765, shows 100 times higher affinity for MT2 than for MT1, but appears to be only a partial agonist for MT2 receptors. In preclinical tests in rats, relatively high doses of UCM 765 (e.g., 80 mg/kg) demonstrated anxiolytic activity in models of novelty-induced suppressed feeding and on the elevated plus maze [24]. It remains to be clarified whether the MT1 or the MT2 activation was responsible for the observed anxiolytic action of this new compound.

It was reported that MT1 knockout mice display depression-like behaviors in the Porsolt swim test [25]. However, these results have to be interpreted with caution because they were obtained in C57BL/6 mice, a strain known to be melatonin deficient [26]. Furthermore, it appears that this type of melatonin deficiency in mice favors depression-like behaviors [27,28].

In addition to new synthetic melatonin receptor ligands, an appropriate dose of melatonin (i.e., a low dose operative at the receptor level) might also be considered for therapeutic purposes. For example, winter depression (seasonal affective disorder; SAD) is a mood disturbance that occurs year after year in susceptible subjects. It was suggested that circadian phase shifts are at the core of the pathology of this disorder. Corrective changes in these phase shifts can be

achieved with the administration of very low doses of melatonin (0.225-0.3 mg/person/day), i.e., doses that do not induce sleepiness [29].

In spite of the widespread use of antidepressants in the elderly population, elderly depressed subjects aged 75 years and over are underrepresented in clinical trials of potential antidepressants. Hence, the principle of depression treatment is derived mostly from studies employing young adults and healthy elderly [30]. It was suggested that the efficacy of antidepressant therapy with SSRI may be reduced in elderly subjects [31]. Melatonin levels are known to be reduced in elderly people [32]. According to our hypothesis, aging-reduced melatonin levels might contribute to the reduced efficacy of antidepressant treatments in the elderly.

Testing the hypothesis

Prospective clinical studies could be designed to evaluate the contribution of endogenous melatonin and melatonin receptors to therapeutic outcomes of antidepressant treatment. Several factors have to be considered in designing such studies. First, for endogenous melatonin to be effective, a subject must present an appropriate pattern of brain melatonin receptor expression. For example, MT1 and MT2 expression is altered in the brain of Alzheimer's patients [13-15]. Furthermore, it is conceivable that genetic polymorphisms of melatonin receptors, for example MT2 [33] and GPR50 [12] could also influence the brain melatonin receptor pattern. We postulate that in conditions of illness- or polymorphism-induced alterations of melatonin receptor expression melatonin may not be effective as antidepressant and it might be necessary to characterize the receptor status of subjects enrolled in studies.

Second, an appropriate, i.e., antidepressant, dose of melatonin must be identified. We hypothesize that this will be a very low, i.e., physiological dose of melatonin and that higher doses of melatonin may be ineffective, e.g., due to receptor down-regulation or receptor type-specific MT1 or MT2 internalization [34]. For example, administering slow-release melatonin in doses of 5-10 mg, which results in serum melatonin concentrations 100 times higher than the usual nighttime peak, was ineffective in treating depression [35,36].

Finally, since prolonged treatment with classical antidepressants may create a melatonin receptor expression pattern that favors melatonin's antidepressant activity, an appropriate schedule of combined antidepressant + melatonergic drug administration would have to be established. This may involve initial treatment with antidepressants only (to establish the new melatonin receptor expression pattern) followed by an introduction of supplemental therapy with melatonin or synthetic melatonin receptor agonists.

Conclusion

Recent research points to melatonin receptors as putative mediators of physiological actions of melatonin and as possible targets for therapeutic approaches. The evidence of melatonin receptor expression in the CNS, findings of altered MT1 and MT2 expression after prolonged antidepressant treatments, and suggestion that the pattern of MT1/MT2 receptor dimerization may significantly modulate melatonin receptor signaling prompted us to hypothesize that the pattern of melatonin receptor expression in the brain may influence antidepressant treatment. If this hypothesis is confirmed, novel and individualized antidepressant treatments could be developed that would take the characterization of patients' melatonin receptors into account.

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