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Contrasting Findings on Melatonin Concerning Inflammation and Glucose Tolerance - Consequences to the Development of Melatonergic Drugs

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Abstract

The pleiotropy of melatonin is a reason for using this hormone or synthetic melatonergic agonists for testing their suitability in various diseases and disorders. However, it is important to remain aware that many preclinical findings cannot be translated to humans, because of the different relationship between melatonin and sleep or activity in diurnally compared to nocturnally active mammals. Other uncertainties concern the dual role of melatonin as an either anti- or proinflammatory agent, depending on conditions. A particular problem has emerged by findings on prodiabetic actions of melatonin in humans, which strongly contrast with antidiabetic results obtained in rats. As these undesired actions are gradually receptor subtype-dependent, it may be worthwhile to test in the future agonists that are more strongly subtype-selective.

Keywords: Inflammaging; Inflammation; Insulin Resistance; Melatonin; Type 2 Diabetes

Introduction

Melatonin is a highly pleiotropic regulator that exerts effects in the majority of mammalian cells. In the pineal gland, it is mainly synthesized at night, released to the circulation and, via the pineal recess, into the third ventricle of the brain. It transmits the information 'darkness' to peripheral organs and to brain areas as well. This association with darkness already implies a profound difference between nocturnally active rodents and day active species such as the human. In rats and mice, high melatonin is related to enhanced alertness, locomotor activity and food intake, whereas the opposite is the case in humans, in whom melatonin acts as a sleep-promoting compound. The correlation with darkness is, except for the retina, either absent or less expressed in melatonin synthesized in extrapineal sites. Concerning immunological actions of melatonin, the gastrointestinal tract (GIT) and leukocyte subtypes are of particular interest, because they synthesize melatonin and express melatonin receptors [1]. Notably, the amounts present in the GIT are about 400 – 500 times higher than in the pineal gland and in the circulation. Functions of extrapineal melatonin have been poorly considered in the context of drug development.

The short half life of melatonin in the circulation (20 - 30, maximally 45 min) has prompted investigators to develop synthetic melatonergic agonists with longer persistence in the blood [2-6]. Additionally, the various synthetic agonists differ with regard to receptor affinity and receptor subtype specificity. However, most clinical studies on these compounds have focused on applications in sleep promotion [2-4,7] and, partially, treatment of depression [8,9].

Pro- or Antiinflammatory Actions

With regard to the two critical points addressed in this article, namely, (a) the anti-/pro-inflammatory balance and (b) glucose tolerance, immunological and diabetes-related effects shall be particularly considered. In leukocyte preparations or cultures of transformed myeloid or lymphocytic cell lines, melatonin induced mostly proinflammatory responses [10,11]. Prevailing effects consisted in up regulation of the proinflammatory cytokines IL-1β, IL-2, IL-6, IL-8, IL-12, IFNγ, and TNFα, down regulation of the antiinflammatory cytokine IL-10, and, in monocytes, strongly enhanced production of reactive oxygen species. These findings, which imply a prooxidative role by stimulating inflammation, markedly contrast with the otherwise well-documented antioxidative properties of melatonin [1,12]. However, antiinflammatory actions of melatonin have been also reported [13,14].

These were particularly observed in response to strong inflammatory insults, such as endotoxemia and sepsis, and comprised down regulation of proinflammatory mediators, cytokines as well as NO and prostaglandins. Additionally, decreases of mitochondrial electron leakage reduced the inflammation-

enhancing damage by free radicals. Effects included up regulation of respirasomal subunits, enhancement of reduced glutathione and glutathione peroxidase-4, and decreases of reactive nitrogen species, especially peroxynitrite [12-14]. Antiiflammatory actions were especially reported for various tissues of senescent rodents, including down regulation of IL-1β, IL-6 and TNFα as well as up regulation of IL-10. These changes were associated with reduced expression of iNOS (inducible NO synthase) and up regulation of the antiaging factor sirtuin 1 (SIRT1). These findings indicate a role of melatonin in counteracting inflammaging [12-14]. However, a problematic proinflammatory effect remains especially in humans, namely, the observed aggravation of arthritis [15,16]. The contrasting effects of melatonin under different conditions remain to be clarified in detail.

Contrasting findings concerning type 2 diabetes

Up regulation of SIRT1 by melatonin was described in the gerontological context, contrary to findings in tumor cells [17]. These results are of importance insofar as SIRT1 is also an amplitude-enhancing accessory component of both central and peripheral cellular circadian oscillators. Circadian amplitudes including that of the melatonin rhythm typically decline during aging [17]. Moreover, SIRT1 was reported to counteract insulin resistance [17,18] and to possess antiinflammatory properties [19]. These associations of melatonin with SIRT1 contrast with reports on prodiabetic actions of melatonin in humans [20,21].

As recently discussed [17], these findings in humans are at variance with numerous preclinical results on antidiabetic actions in rodents. It seems important to be aware of the above-mentioned differences between humans and nocturnal animals concerning the association of melatonin with phases of food intake. In humans, melatonin was shown to decrease glucose tolerance, and this was aggravated in carriers of a prodiabetic risk allele of the gene of the melatonin receptor MT_2 (G allele of *MTNR1B* carrying the SNP rs10830963) [22], which is notably over expressed in beta cells [20,21]. However, the situation turns out to be more complicated, as dysfunctional *MTNR1B* alleles are also prodiabetic, as type 2 diabetes is associated with decreases in melatonin, and as the strong up regulation of the G allele is typically observed in midlife, when both melatonin and circadian amplitudes are already substantially decreased, especially in the prediabetic state. These declines have been recently discussed in terms of possible causes of the diabetogenic G allele up regulation [17].

Conclusion

Considerations on receptor subtype selectivity

The use of synthetic melatonergic drugs has to consider these problems of poor translatability from rodents to humans. Caution is due especially in elderly patients, which may suffer from comorbidities such as (a) arthritis or other autoimmune diseases, or (b) diabetes, prediabetic states or metabolic syndrome. Moreover, the suitability of a melatonergic agonist may depend on its relative affinity to the two main receptors, MT_1 and MT_2 (encoded by *MTNR1A* and *MTNR1B* genes, respectively). As far as the immune system is concerned, the prevailing receptor subtype is MT_1 [1]. Proinflammatory complications may be reduced if agonists are used that preferentially act via the MT_2 receptor.

Apart from the demand that such a better suitability in humans remains to be clinically proven, one has also to take into account a difference between most laboratory rodents and the human concerning the receptor subtypes involved in circadian resetting by melatonergic agonists. In most but not all rodents, MT_2 is involved in the resetting of the circadian clock, whereas this subtype is much less expressed in the human circadian master clock, the suprachiasmatic nucleus (SCN), in which this function is largely taken over by MT_1 [1]. As far as circadian entrainment is desired to reduce sleep difficulties or psychiatric problems related to circadian misalignment, a preferentially MT_2-selective agonist should be expected to fail. On the other hand, the role of MT_2 over expression in type 2 diabetes may be taken as a hint to test MT_1-selective agonists in patients with a diabetic risk.

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