

Melatonin: recent developments in research of melatonin and its potential therapeutic applications.

## **Editorial**

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This Themed Issue was prompted by a symposium at the annual meeting of the British Pharmacological Society held, in London, in 2016. It was obvious that the session had barely scratched the surface of what has been discovered about the pharmacodynamics of melatonin and that a Themed Issue on this compound in the *British Journal of Pharmacology* was long overdue. As will become clear, melatonin has a wide range of actions, only some of which are mediated by melatonin receptors (MT<sub>1</sub> and MT<sub>2</sub>); others include free-radical scavenging as well as targets on mitochondrial membranes and the cell nucleus.

Melatonin was first discovered over a century ago and it is more than 50 years since its isolation from pineal tissue extracts and the first report that its production follows a circadian rhythm. That aspect of its function has attracted a great deal of attention: most members of the lay public are aware that melatonin comes out at night (it is known as the ‘Dracula hormone’) and some people take it to sort out their jet lag, despite the skepticism about its beneficial effects for that indication. What is less well-known is that other aspects of health and disease, such as neurodegeneration, diabetes or cancer, are also influenced by melatonin, either directly or indirectly. This collection of articles draws attention to this diverse spectrum of actions and explains the underlying mechanisms, insofar as that is possible

To start on familiar territory, Zisapel updates the evidence for regulation of sleep rhythms by melatonin. Whereas the suprachiasmatic nucleus (SCN) is the ‘metronome’ for the circadian cycle (and many other aspects of internal body state, such as thermoregulation and autonomic arousal), melatonin is a major contributor to the process of entraining its rhythmic activity. Secretion of this hormone from the pineal is influenced by light and it serves as a signal for ‘darkness’, even in nocturnal animals. This hormone prevents arousal, which is mediated by the SCN, and promotes (but does not induce) sleep. Zisapel discusses evidence that the epicenter for this latter action is probably the precuneus, in the cerebral cortex, but involves several other brain regions, collectively known as the ‘Default Mode Network’ (DMN).

In fact, melatonin receptor antagonists are now approved for treating sleep disorders of the blind. Because melatonin secretion and melatonin receptors (including the MT<sub>1</sub> subtype, which are densely expressed in the SCN) decrease with age, this hormone might also have some

benefit in treating insomnia in the elderly. However, its half-life is less than 1h and so any therapeutic action is likely to depend on a formulation that provides prolonged release of melatonin (PRM). In that respect, this field can claim translational success because PRM now has regulatory approval for short-term treatment (<3 weeks) of insomnia in the elderly. However, Zisapel also comments on the interesting, bidirectional association between disrupted sleep rhythms and other disorders, such as hypertension and Alzheimer's Disease (AD). An association between sleep disruption and obesity can be added to that list too. She goes on to suggest that, in the case of AD, overactivity of the DMN during the night could promote  $\beta$  amyloid deposition, which is thought to exacerbate neurodegeneration. If so, then melatonin could have beneficial effects in prevention of AD and other disorders associated with mental ageing. Subsequent reviews in this series endorse that view and offer different types of mechanistic evidence.

Disruption of the sleep-waking rhythm has long been associated with psychiatric disorders, especially those that affect mood and cognitive performance (such as depression and Attention Deficit Hyperactivity Disorder). Indeed, agomelatine, which is an agonist at  $MT_1$  and  $MT_2$  receptors (as well as a 5-HT<sub>2c</sub> receptor antagonist) was developed as an antidepressant, but its approval by licensing authorities was thwarted by a lack of convincing evidence for efficacy. Notwithstanding this set-back, Valdes-Tovar et al. (2018) review the evidence that beneficial effects of melatonin in depression might not be a primary action but could arise as a secondary consequence of it resetting disrupted circadian rhythms. To support that view, they go on to discuss evidence that melatonin regulates neurogenesis and neuroplasticity in the hippocampus, as do antidepressants with confirmed clinical efficacy. Moreover, its effects in a range of preclinical procedures that are used as predictive screens for antidepressant drugs (e.g., the Forced Swim Test and the Tail Suspension Test) seem to be mediated by activation of melatonin receptors, with the clock genes (*Per1* and *Per2*) and BDNF production as downstream, intermediate targets.

What remains to be established is whether or not neurogenesis in the hippocampus underlies the beneficial effects of antidepressants on mood, as is assumed in this article, or whether this neurogenesis is more relevant to the relief of cognitive impairment, which can be

profound in depression and related psychiatric disorders. Whatever, evidence covered in this review suggests that melatonin might be a useful adjunct to established antidepressant treatments, even if there is little enthusiasm for using it as an antidepressant in its own right.

Continuing this theme, Bahna and Niles discuss recent findings that melatonin has profound epigenetic influences that could influence mood. They draw attention to the neurobiological effects of sodium valproate (which is an established treatment for mild mood disorder) and the upregulation of MT<sub>1</sub> and MT<sub>2</sub> receptor expression in the brain following treatment with this drug. This process recruits a wide range of underlying mechanisms: DNA methylation, inhibition of histone deacetylase (HDAC) enzymes, regulation of non-coding RNAs and posttranslational modification of histone proteins, all of which modify gene expression. Whereas some actions are mediated directly, others involve melatonin receptors. This leads to the interesting possibility that valproate, either alone or in combination with melatonin, could have beneficial effects in treating neurological and psychiatric disorders that are associated with a functional deficit in melatonin and/or its receptors.

Another interesting hypothesis is offered by Arribas et al. (2018), who review evidence that protective effects of melatonin rest on its regulation of the activity of phosphoprotein phosphatases, which comprise three groups: Tyr phosphatases, Ser/Thr phosphatases and those with a dual action. The Ser/Thr superfamily are the focus of this review and the authors propose that melatonin could have a neuroprotective effect that is mediated by augmenting directly the activity of the PPP family of these enzymes. Their range of actions, together with the number of their polymorphisms and endogenous inhibitors is truly breathtaking. Arribas et al. suggest that, by augmenting the function of PPP enzymes, melatonin could have beneficial effects in conditions ranging from neurodegenerative disorders (such as Alzheimer's and Parkinsons' diseases) as well as light-sensitive retinopathies, cancer, pain and cognition.

The next theme turns to melatonin as a mediator of the circadian rhythm in inflammatory disorders, including bone disease, which is reviewed by Jahanban-Esfahlan et al. (2017). Inhibition of the proinflammatory transcription factor, NF- $\kappa$ B signaling is thought to be particularly important in this respect, not least because it promotes (extra-pineal) synthesis of melatonin in macrophages, but whether this is beneficial, or harmful in models of

inflammation-induced arthritis currently unclear. By contrast, melatonin does not seem to have beneficial effects in osteoarthritis, which actually strengthens the evidence for the putative functional link between melatonin, the immune system and inflammation. The authors review possible mediating mechanisms and, in so doing, provide a fascinating summary of the evidence linking circadian rhythms, pro-inflammatory cytokines, clock genes and clinical prognosis in arthritis.

This theme is continued in the review from a group that has contributed pioneering work on the regulation of melatonin production within the pineal *versus* immune competent tissues (the 'immune – pineal axis'). On the basis of a portfolio of endocrine, paracrine and autocrine actions for melatonin, Markus et al. explain how melatonin could affect processes as diverse as: migration of leukocytes through the vascular endothelium; macrophage and microglia phenotype; the life cycle of infective parasitic organisms; tumour growth and neurodegeneration. Markus et al. propose that synthesis and release of melatonin switches between the pineal gland and immune competent cells, and back again, and that this process is a component of the fine control of the inflammatory response. A clear stream of evidence, throughout this review, is that the NF- $\kappa$ B pathway has a fundamental role in co-ordinating the 'switch' and could help explain why inflammatory responses have a circadian rhythm.

There is also a good deal of evidence that melatonin prevents cancer growth, which is interesting in view of the strikingly higher incidence of some cancers in shift workers. In their review, Li et al. cite evidence from studies of haemopoietic neoplasms, mainly as specific examples of what is possibly a more general case. They offer evidence that melatonin promotes the death and prevents proliferation of a range of different cancer cells. Possible mechanisms are discussed, which might vary with the type of cell and/or cancer and do not depend on melatonin receptors. It is interesting that the cytotoxic effect of melatonin in cancer cells seems to involve production of reactive oxygen species (ROS) whereas, in normal cells, melatonin has the opposite effect (antioxidant effects) because it is a scavenger of oxygen, nitrogen and hydroxyl radicals. Explanation of this paradox could be crucial. Also mentioned is evidence that melatonin protects bone marrow and lymphoid tissue during immunotherapy and promotes bone marrow regeneration during chemotherapy. These observational studies

are fascinating and there is clearly scope for much more research in this field, followed by exploitation of the underlying mechanisms, when they have been identified.

The final theme covers the molecular pharmacology of melatonin receptors. In their review, Cecon et al. (2017) make a gentle start by explaining that  $MLT_1$  and  $MLT_2$  are both G protein-coupled receptors, with several coupling targets, before going on to outline their distribution, structure, function and pharmacology. The authors then discuss the possibility of developing multi-target-directed, 'hybrid ligands', which combine melatonin with other drugs, to achieve additive therapeutic effects. Examples include: tacrine / melatonin and donepezil / melatonin. In fact, they point out that agomelatine could be regarded as considered just such a hybrid.

Subsequent sections of this review open a Pandora's box by describing the evidence for melatonin receptor biased-ligands. Melatonin receptors are predominantly, but not invariably, coupled to Gi/o proteins and material in this review makes it clear that this aspect of the pharmacodynamics of melatonin depends on the mixture of receptors and their environment. Environmental differences include: cell type; cell context-dependent receptor expression; receptor homo- and heterodimerization; and even features of the lipid membrane. These variables also influence epigenetic responses to melatonin and Cecon et al. suggest that this could explain why the effects of melatonin on circadian clock gene expression depend on cell type. However, the coup de grace is the evidence that over 300 different proteins interact with  $MT_1$  and only about 50 of them overlap with proteins that interact with  $MT_2$ . Evidently, achieving a comprehensive understanding of the regulation of these receptors *in vivo* is not going to be straightforward.

In an accompanying research paper from this group, Clement et al (2017) provide evidence that the function of the  $MT_1$  receptor depends on the structure of the second extracellular (E2) loop. This is gleaned from sequencing of the GPR50 (loss of function) orphan receptor, which binds melatonin in lower species, but not mammals. Their paper describes the results from  $MT_1$ -GPR50 chimera studies, in combination with molecular modelling *in silico*, and leads to the conclusion that it is the primary and secondary structure of this loop that determines its ligand binding and options(s) for signal transduction. It turns out that GPR50 forms heterodimers with

MT<sub>1</sub>, which blunts activation of this receptor; Clement et al. propose that this could be important for research of melatonin and mental disorders.

In summary, this themed review does not help us to answer the question “what is melatonin for?”, unless it has a fundamental role in maintenance of health and prevention of a wide range of diseases by serving as the chemical transducer for light entrainment of circadian rhythms. Whether or not this is the case, this collection of articles provides a fascinating insight into the pharmacodynamics of melatonin, but it is clear that attempts to uncover the details of the underlying mechanisms is not a job for the feint-hearted.

## References

- Arribas RL, Romero A, Egea J, de los Rios C. (2018) Modulation of serine/threonine phosphatases by melatonin: therapeutic approaches in neurodegenerative diseases. *Br J Pharmacol* (in press)
- Bahna SG, Niles LP. (2017) Epigenetic regulation of melatonin receptors in neuropsychiatric disorders. *Br J Pharmacol*. doi: 10.1111/bph.14058. [Epub ahead of print] Review.
- Cecon E, Oishi A, Jockers R. (2017) Melatonin receptors: molecular pharmacology and signalling in the context of system bias. *Br J Pharmacol*. doi: 10.1111/bph.13950. [Epub ahead of print] Review.
- Clement N, Renault N, Guillaume JL, Cecon E, Journé AS, Laurent X, Tadagaki K, Cogé F, Gohier A, Delagrangé P, Chavatte P, Jockers R. (2017) Importance of the second extracellular loop for melatonin MT<sub>1</sub> receptor function and absence of melatonin binding in GPR50. *Br J Pharmacol*. doi: 10.1111/bph.14029. [Epub ahead of print]
- Jahanban-Esfahlan R, Mehrzadi S, Reiter RJ, Seidi K, Majidinia M, Baghi HB, Khatami N, Yousefi B, Sadeghpour A. (2017) Melatonin in regulation of inflammatory pathways in rheumatoid arthritis and osteoarthritis: involvement of circadian clock genes. *Br J Pharmacol*. doi: 10.1111/bph.13898. [Epub ahead of print] Review.
- Li T, Yang Z, Jiang S, Di W, Ma Z, Hu W, Chen F, Reiter RJ, Yang Y (2017) Melatonin: does it have utility in the treatment of haematological neoplasms? *Br J Pharmacol*. doi: 10.1111/bph.13966. [Epub ahead of print]

Markus RP, Fernandes PA, Kinker GS, da Silveira Cruz-Machado S, Marçola M. (2017) Immune-pineal axis - acute inflammatory responses coordinate melatonin synthesis by pinealocytes and phagocytes. *Br J Pharmacol.* doi: 10.1111/bph.14083. [Epub ahead of print] Review.

Valdés-Tovar M, Estrada-Reyes R, Solís-Chagoyán H, Argueta J, Dorantes-Barrón AM, Quero-Chávez D, Cruz-Garduño R, Cercós MG, Trueta C, Oikawa-Sala J, Dubocovich ML, Benítez-King G. (2018) Circadian modulation of neuroplasticity by melatonin: a target in the treatment of depression. *Br J Pharmacol.* doi: 10.1111/bph.14197. [Epub ahead of print] Review.

Zisapel N. (2018) New perspectives on the role of melatonin in human sleep, circadian rhythms and their regulation. *Br J Pharmacol.* 2018 Jan 10. doi: 10.1111/bph.14116.