INTERVENTION INSIGHTS

Melatonin: hormone of the night

Melatonin is phylogenetically an ancient biological signalling system and has been identified as present in all major organisms, including bacteria, plants, invertebrate and vertebrate species (1). It appears to be a molecule with a multitude of biological functions, signalling not only the time of day and of the year but, perhaps, possessing immunomodulatory and cytoprotective effects (2). It is certainly among the first biological signals to appear on earth (3).

Melatonin is nocturnally derived by synthesis from tryptophan via serotonin, principally in the pineal gland, but extra-pineal sources of melatonin are also recognised, e.g. in the retina and gastrointestinal (GI) tract (2). The physiological and pharmacological mechanisms controlling the secretion of the hormone, at least in mammals, have been recognised for several decades (4). Regulation of synthesis is mediated by the retinohypothalamic tract, which projects from the retina to the suprachiasmatic nucleus (SCN), the major circadian oscillator in the body. Fibres pass from the SCN to the paraventricular nucleus, medial forebrain and reticular formation to influence the interomedial dorsal horn cells of the spinal cord where preganglionic sympathetic neurons innervate the superior cervical ganglion (SCG). The fibres of the SCG terminate on pinealocytes and regulate melatonin synthesis by releasing noradrenaline on to β-receptors (4). The absence of light decreases activity in the SCN, while pinealocyte activity is increased, particularly the production of the synthesis limiting enzyme *N*-acetyl transferase (4). Melatonin concentrations in plasma rise with the onset of darkness and begin to decline again in the early morning. This circadian rhythm persists in vertebrates irrespective of whether the animal is active at night or during daylight. Actions of melatonin are most likely mediated through a set of membrane receptors, MT1 and MT2 (5). These belong to the G-protein coupled seven trans-membrane spanning domain class of receptors. Each of the receptors may have particular functions such as induction of phase shifts (MT2) or suppression of neuronal firing (MT1). In addition to central effects some peripheral actions, e.g. vasoconstriction (MT1) and vasodilation (MT2), may also be mediated by melatonin receptors (5). Thus, several physiological functions have been proposed for melatonin.

Melatonin has been used as a marker of circadian phase, and plays an important role in the setting of circadian rhythms (6). Perhaps one of the better known uses of melatonin is its purported efficacy as a reliever of the symptoms of 'jet lag' (7). Antioxidant properties of melatonin have attracted attention, and its role as an oncostatic agent has also been examined (2,8). In psychiatric research, melatonin is of some interest, principally because of apparent circadian rhythm disturbances in major depressive disorder (9). The role of melatonin in sleep, as a probable signal for sleep onset, has clear implications for the treatment of psychiatric patients.

Melatonin and mood disorders

The interrelatedness of melatonin and circadian rhythms has been the impetus for studies in patients with major depression, examining both the absolute concentrations of melatonin and variations in circadian secretion patterns. With respect to melatonin concentrations findings have been mixed, but generally the amplitude of secretion (and therefore total amount of melatonin secreted) tends to be lower in depressed patients than matched controls (10). Antidepressant treatment tends to restore concentrations towards normal values (11). There are two fundamental difficulties with these findings. Many medications can decrease melatonin concentrations by interference with synthesis. Most importantly benzodiazepines are well-recognised suppressors (12). Thus, findings need to account for the presence of these agents as well as a range of other medications (e.g. β-blockers), which can also suppress melatonin secretion. Secondly many drugs can increase melatonin concentration by interference with liver metabolism of the hormone. Melatonin is principally metabolised by CYP1A2 and CYP1A1 leading to a hydroxylated form of the compound, which is subsequently conjugated and excreted in urine (3). Clearly inhibitors of these enzymes (including some antidepressants such as fluvoxamine) will increase circulating concentrations of the hormone, independent of fundamental changes in the biochemistry or physiology of the synthetic system. Thus, the diagnostic or prognostic value of the measurement of melatonin plasma concentrations is unlikely to be clinically useful.

The nocturnal secretion of melatonin is dose dependently suppressed by full spectrum white light (13). In patients with bipolar I disorder and seasonal affective disorder, it has been demonstrated that this sensitivity is increased compared to healthy controls (14). While not a universal finding, it may suggest dysregulation of the melatonin system in these disorders, as well as an alteration of circadian phase in patients where the abnormality is observed. More

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controversially light sensitivity has been proposed as an endophenotype of bipolar disorder (14). At present, data are lacking with respect to the sensitivity and specificity of the findings in bipolar disorder compared to other psychiatric conditions or within the bipolar spectrum. As in unipolar depression medication effects are likely to be a confounder of the interpretation of any findings. However, while mood stabilisers do not significantly interfere with light sensitivity (15,16), they have profound impacts on the circadian system principally via the clock genes, which regulate the circadian clock.

Melatonin as a hypnotic

The rise in the nocturnal secretion of melatonin about 2 h before an individuals' habitual bedtime correlates with an increase in sleepiness, suggesting that melatonin may play a role in the regulation of sleep (17). Endogenously administered melatonin induces sleep indirectly, by causing vasodilation in the hands and feet and thereby heat loss, with a concomitant decline in basal body temperature. This in turn facilitates sleep onset, but melatonin itself has little effect on polysomnographic sleep architecture (18). Numerous studies have investigated the propensity of melatonin to induce sleep. Two recent studies suggest that a prolonged release (PR) formulation of melatonin improved sleep quality in subjects over 55 years of age with primary insomnia. In a randomised, placebo-controlled trial in 170 patients (mean age 68.5 years) 2 mg of PR melatonin significantly improved sleep quality and morning alertness compared to placebo (19). An independently conducted study in 354 subjects (mean age 65.7 years) showed similar results (20). In neither study was there evidence for rebound insomnia on cessation of melatonin, nor was there evidence of a withdrawal syndrome. The data suggest that this formulation of melatonin may offer some advantages over existing hypnotic drugs. The application of melatonin in this context requires that it be administered about 1–2 h before bedtime. It is unlikely that melatonin will be useful in all forms of sleep disturbance because of the circadian shifting ability of the hormone. Administered at an inappropriate time, melatonin could exacerbate an existing circadian rhythm disturbance (e.g. phase advance). Knowledge of circadian phase can be useful for exploiting the phase shifting ability of bright white light. Both melatonin and light are capable of shifting phase but in opposite directions. Thus, it is possible to use melatonin at night or light in the early morning to achieve the same phase shift.

Conclusions

Examination of melatonin secretion and light sensitivity may provide an opportunity to shed light on the aetiology of some psychiatric disorders, particularly bipolar disorder. Although several studies have examined this as a potential endophenotype of illness confirmatory studies and delineation of parameters affecting response are lacking. Differential diagnosis based on a biological marker would be of both clinical utility and heuristic value.

Exploitation of the ability of melatonin to prepare the body for sleep readiness may provide a safe and effective alternative to the use of hypnotic agents in psychiatric patients. Clearly melatonin has a role to play in subjects with sleep disturbance arising from alterations of circadian phase. In this context, the phase shifting properties can be utilised to advantage. Clearly other disorders where circadian abnormalities are suspected can also be treated with melatonin. The alternative use of bright light therapy is also a possibility in these conditions. In Alzheimer's dementia the 'sundowning syndrome' responds well to an alteration in environmental lighting (21). Melatonin might also be exploited in the same condition (22). This therapeutic opportunity has led to the development of a number of agents that impact the melatonin system. These have similarly targeted both mood and sleep disorders.

The broad range of biological effects attributed to melatonin will no doubt ensure that it remains a 'molecule of interest' into the future.

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