Melatonin has multiorgan effects

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Melatonin, widely used to counter transatlantic travel jet lag and insomnia, is synthesized in the suprachiasmatic nucleus of the anterior pituitary gland. Its release into the circulation is stimulated by the onset of darkness, followed by a progressive decrease in blood levels with the onset of dawn. Melatonin administration can maintain the quality of sleep and help to counteract age-induced cognitive decline. Melatonin can also limit the severity of a variety of cardiovascular and cerebrovascular diseases, diabetes, and cancer.

Keywords Melatonin • Sleep • Cardioprotection • Anticancer • Day–night cycle • Multiorgan

Introduction

Melatonin is widely used to counter transatlantic travel jet lag and insomnia. Melatonin is less well known for its multiple and widespread physiological and pharmacological effects. The multiorgan targets of melatonin, as here reviewed and as shown in Figure 1, have important implications for optimal health at a time when cardiovascular diseases (CVDs) are the main causes of death and disease in the developed world and soon will be so in the developing world. One preventative approach to CVD is adherence to the traditional Mediterranean diet. Here, we propose that the unique properties of melatonin, a naturally occurring hormone best known for counting jet lag also provides cardiovascular protection and limits cancer. The well-known diurnal pattern of variation of blood melatonin levels has the nocturnal rise that promotes sleep followed by a gradual fall after midnight until low levels in the early morning. Melatonin is also found in red wine or even in grape juice in which it has cardioprotective effects. As reviewed below, a wide range of other health benefits are now been attributed to melatonin. These multiple mechanisms are the topic of this review.

Melatonin synthesis physiological properties

Melatonin (N-acetyl-5-methoxytryptamine) plays a major role in regulating the circadian light-sensitive biological clocks that promote sleep when darkness prevails or help waking up with the morning light. Melatonin is synthesized primarily in the pineal gland and its secretion into the blood stream is regulated by the environmental light/dark cycle via the suprachiasmatic nucleus. The initial event is that very sensitive ocular photoreceptors stimulate the formation of melanosin within a subset of photosensitive retinal ganglion cells, which in turn send signals to the pineal gland from which release of melatonin, synthesized from serotonin, is either stimulated or inhibited. Physiological levels of melatonin vary from 5 to 200 pg/mL function according to the time of the day.

The exact site in the brain where melatonin acts to induce sleep is not yet established. A clue comes from the mechanisms underlying insomnia, a recent proposal being that there are abnormalities in the sleep patterns in the ventromedial prefrontal cortex prefrontal lobes during episodes of rapid eye movement in sleep. That may be where melatonin acts centrally.

Experimentally, melatonin is a powerful antioxidant molecule, with also proven antihypertensive and lipid lowering effects. Melatonin even at low concentrations confers protection against myocardial ischaemic–reperfusion injury (IRI) by activation of protective downstream signalling pathways. Protective mechanisms include the following pathways: Janus kinase 2/signal transducers and activators of transcription 3, and nuclear factor erythroid 2-related factor 2 (Nrf2). In human, leucocytes melatonin protected from free radicals acting on the MT1/MT2 receptors. In patients undergoing coronary artery bypass, the protective dose was 10 mg as shown by increased levels of Nrf2 activity.

Regarding possible effects anti-inflammatory effects, the data give no clear clinical message as yet. Thus, larger trials are required to establish that melatonin reduces inflammatory markers. Experimentally, melatonin reduced the proinflammatory marker IL-1β (P < 0.01) but not the levels of TNF-α and IL-6.

Melatonin molecular effects

The pathway whereby melatonin crosses the cell membrane involves components of the SLC2/GLUT family of glucose transporters.
Melatonin attenuated glucose-induced tumour progression in mice with prostate cancer and prolonged their lifespan. Melatonin also experimentally restored glucose transporter-4 loss in adipocytes. Melatonin is capable of influencing in development of diabetic complications by neutralizing the unnecessary production of reactive oxygen species (ROS), protection of beta cells. These observations suggest the potential use of melatonin, with few or no serious side effects, to inhibit the development of adverse effects of hyperglycaemia in prediabetes and diabetes.

Melatonin pretreatment attenuated cerebral ischaemic–reperfusion mitochondrial injury by activation of the Silent information regulator 1 (SIRT1) which is a histone deacetylase that gives highly effective protection against IRI. The melatonin-induced upregulation of SIRT1 was also associated with an increase in the anti-apoptotic factor, Bcl2, and a reduction in the pro-apoptotic factor Bax. In adult mice subject to IRI, melatonin gave cerebral protection by reducing infarct volume and brain oedema with increased neurological scores.

**Widespread health benefits of melatonin**

Among the remarkable protective effects of melatonin are protection from cancer by acting on glucose transporters, lessening of insulin resistance associated in experimental type 2 diabetes, followed by prevention of mitochondrial dysfunction in experimental ischaemic stroke and anti-apoptotic effects. These remarkable properties will now be reviewed. Adequate sleep is required for normal daytime cognitive functions. Melatonin has a hypnotic/sedative effect on cognition when given orally. This is explained by the role of melatonin in circadian rhythm regulation, an effect mediated by stimulation of the melatonin receptors MT1 and MT2. Binding of melatonin to the brain MT1 receptor acts via the G-coupled protein pathway that enhances binding of gamma-aminobutyric acid (GABA) to the GABA_A receptor. This results in a high-dose anaesthetic effect.

Melatonin induces sleep even when several circadian rhythms are out of phase with each other and with the external environment. Melatonin is over-the-counter in the USA while in most European countries, it is available as a prescription drug (example: Circadin). Melatonin acts both by inducing sleep and by restoring the inherent sleep rhythm that is related to the rise and fall of blood melatonin levels. Melatonin therapy also helps to restore these human circadian rhythms resulting in better cognition and less day time fatigue. Furthermore, melatonin can improve sleep duration even in totally blind subjects.

Direct proof of an effect on disordered sleep rhythm comes from studies on the Angelman syndrome a rare neurodevelopmental disorder which is associated with an abnormality of chromosome 15q11-q13. In those with this sleep disorder, the night-time serum melatonin levels were lower than those of the controls. Serum melatonin levels were altered (peak levels in affected patients 60 vs. 108 ng/L in controls; P < 0.01), whereas the peak melatonin nocturnal levels in controls were normal. In children with the 24-h motor activity of this syndrome, such activity decreased during
the total sleep period following melatonin treatment, and an increase in the duration of the total sleep period.\textsuperscript{28}

**Melatonin and cardioprotection**

Melatonin invokes sleep, thus raising the hypothesis that melatonin-enhanced sleep could decrease the elevated blood pressure associated with insomnia. Insomnia associated with physiological hyperarousal was associated with an increased risk of hypertension.\textsuperscript{28} Of note, chronic insomnia with symptoms lasting 6 months or more was associated with an increased risk of hypertension.\textsuperscript{28} In 16 hypertensive patients treated with beta-blockers, 3 weeks of nightly melatonin 2.5 mg improved sleep quality besides increasing total sleep time (+36 min; \(P = 0.046\)).\textsuperscript{29} Add-on prolonged-release melatonin (PRM) was used for anti-hypertensive therapy.\textsuperscript{30} The quality of sleep and behaviour following awakening improved substantially with PRM compared with placebo (\(P < 0.0001\)).

In 16 hypertensive patients already treated with beta-blockers, 3 weeks of nightly melatonin (2.5 mg) improved total sleeping time (\(P = 0.046\)) and the onset of sleep (\(P = 0.001\)), without apparent tolerance and without rebound sleep disturbance when melatonin was withdrawn,\textsuperscript{31} thus suggesting that melatonin is implicated in cardioprotection in IRI. The protective effects of melatonin in the heart after experimental myocardial infarction (MI) include inhibition of the opening mitochondrial permeability transition pore (mPTP) that potentially mediates lethal damage.\textsuperscript{32} Reperfusion ventricular arrhythmias in spontaneously hypertensive rats were also inhibited.\textsuperscript{33}

After experimental MI, melatonin synthesis in the pineal gland increased substantially.\textsuperscript{3} One day thereafter, synthesis of pineal melatonin increased by 4.3 times (\(P < 0.001\)), which was associated with the increased concentration of melatonin in the plasma (\(P < 0.001\)) and left ventricle (\(P = 0.001\)). The molecular mechanism of such benefits may include decreased formation of free radicals during oxidative stress and reduced superoxide generation during reperfusion.

**Melatonin and cerebroprotection**

Experimentally, melatonin has anti-apoptotic effects in transient brain ischaemia. It strongly promotes the potentially lethal opening of the mPTP in isolated brain mitochondria from striatal neurons after middle cerebral artery occlusion in mice.\textsuperscript{34} In early experimental stroke, whether caused by embolism or haemorrhage, there is a defined period after the insult has occurred within which the cerebral cells take to die. The mechanism may involve neuronal oxidative stress, which suggests that therapy should be directed towards blocking the generation of such stress.\textsuperscript{35} An early timing of such therapy would be essential. In cerebral artery occlusion in monkeys 30 min to 4 h of ischaemia caused multiple, non-confluent deep infarcts with prominent grey matter necrosis.\textsuperscript{36} Such brain cells are threatened by death and could be rescued by timely reperfusion within 4 h in mice.\textsuperscript{37} Disruption of the blood–brain barrier permeability decreased by 53% (\(P < 0.001\)). Transplantation of melatonin-secreting cells protected against experimental stroke.\textsuperscript{38} In the development of stroke, melatonin decreased inflammation as a contributory mechanism.\textsuperscript{39} Exogenous melatonin treatment and transplantation of melatonin-secreting cells both have supporting laboratory data.\textsuperscript{38}

In searching for a therapy against the adverse cellular effects of an early stroke, melatonin had experimental anti-apoptotic effects in transient brain ischaemia. It strongly promoted the potentially lethal opening of the mPTP in isolated brain mitochondria from striatal neurons after middle cerebral artery occlusion in mice.\textsuperscript{30} Theoretically, the mPTP could be blocked with expected salvage of threatened brain tissue, yet firm data are presently lacking. The logical next step would be to gather data from a clinical trial.

**Melatonin, obesity, and diabetes**

Melatonin supplementation may act to prevent the adverse health consequences of obesity. In a double-blind, placebo-controlled trial, 44 obese women were randomly given placebo or 6 mg melatonin with a low-calorie diet for 40 days, melatonin decreased serum TNF-\(\alpha\) (\(P = 0.02\)) and IL-6 (\(P = 0.03\)).\textsuperscript{41} The proposed mechanism was two-fold, anti-inflammatory, and decreased oxidative stress. Melatonin also has direct anti-diabetic effects, hence potentially relevant to the therapy of type 2 diabetes.\textsuperscript{42} Experimentally, one mechanism proposed is that melatonin can neutralize the production of ROS.\textsuperscript{43} The G\(\beta \gamma\) receptor and the phosphatidylinositol 3-kinase signalling cascade mediate melatonin effects in pancreatic cells.\textsuperscript{15} The prediabetic rat is a model of diet-induced obesity, in which chronic melatonin consumption (4 mg/kg/day) reduced the gain of body weight together with reduced visceral adiposity, serum insulin and triglyceride, besides protecting the heart against IRI.\textsuperscript{15} The molecular mechanisms involved PKB/Akt and extracellular signal-regulated kinase (ERK)\textsubscript{42}/44 activation. As might be expected, immunoreactive melatonin was appropriately found in pancreatic islet cells.\textsuperscript{44}

**Melatonin has anti-cancer properties**

Recently, the benefits of melatonin in the treatment of cancer, both in vitro and in vivo, have been reported and carefully analysed by the US Department of Health, showing the importance of the concept of the topic. As the value of melatonin for cancer therapy has been disputed, Wang et al.\textsuperscript{45} performed a systematic review of randomized controlled trials of melatonin in solid tumour cancer patients and observed its effect on tumour remission, 1-year survival, and side effects due to radiochemotherapy. The patients had a variety of solid malignancies of the lung, breast, liver, gastrointestinal tract, head, and neck. In such patients, there were more remissions (16.5 vs. 32.6%, \(P < 0.00001\)), 1-year survival rate was better (28.4 vs. 52.2%, \(P = 0.001\)), and there was less thrombocytopenia (\(RR = 0.13; P < 0.00001\)).

The US Department of Health analysis of this major prospective study was that the overall trial quality of this trial was acceptable, though somewhat impaired in that blinding or use of placebo was not present in any of the trials (https://nccih.nih.gov/health/melatonin). Also, loss to follow-up was unknown in most trials. Despite these defects, there was clear benefit with melatonin in the therapy of these cancers. In the specific case of advanced prostate carcinoma in patients, lower urinary levels of a melatonin metabolite were associated with an increased risk for cancer.\textsuperscript{46} In 761 patients, there were more remissions (16.5 vs. 32.6%, \(P < 0.00001\)) 1-year survival rate was better (28.4 vs. 52.2%, \(P = 0.001\)), and there was less thrombocytopenia (\(RR = 0.13; P < 0.00001\)). Regarding the basic mechanisms, members of the SLC2/GLUT family of glucose transporters have a central role. Melatonin interacts at the same location in GLUT1 as does glucose. Thus, there is a facilitated transport of
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How do these basic studies relate to cancer in humans?

An Icelandic population study evaluated the prospective association between levels of the primary urinary metabolite of melatonin, aMT6s, and the risk of prostatic carcinoma in 928 men. Lower levels of aMT6s were associated with an increased risk for advanced prostatic carcinoma. There was a four-fold increased risk for advanced cancer compared with men with aMT6 levels above the median (hazard ratio: 4.04). In women in five prospective case–control studies, there was an inverse relationship between carcioma and levels of urinary aMT6. Women with the highest values of aMT6s also had a lower risk of breast cancer.

The blood melatonin levels in women might have implications for the occurrence of hormonal-dependent breast cancer. Melatonin has potential oncostatic activity so that the link between night work and breast cancer risk was studied in the Nurses’ Health Study studied over 14 years. Among 78 562 women, without cancer at baseline, 2441 developed invasive breast cancer at follow-up. The relative risk was 1.08 (95% confidence interval (CI), 0.99 – 1.18). The risk was further increased among women who worked 30 or more years on the night shift (RR = 1.36; 95% CI = 1.04 to 1.78). An indirect speculation, based on this study, is that sustained insomnia could be a cancer risk.

Exposure of xenograft-bearing rats to dim light at night (LAN) completely suppressed elimination of the normal pattern of increased blood melatonin levels at night. The result was unexpressed high rates of tumour metabolism and growth. The authors propose that this mechanism may help to explain why women working rotating night shifts have higher risks of breast and other cancers.

Melatonin and mood disorders

The sleep-wake cycle changes with age, with prominent sleep phase delay during youth and reduced circadian strength in older persons. Aging is one of the major contributors to accelerated morbidity and mortality with an established increasing incidence of CVD, hypertension, and stroke. In a cohort of elderly Japanese persons, the HEIJO-KYO cohort, urinary melatonin excretion was significantly associated with decreased night-time systolic blood pressure (SBP), independently of age, gender, body mass index, current smoking status, diabetes, and daytime physical activity. Specifically, an increase in the urinary melatonin excretion from 4.2 to 10.5 μg (25th to 75th percentile) went with a 2.0 mmHg decrease in night-time SBP. Thus, melatonin secretion was inversely associated with night-time blood pressure in that elderly population not reviving antihypertensive drug therapy.

In a study on over 1000 elderly persons (mean age, 72 years), melatonin secretion was significantly and inversely associated with white blood cell (WBC) and platelet counts which were taken as markers of inflammation. Melatonin secretion was inversely associated with WBC and platelet counts in this elderly population. Regarding mechanisms for this clinical benefit, animal data suggest that growth hormone and melatonin can help to prevent cardiac aging, as well as reducing the nocturnal blood pressure.

Melatonin and for early cognitive decline

Cognitive impairment inevitably increases with ageing. But when does age-related cognitive decline begin? In healthy educated adults even in their 20s and 30s, certain limited aspects of such decline had already started. Hypertension predisposes to early cognitive decline. The deterioration in mild cognitive declined could be countered by fast-release melatonin 3–9 mg given at bedtime for up to
3 years. Those treated with melatonin added to their prior medication, often donepezil, performed better in the Mini-Mental State Examination and in the Alzheimer’s disease (AD) Assessment Scale. Furthermore, depression scores decreased in melatonin-treated patients, while the quality of sleep and wakefulness also improved. But when does age-related cognitive decline begin? Controversially, the decline in healthy educated adults could start even when they were only in their 20s and 30s. When could melatonin be started to counter this age-related adverse effect? Sensitive testing with a complex video game (StarCraft 2), using a dataset of 3305 players, showed that age-related slowing began early and not late in life. 

An overt decline of cognitive capacities, such as reasoning, memory, and semantic fluency, could be detected in middle age (age 45–49). In that study of cognitive decline on 5198 men and 2192 women, aged 45–70 over 10 years, all cognitive scores, except vocabulary, declined in all five age categories (age 45–49, 50–54, 55–59, 60–64, and 65–70 at baseline), with faster decline in older people. From the point of view of maintaining full cognition and lessening the inevitable rate of decline in middle age, the implication is that is that melatonin could beneficially be started even before middle age, yet there are no trials as yet to prove this point.

**Melatonin in other conditions**

**Alzheimer’s disease**

Poor sleep quality is a major aspect of AD, as recently suggested. Endogenous melatonin levels would have already fallen at the preclinical stages of AD so that added melatonin therapy is logical. In a 6-month trial in patients with mild to moderate AD given melatonin in the PRM preparation, sleep efficiency improved in the melatonin group vs. placebo after 24 weeks of treatment (P = 0.017).

**Pregnancy**

Melatonin, produced in the ovary and placenta, acts on the foetus. Furthermore, at the time of parturition, the maternal melatonin rhythm is increased to induce uterine contractility. When ova were collected for in vitro fertilization-embryo transfer, melatonin treatment improved implantation and pregnancy rates. Melatonin projected male gametes from oxidative damage and preserved their viability. Melatonin preserves the integrity of the ovum prior to and at the time of ovulation. Furthermore, when ova were collected for in vitro fertilization-embryo transfer, treatment with melatonin improved implantation and pregnancy rates.

**Renal and hepatic disease**

In animal models of chronic kidney disease (CKD) involving experimental hypertension, diabetes mellitus, and models of nephrotoxicity, melatonin attenuated the CKD. Melatonin reduced the oxidative burden, inflammatory changes, and apoptosis. In haemodialysed patients, melatonin attenuated sleep disturbances. Experimentally, melatonin-activated p38, ERK, and nuclear factor-κB in human dental pulp stem cells. The authors suggest that combined treatment of grafted human dental pulp stem cells and melatonin could be a viable future approach for the treatment of human liver cirrhosis which at present has no adequate therapy. More direct experimental evidence is that melatonin decreases the severity of induced hepatic fibrosis.

**Sleep quality and potentially carcinogenic urban lighting**

As melatonin promotes sleep, and as breast cancer is related to poor sleeping patterns, it follows that melatonin use could be associated with decreased breast cancer. What are the data? Tumour growth in nude rats bearing human breast cancer xenografts could be indirectly linked as tumour growth was accelerated by exposing the rats to LAN. Their study established that artificial LAN, even at minimal levels, accelerated human breast cancer xenograft growth.

Are the cancer links to city lighting applicable for both genders, in women for breast cancer and for men prostate cancer? An Icelandic study evaluated the prospective association between the urinary melatonin metabolite (αMT6) levels and risk of prostatic carcinoma in 111 men. Lower levels of αMT6 were associated with an increased risk for advanced prostatic carcinoma, with a four-fold increased risk for advanced cancer compared with men with αMT6 levels above the median (hazard ratio: 4.04; 95% CI, 1.26–12.98). Thus, there are links between hormonally induced cancers and the anti-cancer activity of melatonin in both men and women.

What is the implication for current city dwellers? They pay a health price for the easy access to LAN, namely perturbations in melatonin rhythm with implication for the risk of hormonally related cancers. The cause is a disorganized circadian system called chronodisruption. Blue light, particularly beneficial during the daytime, is more disruptive at night, and induces the strongest melatonin inhibition. The remedy would be the development of lighting systems for large cities that preserve the natural melatonin rhythm, thereby reducing the health risks induced by chronodisruption.

**Melatonin in clinical trials for patients with coronary heart disease**

Recently, a relevant experimental study found beneficial effects of melatonin in countering oxidative stress in IR. Clinically, Nrf2, limited oxidative stress that occurred during and after coronary artery bypass grafting (CABG). Thirty volunteers undergoing CABG were randomized to receive 10 mg oral melatonin before sleeping at night for 1 month before surgery. In those randomized to melatonin, cellular damages resulting from CABG surgery via theNrf2 pathway were attenuated (melatonin group given Nrf2 compared with placebo: 15.2 ± 4.6 pmol/L, 0.28 ± 0.01 vs. 1.1 ± 0.59 pmol/L, 0.20 ± 0.07, P < 0.05).

There are several clinical trials underway. The background for these clinical studies is that experimentally induced MI, as studied in rodents, influenced the synthesis, concentration, and receptor expression of endogenous melatonin. In response to experimental MI, melatonin synthesis in the pineal gland increased rapidly, suggesting an important role for endogenous melatonin in post-MI cardioprotection. The day/night pattern of changes in melatonin blood levels may help to explain the timing of human infarcts.
Hypothetically ROS generated during myocardial IRI could influence ischemia-modified albumin (IMA) levels as studied in in 27 patients with ST-segment elevation MI (STEMI) undergoing primary angioplasty. Circulating IMA was negatively correlated to melatonin in these patients.

The MAREA trial is testing the hypothesis that in patients with acute myocardial infarction (AMI) melatonin will confer cardioprotection against IRI. If successful, the finding would support the use of melatonin in therapy of IRI of the heart. The background is that intra-platelet melatonin levels predict angiographic no-reflow after primary percutaneous intervention in patients with STEMI.

In planning trials of melatonin in AMI, platelet reactivity could be a useful marker of beneficial effects as studied in 494 STEMI patients with a median follow-up of 2.3 years of whom 58 suffered from a cardiovascular death. High levels of High on-treatment Platelet Reactivity and of C-reactive protein identified a subgroup of patients at higher risk of cardiovascular death.

In the MAREA trials the acronym stands for: Melatonin as an Adjunct in patients with acute myocarDial Infarction undergoing primary Angioplasty. In the first MAREA study circling IMA correlated negatively to melatonin in STEMI patients, leading the authors to suggest that melatonin might exert a beneficial effect as a radical scavenger in human myocardial ischaemia—reperfusion. Low intra-platelet melatonin concentrations in 180 consecutive patients with a first STEMI predicted angiographic no-reflow after primary percutaneous coronary intervention (pPCI) in patients with STEMI. Decreased levels of melatonin in serum predicted adverse left ventricular remodelling after AMI. These ongoing studies on patients with AMI in the MAREA trials test the hypothesis that melatonin will confer cardioprotection against IRI.

In Denmark, the IMPACT trial has started. Owing to its relatively high-protoxic profile, melatonin is an easily implementable drug in the clinical setting, and melatonin has the potential to reduce morbidity and mortality in patients with AMI. The IMPACT trial aims to evaluate the preventive effect of intracoronary and systemic melatonin on the severity of ischemic—reperfusion injuries following pPCI in early AMI. The primary outcome measure are: death, sustained ventricular arrhythmias, resuscitation from cardiac arrest, cardiogenic shock, heart failure, major bleedings, stroke, need for revascularization, recurrent ischaemia, re-infarctions, and re-hospitalization; MRI of the heart focusing on quantification infarct size, area at risk and myocardial salvage index, secondary outcome measures: serum creatinine kinase Myocardial Band (CK-MB) 96 h after PCI; clinical events within 90 days of PCI; high-sensitive Troponin T or Troponin I.

**Summary**

Melatonin is a hormone with multiple sites of impact, with its major effect in regulating the physiological light—darkness cycle and the subjective states of wakefulness and sleep. Melatonin is synthesized in the suprachiasmatic nucleus of the anterior pituitary gland. Physiologically, the initial stimulatory event to its release is the onset of darkness light acting on very sensitive ocular photoreceptors. The pathways of melatonin synthesis and its physiological properties are reviewed. The melatonin-induced hormonal changes are many, including upregulation of SIRT1 with an associated increase in the anti-apoptotic factor, Bcl2. The normal sleep rhythm depends on a 24 h pattern of rise and fall of circulating melatonin with the rhythm of its action on the brain. As normal sleep is an imperative component of mental and cardiovascular health, the pattern of secretion of melatonin has now been widely studied and is here reviewed in countering the cognitive decline of ageing, maintaining the quality of sleep, sustaining mental health prevention and prevention of some aspects of cardiovascular and cerebrovascular diseases, diabetes, and cancer. Currently there are large clinical trials underway to test the efficacy of melatonin in patients with acute coronary heart disease.

**Conflict of interest:** none declared.

**References**


