Editorial

Melatonin and Cardiovascular Disease: Myth or Reality?

Melatonina y enfermedad cardiovascular: ¿mito o realidad?

Alberto Domínguez-Rodríguez, a, * Pedro Abreu-González, b and Russel J. Reiter c

aServicio de Cardiología, Hospital Universitario de Canarias, La Cuesta, La Laguna, Santa Cruz de Tenerife, Canarias, Spain
bDepartamento de Fisiología, Universidad de La Laguna, La Laguna, Santa Cruz de Tenerife, Canarias, Spain
cDepartment of Cellular and Structural Biology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas, United States

Article history:
Available online 13 January 2012

Cardiovascular diseases are the leading causes of death in Spain, with ischemic heart disease being the main cause of cardiovascular deaths. Treatment for one common cardiovascular condition, STEMI-segment elevation acute myocardial infarction (STEMI), has changed considerably in recent years. The recognition that thrombotic occlusion of a coronary artery results in a wavefront of irreversible myocardial cell injury extending from the sub-endocardium to the subepicardium in a time-dependent fashion led to the introduction of reperfusion therapy for myocardial infarction. However, restoration of blood flow to previously ischemic myocardium results in the so-called ischemia/reperfusion (I/R) injury. The I/R combination causes numerous and collateral reactions in tissues, culminating in the alteration of essential molecules and organelles in a number of cells including components of the coronary endothelium and myocardium with the recruitment of circulating blood elements, eg, leukocytes and platelets. During the transient ischemia and the period of reperfusion many cells generate byproducts of oxygen that are toxic to the heart. Indeed, the partially reduced oxygen metabolites, both reactive oxygen species (ROS) and reactive nitrogen species (RNS), account for much of the cardiac damage that occurs during I/R injury.

Solid evidence exists that melatonin influences the cardiovascular system. Melatonin is a multifunctional indolamine that counteracts virtually all pathophysiologic steps and displays significant beneficial actions against ROS/RNS-induced cellular toxicity. This protection is related to melatonin’s potent antioxidantive and anti-inflammatoriy properties. Melatonin has the capability of scavenging both ROS and RNS, including those formed from peroxynitrite, and blocking transcriptional factors, which induce proinflammatory cytokines. Accumulating evidence suggests that this nontoxic indolamine may be useful either as a sole treatment or in conjunction with other treatments for inhibiting the biohazardous actions of nitrooxidative stress.

MELATONIN AND ITS RHYTHM

Melatonin, an endocrine product of the pineal gland, is formed predominantly during nighttime. Light has an inhibitory effect on pineal melatonin secretion. Melatonin release is synchronized with daylight cycle via a multisynaptic pathway between the eyes and the pineal gland. Light stimulates the retina to modulate the activity of suprachiasmatic nucleus (SCN), the master biological clock. The SCN controls pineal melatonin synthesis and release via the peripheral sympathetic nervous system, which involves synapses in the intermediolateral cell column of the thoracic cord and its projection towards the superior cervical ganglia; postganglionic sympathetic fibers eventually terminate on pinealocytes within the pineal gland. The rate-limiting enzyme in the melatonin synthesis is regulated by norepinephrine and released from sympathetic nerve endings to pinealocytes β1- and α1-adrenoceptors. The concentrations of melatonin in the sera of healthy subjects reach 10–10 to 10–12 mol/l during the night with much lower values being present during the day. Mounting evidence documents that melatonin has crucial roles in a variety of cardiovascular pathophysiologic processes: this indoleamine has anti-inflammatory, antioxidant, antihypertensive and possibly antilipidemic functions (Fig. 1).

Melatonin also mediates a variety of physiological responses through membrane receptors and nuclear binding sites. The presence of melatonin receptors in cardiomyocytes was suggested by binding studies and immunostaining in chick hearts. Subsequently, M T1 and M T2 membrane receptors have been identified on left ventricle cardiomyocytes of the human heart. The role of melatonin in human ventricular function is still unclear. Isolated rat papillary muscle it possesses antiadrenergic effects and causes a reduction in the force of contractions. Likewise, M T1 and M T2 receptors are present in human coronary arteries from pathology samples and also from healthy controls. Animal studies suggest that melatonin has dual effects on the vasculature, depending on the specific receptor type activated, with vasoconstriction occurring after M T1- activation and vasorelaxation after M T2- activation.

MELATONIN AND CARDIOVASCULAR DISEASE

Atherosclerosis is a chronic vascular disease in which inflammation and oxidative stress are commonly implicated as major
Melatonin
With The

Figure 1. Physiological regulation of melatonin by the light/dark environment as detected by the retina. MEL, melatonin; RHT, retino-hypothalamic tract; SCG, superior cervical ganglia; SCN, suprachiasmatic nucleus.

The administration of pharmacological doses of melatonin reduces blood pressure as a consequence of various mechanisms including a direct hypothalamic effect, a lowering of catecholamine levels, relaxation of the smooth muscle wall, and most importantly, its antioxidant properties. There are several reports indicating that melatonin may have a hypotensive effect. With a large clinical trial using melatonin as a hypertension treatment, many important questions could be answered, such as the optimum melatonin dose and application regimen and patient selection to achieve the greatest possible benefit from melatonin treatment. Based on the accumulated evidence, melatonin seems to be a candidate drug for treatment of hypertension since the number of patients with well-controlled hypertension is alarmingly low worldwide.

Moreover, there is favorable evidence that the circadian rhythm of melatonin influences insulin secretion and the endocrine pancreas, reduces blood glucose and HbA1c, and restores liver enzymes in diabetic rats. Although little is known about how melatonin reduces plasma glucose in humans, type 2 diabetic patients show a reduced diurnal serum melatonin level and increased pancreatic melatonin-receptors. The role of pineal melatonin in preventing or delaying diabetes onset, however, is not clarified, since studies showing beneficial effects of melatonin have been conducted only after onset of the clinical manifestation of diabetes. Nevertheless, a recent comprehensive review has documented a variety of melatonin actions on the physiology of endocrine pancreas that would be expected to reduce the incidence of diabetes.

Patients with coronary artery disease have low melatonin production rates and blood melatonin concentrations correlate with the severity of the disease, i.e., greater reductions in melatonin production are observed in patients with a higher risk of myocardial infarction and/or sudden death. It is uncertain whether low melatonin levels in these patients are the result of melatonin “consumption” caused by scavenging of the elevated free radical production, or represent lower melatonin production, and hence less protection against oxidative stress.

**POTENTIAL UTILITY OF MELATONIN AS AN ANTIOXIDANT DURING ST-ELEVATION MYOCARDIAL INFARCTION**

There is evidence for cardioprotective effects of melatonin against I/R injury (Fig. 2). Melatonin reduces the infarct size/risk area and the incidence of reperfusion arrhythmias. Since ischemia
The intervention of melatonin for the restoration of cardiac function after an ischemia/reperfusion episode. IV, intravenous; MEL, melatonin; NO, nitric oxide; PCI, primary percutaneous coronary intervention; STEMI, ST-segment elevation acute myocardial infarction.

Conflict of Interest

None declared.

References

13. Domínguez-Rodríguez A, Abreu-González P, Jiménez-Sosa A, Avanzas P, Bosa-Ojeda F, Kaski JC. Usefulness of intraplatelet melatonin levels to predict...
