Effect of Endogenous Melatonin Hormone on Cardiovascular System: A Review of Literature

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ABSTRACT

Melatonin (MLT) "N-acetyl-5-methoxytryptamine"; a pineal hormone; has a diurnal variation and may be necessary for the suprachiasmatic nucleus (SCN) and peripheral tissue's molecular circadian clocks to be synchronized, has powerful receptor-dependent and receptor-independent effects on a number of cardiovascular (CV) variables, including endothelial cells function, thrombus formation, blood pressure (BP), and heart rate (HR). MLT possesses antioxidative, anti-inflammatory, chronobiotic, and perhaps epigenetics regulatory characteristics. Low blood concentrations of MLT have been found in persons who have coronary artery disease (CAD), arterial hypertension (HT), and congestive cardiac failure. The physiological function of endogenous MLT and its circadian rhythm in the human CV system is reviewed in this article.

Keywords: melatonin, cardiovascular, circadian rhythm, cardioprotection.

تأثير هرمون الميلاتونين الداخلي على نظام القلب والأوعية الدموية: مراجعة مقالة

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الخلاصة

هرمون الميلاتونين الصنوبرى(N-acetyl-5-methoxytryptamine)) ، الذى له تباين يومى ويمكن أن يشارك فى تزامن الساعات البيولوجية فى الأنسجة المحيطية والنواة فوق التصالبية، له تأثير قوى بواسطة المستقبلات والتأثيرات المستقلة عن المستقبلات على عدد من متغيرات القلب والأوعية الدموية، بما فى ذلك وظيفة الخلايا البطانية، وتكوين الجلطة، وضغط الدم، ومعدل ضربات القلب. يمتلك الميلاتونين خصائص كمضاد للأكسدة، مضاد للالتهابات، مؤقت بايولوجى، وربما الخصائص التنظيمية اللاجينية. لقد لوحظ أن الأشخاص المصابين بمرض الشريان التاجى، وارتفاع ضغط الدم الشريانى، وفشل القلب الاحتقانى لديهم مستويات منخفضة من الميلاتونين. فى هذه المقالة تتم مراجعة الوظيفة الفسيولوجية للميلاتونين الداخلى وإيقاعها اليومى فى نظام القلب والأوعية الدموية لدى الانسان.

الكلمات المفتاحية : ميلاتونين، القلب والأوعية الدموية، تواتر يومي، حماية القلب.

INTRODUCTION

The only neuroendocrine hormone known to be made by the pineal gland (PG), melatonin (MLT), "N-acetyl-5-methoxytryptamine", is secreted in response to darkness, so named as "hormone of darkness" [1,2]. Photosensitive retinal ganglion cells sense photic input, that is then sent to the SCN in the hypothalamus, paraventricular nucleus (PVN), the inter-mediolateral nucleus in the spine, and to superior cervical ganglia by adrenergic sympathetic preganglionic neurons, that innervate the PG [3], to control the inhibition or stimulation of MLT secretion, which is made from tryptophan[4]. MLT undergoes hepatic metabolization and is eliminated in urine in form of 6-sulfatoxymelatonin (aMT6s)[5]. Numerous other tissues, as the gastrointestinal tract, retina, testes, cochlea, bone marrow, and thymus, as well as immune system cells, glial cells, and astrocytes, are also able to synthesize MLT [6-9], besides the PG. Depending on the time of day, the physiological levels of MLT range from 5 to 200 pg/mL[10].

Melatonin takes part in several biological processes; by two G-protein-coupled receptors (Fig.1) called MT1 and MT2; as circadian rhythm control, sleep, immune system, BP, regulating behavior and mood, removing free oxygen radicals, retinal injury protection, tumor growth inhibition, etc[11]. Furthermore, MLT possesses an affinity for other binding locations, initially believed to be MT3 membrane bound receptor, however, was then known as a quinone reductase 2 (NQO2 or QR2)[8].

Because of its amphiphilicity, MLT can enter the cellular organelles, and nuclear envelopes and interacting immediately with intracellular molecules, this is known as non-receptor mediated actions[12.] MLT is recognized to be an efficient antioxidant through working as a good direct free radical (FR) scavenger, binding to transition elements to prevent the development of the hydroxyl radical and stimulating the transcription and activity of antioxidant enzymes. In addition, because it is concentrated in the mitochondria, where FRs are created spontaneously during cellular respiration, MLT shields lipids, proteins, and DNA from oxidative damage[13-19].

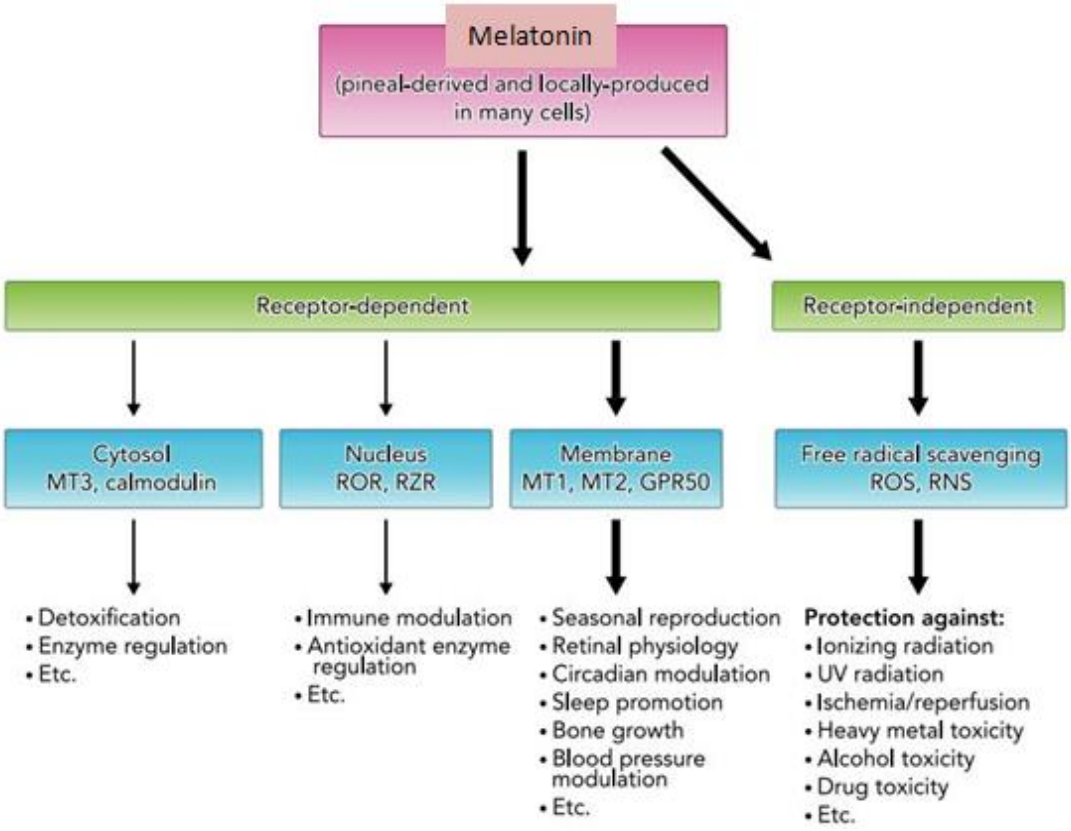

Fig.1 Summary of Melatonin Action[20]

Melatonin has well-known effects on the CVS (Fig.2). It has been demonstrated to play a fundamental part in the control of the CVS, particularly BP, since the 1960s[21,22]. MLT is a key regulator of many other CVS parameters, including HR and vascular resistance, in addition to BP. It controls the CVS through immediate, prospective, and chronobiotic effects that are both receptor- and non-receptor-mediated. The two most significant non-receptor mediated effects are MLT's ability to regulate mitochondrial function and antioxidant processes. The heart (coronary arteries, left ventricle, and cardiomyocytes), blood vessels, and central nervous system regions involved in CVS control all have MLT receptors[23-28].

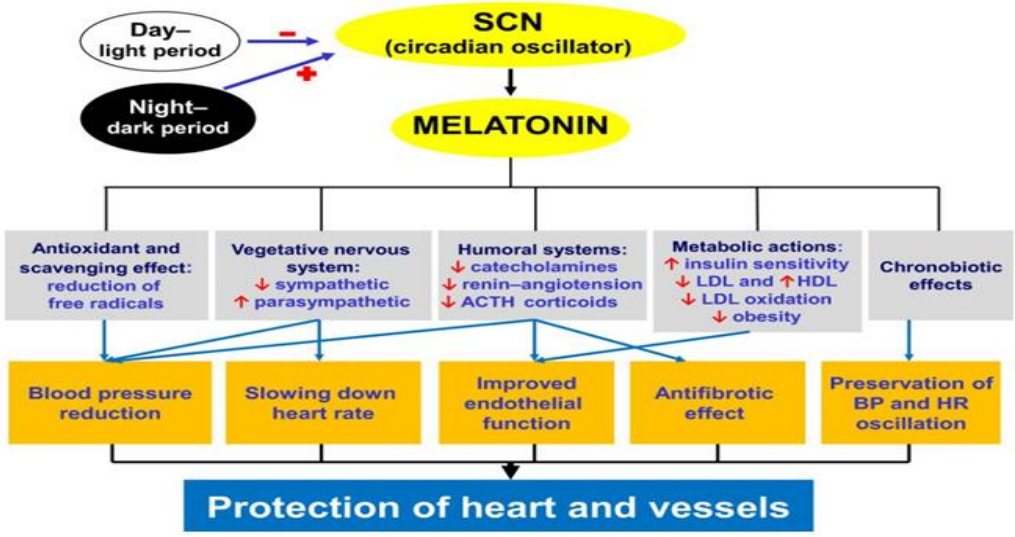

Fig.2 Cardiovascular protection Role of Melatonin[29]

Melatonin and Blood Pressure

Circadian differences in BP and catecholamines concentrations; were seen in many research; rise during the day's active phase and decrease during the day's resting phase [12,30]. Yildiz and Akdemir studied the endogenous effects of MLT on BP and arterial distensibility, which was determined by the aortic pulse- wave velocity (PWV). The diurnal levels of MLT were shown to be negatively correlated with the aortic PWV [31]. These effects may be attributable to melatonin's direct action on the artery wall via its receptor; MT1 activation results in vasoconstriction, whereas MT2 activation results in vasodilation; or to the modification of autonomic activity[32-34] by acting centrally in the hypothalamic PVN, likely decreasing the hypothalamic-pituitary-adrenal axis and sympathetic outputs, in the region postrema, controlling the baroreflex operating point, decreasing the sympathetic activity and stimulating the parasympathetic activity, in the caudal and/or the rostral ventrolateral medulla controlling HR[35-39]. Some researchers believe that melatonin's ability to stop endothelial nitric oxide synthase from becoming methylated is what causes it to have a vasodilator effect[40]. Additionally, MLT plays a crucial role in the epigenetic regulation of adult BP, which is programmed during fetal and/or neonatal development[41,42]. MLT is directly engaged, through immediate actions, in the regulation of the anticipated BP dipping that happens nightly in humans, in addition to controlling daily BP rhythm .[43-45].

Effect of Melatonin on Heart rate and Rhythm

Melatonin can lower HR in humans, so it has sympatholytic properties. There are various ways in which MLT might decrease the sympathetic drive through negative feedback. First, MLT increases GABAergic signaling, which is implicated in the inhibition of the PVN by the SCN[46,47]. The capacity of MLT to boost the bioavailability of NO may also further enhance the suppression of the PVN, as NO production increases GABAergic inhibitory action in PVN.[36,47]

The MLT′s receptor-dependent and independent actions allow it to exert its electrophysiological effects at a variety of levels. Several investigations supported antiarrhythmic defense and linked it to MLT's extraordinary antioxidant characteristics. MLT delayed the activation of the epicardial action potential and stopped QRS widening. MT1 may be responsible for the action potential shortening. Through intracellular signaling, MT1 and MT2 may also indirectly influence several effects on cardiac electrophysiology as increasing phospholipase C, decreasing cAMP, and activating protein Kinase C.[48]

Melatonin and Cardiomyocytes

Melatonin 1 and MT 2 were presented in heart muscles. Though the precise function of MLT in human ventricular function is uncertain, receptor-dependent and receptor-independent actions are expected to be implicated in the effect of MLT in cardiac failure. Most of the research evaluating the

association between MLT and HF focused on the protecting effect of MLT by its antioxidant feature instead of its immediate action on MT1 and MT2 receptors; by this feature, it can protect ischemia-reperfusion injury (IRI) caused by free oxygen radicals. MLT enhances coronary flow and heart function by MT1 and MT2, ß-adrenoceptors, and regulation of nitric oxide synthase (NOS).[34,49,50] MLT also prevented cardiac apoptosis, preserved ischemic cardiomyocytes' mitochondrial structural strength, encouraged ATP generation, and enhanced cardiac performance.[51]

Melatonin and Platelets Function

Many physiological reactions in human platelets can be inhibited by MLT, as the aggregation phenomena, ATP and serotonin release (indices of the secretory mechanism of the platelet), and thromboxane B2 synthesis.[52,53]

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Melatonin and Endothelium

Melatonin is crucial for protecting endothelial cells against the production of free radicals and associated biochemical injuries. MLT has strong protective properties by decreasing lipid, BP and rising NO bioavailability. Also, it's shown that inhibiting the nocturnal surge of MLT is linked to an increase in the expression of endothelial cell adhesion molecules.[54]

Melatonin and some Cardiovascular Diseases

Melatonin production in humans declines with aging and it is also markedly reduced in several age-related disorders, such as CV disease. Physiological-temporal circadian rhythm is disturbed by social and commercial stress like shift employment, which may be the cause of chronic illnesses like CVdisease.[48,52]

The production rates of MLT are low in patients with CAD and blood MLT level and disease severity are correlated. When there has been an acute coronary syndrome, reactive species of oxygen and nitrogen play a crucial role in the development of heart damage during IRI. The documented reduced serum concentration of MLT in this population raises the risk of additional cardiac harm from IRI because MLT has been characterized as a strong FR scavenger which it guards from reactive species of oxygen and nitrogen with higher efficiency. Additionally, under situations of high oxidative stress, such as acute coronary syndrome, MLT indirectly activates anti-oxidative enzymes such as superoxide dismutases (SOD), glutathione peroxidase (GPx), glutathione reductase (GR), and G6PD, this reduces molecular damage.[55-57]

Melatonin acts as a rhythmic regulator for normal cardiac rhythm and a potential preventative agent for ventricular fibrillation. It has remarkable acute and chronic anti-arrhythmic properties due to its pleiotropic actions.[58] In pinealectomized mice, reperfusion arrhythmias worsen, indicating a protecting role for endogenous physiological MLT levels.[48]

In those with acute myocardial infarction, Dominguez-Rodriguez et al. found a correlation between nocturnally elevated serum concentrations of oxidized low-density lipoprotein (ox-LDL); a significant contributor to endothelial dysfunction, atherosclerosis development, and plaques instabilities by numerous mechanisms; and decreased circulating MLT levels. MLT has the potential to reduce total cholesterol, rise high-density lipoprotein (HDL) concentrations, and decrease the oxidation of LDL; changes that are often preventative of CV disease.[8,49,56,59,60] .

Low aMT6s in urine was described in CHF and no discernible variations in the decreased urinary aMT6s values between individuals with acute and chronic CHF were found.[61,62]

Rats that have had their pineal glands removed develop HT; MLT replacement either reverses or prevents this effect.[22,63] Patients with HT were found to have decreased serum MLT levels.[33] The non-dipper pattern, which is characterized by a blunted drop in the physiological BP's nocturnal reduction, is linked to HT-related organ damage like left ventricular hypertrophy, micro-albuminuria, decreased arterial compliance, and a bad prognosis for CV events. There have been studies showing that non-dippers' nocturnal MLT release is suppressed in hypertensive patients.[45,64,65]

CONCLUSION

Endogenous MLT would be a naturally cardio-protective agent with therapeutic promise. MLT rhythmicity seems to have essential roles in many CV activities as an antioxidant, an anti-inflammatory agent, a chronobiotic and perhaps as an epigenetic regulator.

Its rise at night is linked to normal CV function. On the other side, lowered MLT levels are associated with diseases. MLT levels are declined by chronodisruptors and aging. MLT is a hopeful treatment for CV illnesses as myocardial IRI, HT, and heart failure.

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Conflict of Interest

The author declares that there are no conflicts of interest regarding the publication of this manuscript.

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