Protective Effects of Melatonin and Its Supplements on the Arterial Mechanics

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ABSTRACT

Melatonin (5-methoxy-N-acetyltryptamine), a neurohormone, is synthesized from tryptophan taken up by the pineal gland cells. It affects several cardiovascular functions such as arterial blood pressure, heart rate, cardiac rhythms, and mechanical properties of the large arteries and aorta. Melatonin and its supplements, generally made in a laboratory, can improve several cardiovascular functions such as arterial blood pressure and arterial mechanics.

Key Words: Melatonin; supplement; arterial mechanics

Melatonin ve Takviyelerinin Arter Mekanikleri Üzerindeki Koruyucu Etkileri

ÖZET

Bir nörohormon olan melatonin (5-*methoxy-N-acetyltryptamine*), epifiz bezi hücreleri tarafından alınan triptofandan sentezlenir. Arteriyel kan basıncı, kalp hızı, kalp ritmi ve büyük arterlerin ve aortun mekanik özellikleri gibi bir dizi kalp ve damar fonksiyonunu etkiler. Melatonin ve genel olarak laboratuvarda imal edilen supplementleri arteriyel kan basıncı ve arteriyel mekanikler gibi bir dizi kalp ve vasküler fonksiyonu iyileştirebilir.

Anahtar Kelimeler: Melatonin; takviye; arter mekanikleri

INTRODUCTION

Melatonin (5-methoxy-N-acetyltryptamine), a neurohormone, is synthesized from tryptophan taken up by the pineal gland cells. In the pineal gland, serotonin is acetylated (by arylalkylamine N-acetyltransferase) and then methylated (by acetylserotonin O-methyltransferase) to give melatonin[1]. Light exposure to the eyes affects the synthesis and secretion of melatonin[1]. Serum concentrations of melatonin are low during the daylight hours and increase to a peak during the dark phase of the night. Norepinephrine increases arylalkylamine N-acetyltransferase activity by stimulating β_1 and α_{1b} adrenergic receptors[2]. Melatonin inhibits calcium (Ca^{2+}) calmodulin-dependent protein kinase II activity and autophosphorylation by direct interaction with calmodulin[3]. The local renin-angiotensin system may modulate melatonin secretion[4]. Baltatu, et al.[4] demonstrated that the local pineal renin-angiotensin system exerts a tonic modulation of indole synthesis by influencing the activity of tryptophan hydroxylase via angiotensin AT1-receptors. The physiological effects of melatonin depend on membrane receptors in melatonin-responsive cells[1]. MT1 (formerly Mel1a) and MT2 (formerly Mel1b) melatonin receptors are G protein-coupled receptors that generally decrease cAMP and cGMP production. The third receptor MT3 (previously named ML2), which has a lower affinity, is probably not coupled with the G protein. Human MT1 and MT2 receptors were found in some areas of the central nervous system (including the thalamus, hippocampus, retina, preoptic area, and cerebellum) and peripheral organs including adrenal glands, skin, kidney, adipose tissue, immune cells, bone, liver and cardiovascular system[5-8]. Melatonin affects several cardiovascular functions such as arterial blood pressure, heart rate, cardiac rhythms, and mechanical properties of the large arteries and aorta including arterial distensibility, stiffness, and arterial compliance by the receptors[9,10].

Knowledge of the mechanical properties of the large arteries is essential for the treatment of aortic diseases including atherosclerosis and aneurysms. Damage to the arterial wall due

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to endothelial dysfunction is an early stage of atherosclerosis which leads to increased arterial stiffness[11-13]. Atherosclerosis and its effects on the arterial system can be evaluated by some techniques including pulse wave velocity which is defined as the arterial pulse's velocity of moving along the vessel wall, as an indicator of arterial distensibility and plays an important clinical role in patients with higher cardiovascular risk[14]. Pulse wave velocity is inversely related to arterial elasticity, distensibility, and relative arterial compliance. Arterial stiffness is related to arterial pulse wave velocity and can be affected by both structural and functional changes[11-14]. Structural changes involve the composition of the arterial wall including mainly collagen and elastin proteins, smooth muscle cell hypertrophy, and a decrease in extracellular matrix contents. A decrease in elastin and an increase in collagen content at the arterial media could cause arterial stiffening. The increase in aortic stiffness may increase the impedance to left ventricular ejection and then reduce the effective coronary blood flow[13]. Functionally, arteries become wider and less elastic with the aging process as a consequence of the age-related reduction and fragmentation in arterial elastin and increase in collagen content[11-15]. These changes cause increased central blood pressure. This results in an inadequate increase in systolic blood pressure, and a relative decrease in diastolic blood pressure. Finally, pulse pressure increases. Stiffness becomes higher at high pulsatile blood pressure and blood flow is reflected to small vessels, resulting in microvascular damage, during systole[15].

Oxidative stress plays a critical role in atherosclerotic vascular diseases such as hypertension, diabetes mellitus, and coronary artery disease[16]. Melatonin, an antioxidant hormone, shows its effects through the scavenging of reactive oxygen and nitrogen species and enhancing antioxidative enzymes[17]. It protects lipids, protein, and deoxyribonucleic acid (DNA) from oxidative damage in the mitochondria. It was shown to have an antioxidant effect in the ischemic/reperfused heart model[18]. Subjects with high low-density lipoprotein associated with cardiovascular disease have been shown to have low melatonin levels[19]. Also, Yıldız Şahin B et al.[20] studied the association of endogenous melatonin with uric acid, high serum uric acid levels often associated with cardiovascular disease, and traditional cardiovascular risk factors such as plasma lipids, and glucose in healthy young males. This study demonstrated a significant negative correlation between endogenous melatonin and uric acid levels in healthy young males. The impaired suppressive effect of melatonin on sympathetic activity may cause endothelial injury, thrombocyte activation, and rupture of vulnerable plaques[21]. Also, increased sympathetic system activity may affect the production of plasminogen activator inhibitor-1 levels which are associated with vascular thrombosis[22].

Studies have demonstrated associations between melatonin secretion and reduction in night-time systolic blood pressure[23,24]. In humans at rest, melatonin administration decreased heart rate and blood pressure suggesting that melatonin increases cardiac vagal tone in the supine position in awake men. Melatonin administration also may exert suppressive effects on sympathetic tone as evidenced by a decrease in catecholamine and dopamine levels[25]. This effect of melatonin could reinforce the exercise-induced rise in vagal resting tone, which improves exercise performance. Yıldız, et al.[24] investigated the effects of endogenous melatonin on arterial distensibility by measuring carotid-femoral (aortic) pulse wave velocity using an automatic Complior Colson (France) device in 29 healthy young (18-27 years, 19 males) subjects. This study indicated that increased levels of melatonin during the night may cause a decreased velocity of the aortic pulse wave, along with systolic, diastolic, and mean blood pressures and heart rate. Yıldız, et al.[26], also showed that oral melatonin administration, compared to placebo, decreased carotid-femoral (aortic) pulse wave velocity and systolic blood pressure in healthy young men. Administration of melatonin may have an inhibitory effect on sympathetic tone. Obayashi, et al.[27] showed that urinary six-sulfatoxymelatonin excretion, as indices of melatonin secretion, is inversely associated with arterial stiffness measured by cardio-ankle vascular index (CAVI) after adjusting for several major causes of atherosclerosis.

Melatonin Supplementation

Melatonin is readily absorbed after consumption and dietary supplements containing melatonin are useful in some circumstances, including adult sleep disorders and jet lag. Additionally, there is increasing evidence that melatonin protects against a variety of cardiovascular diseases and that supplementation, especially in the elderly, who have decreased endogenous synthesis, may be useful as a cardioprotective. Melatonin is used up to 8 mg/day per oral for up to six months in adults and up to 3 mg/day per oral for up to three months in children. Supplements can be slow- or fast-release.

Some studies have shown melatonin's antioxidant and anti-inflammatory effects that could benefit cardiovascular functions while others have not. Lemley, et al.[28] showed that 5 mg of melatonin supplementation alters uteroplacental hemodynamics and fetal development in an ovine model of intrauterine growth restriction. Also, melatonin supplementation increased uterine artery blood flow, which was determined using color Doppler ultrasonography in mid to late gestating cattle[29]. Chaudagar, et al.[30] explored the effects of melatonin and n-three polyunsaturated fatty acids (PUFA) supplementation on plasma and aortic nitric oxide (NO) levels in isoproterenol (Iso) affected spontaneously hypertensive (SHR) and Wistar rats. Untreated control rats were compared with Iso injected (118 mg/kg, s.c.)

rats, and Iso injected plus supplemented with melatonin (10 mg/kg, p.o.) or PUFA (1.68 g/kg, p.o.) for two months. They found that PUFA modulates plasma and melatonin aortic NO levels of isoproterenol-affected rats in a strain-dependent manner. Brockus, et al.[31] showed that an increase in total uterine blood flow during 20 mg of melatonin supplementation could be related to its antioxidant properties. Despite all this Kim, et al.[32] found no evidence that melatonin supplementation (2 mg melatonin every night) improved cardiometabolic parameters like arterial stiffness determined by cardio-ankle vascular index (CAVI), mitochondrial deoxyribonucleic acid (mtDNA), or insulin resistance compared to placebo between baseline and week six.

In conclusion, melatonin, which is synthesized in the pineal gland, and its supplements, generally made in a laboratory, can improve several cardiovascular functions such as arterial blood pressure and arterial mechanics.

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