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

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 aryalkylamine N-acetyltransferase activity by stimulating β₁ and α₁b adrenergic receptors(2).

Melatonin inhibits calcium (Ca²⁺) 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
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 of the aortic pulse wave, along with systolic, diastolic, and mean blood pressures and heart rate. Yildiz, 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. Brock-us, et al.\(^\text{[31]}\) 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.\(^\text{[32]}\) 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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