



Melatonin for the treatment of sepsis: the scientific rationale

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Abstract: Sepsis affects 30 million people worldwide, leading to 6 million deaths every year (WHO), and despite decades of research, novel initiatives are drastically needed. According to the current literature, oxidative imbalance and mitochondrial dysfunction are common features of septic patients that can cause multiorgan failure and death. Melatonin, alongside its traditionally accepted role as the master hormonal regulator of the circadian rhythm, is a promising adjunctive drug for sepsis through its anti-inflammatory, antiapoptotic and powerful antioxidant properties. Several animal models of sepsis have demonstrated that melatonin can prevent multiorgan dysfunction and improve survival through restoring mitochondrial electron transport chain (ETC) function, inhibiting nitric oxide synthesis and reducing cytokine production. The purpose of this article is to review the current evidence for the role of melatonin in sepsis, review its pharmacokinetic profile and virtual absence of side effects. While clinical data is limited, we propose the adjunctive use of melatonin in patients with severe sepsis and septic shock.

Keywords: Sepsis; septic shock; melatonin; antioxidant

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Introduction

Melatonin is an ancient biological compound sharing amino acid sequence homology with the melatonin present in cyanobacteria (1). It has been suggested melatonin was sequestered by eukaryotes as part of the endosymbiotic theory of evolution and has acquired roles in immunity, as a free radical scavenger and as the master hormonal regulator of the circadian rhythm (2). The circadian rhythm is a ubiquitous evolutionary homeostatic mechanism which acts as a biological clock to guide the differential release and regulation of hormones and to rhythmically alter the expression and translation of thousands of genes (3). It is comprised of complex, interacting, intrinsic cellular circadian clocks, the extrinsic daylight and fasting-feeding cycles and the release of hormonal regulators such as melatonin (4). Melatonin is a polypeptide derived from tryptophan, the synthesis and

release of which is primarily governed by the pineal gland. Its release shows marked intra individual stability, but significant interindividual variability (5). Melatonin displays, however, a range of actions in different organs of the body, through its anti-inflammatory properties, as an oxidant scavenger and as an enhancer of the immune system. With a profoundly safe side-effect profile, melatonin has become a promising focus for research in critically ill patients. Exogenous administration of melatonin has been evaluated for its immunostimulatory, antiinflammatory and antioxidant properties and well as its effects on improvement of sleep cycling and architecture.

Chemistry

Melatonin is mainly produced within the pineal gland,

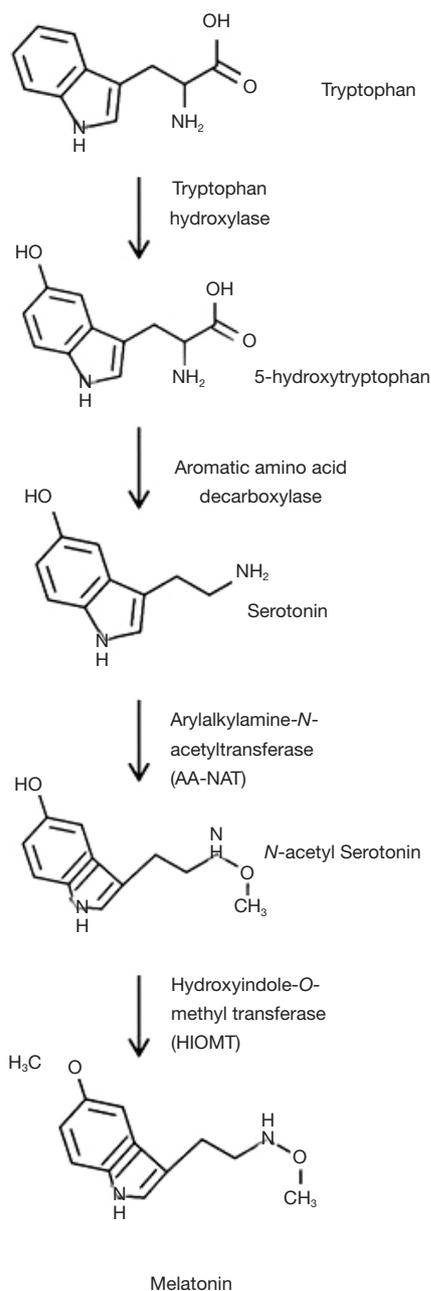


Figure 1 Melatonin biosynthetic pathway. Created with ChemDoodle Web with permission (14).

but extrapineal sources of melatonin include the retina, platelets, skin, lymphocytes, bone marrow cells, cerebellum and the gastrointestinal tract (6,7). N-Acetyl-5-methoxytryptamine is synthesized from L-tryptophan via hydroxylation of the indole ring by tryptophan hydroxylase to produce 5-hydroxytryptophan (5-HTP). 5-HTP is

decarboxylated by aromatic-amino-acid decarboxylase to produce serotonin which is converted by arylalkylamine-N-acetyltransferase (AA-NAT) to N-acetylserotonin and finally, through methylation of the hydroxyl group by hydroxyindole O-methyltransferase (HIOMT), converted in N-Acetyl-5-methoxytryptamine (8,9). Melatonin is a potent scavenger of reactive oxygen and nitrogen species (ROS and RNS) (10,11). It also promotes the activity of enzymes which are able to neutralize oxidants (12,13). The melatonin biosynthetic pathway is illustrated in Figure 1 (14).

Physiology

Melatonin binds to two receptor subtypes: MT1 and MT2. These receptors show significant similar molecular characteristics with 55% overall amino acid homology (15). They are G-protein coupled receptors (GPCRs) which both activate and inhibit a constellation of intracellular signaling pathways including downstream gene transcription targets such as extracellular signal-regulated kinases 1/2 (ERK 1/2) and cAMP response element-binding protein (CREB) (16). MT1 and MT2 alter intracellular signaling via alterations in scaffolding proteins, g-protein subtype availability and dimer formation. MT1 and MT2 are primarily found as homodimers but they form heterodimers with both themselves and other GPCRs (17). Moreover, melatonin can act intracellularly binding both cytosolic calmodulin (18,19) and two receptors of the Z-retinoid nuclear receptors family (20).

The secretion of melatonin from the pineal gland is regulated by activation of the β -1-adrenergic receptors (21) which promotes its biosynthesis through AA-NAT expression. Its release is suppressed principally by blue light which is influenced by both light intensity and the duration of exposure (22). Melatonin is released into the systemic circulation achieving plasma concentration between 80 and 120 pg/mL at night and 10–20 pg/mL during the day (23). The distribution of melatonin receptor subtypes is related to precise biologic functions within the complexity of central nervous system signaling (17,24). However, melatonin receptors have been found in peripheral tissues, including heart and arteries, adrenal gland, kidney, lung, liver and in B and T lymphocytes (25). Plasma melatonin redistributes rapidly after its release and is found within mitochondria, entering through oligopeptide transporters PEPT1 and PEPT2, where it acts as an antioxidant (26). There is emerging evidence that melatonin is produced within mitochondria (2,27,28), as evidenced by its lineage to

cyanobacteria, the very high mitochondrial concentration (26,29), the results of studies of pinealectomy (26), AANAT localization (30,31) and the observation of its synthesis in mammalian oocytes during maturation (32,33). Melatonin is metabolized by cytochrome P450 enzyme CYP1A2 to 6-hydroxymelatonin, conjugated with sulfuric acid (90%) or glucuronic acid (10%) and finally secreted in the urine. Only 5% of the molecule is excreted unchanged (34).

Beneficial effect of melatonin in sepsis

Melatonin has been demonstrated to improve organ function and to increase survival in several models of sepsis (35-39). The beneficial effects of melatonin in these sepsis models are the result of its action on different pathways, some of which we have summarized in this review. There are few clinical trials, mainly on newborns and pediatric patients, that have shown promising results when melatonin is administered for the treatment of sepsis (40-42).

Antioxidant properties

Sepsis is characterized by an oxidative imbalance with oxidant and antioxidant levels related to illness severity (43-47). Free radicals can lead to the damage of protein, lipids, DNA (48) and affect the function of the glycocalyx (49). Melatonin and its metabolites can scavenge ROS/RNS and their action is referred to as the “free radical scavenging cascade” (50). Melatonin has additive advantages over other antioxidants in preventing oxidative damage (51,52). As melatonin reaches high concentrations within mitochondria (53), and together with its metabolites (11,54,55), it has powerful antioxidant action protecting mitochondria from oxidant injury. Melatonin is also involved in the intra-mitochondrial SIRT3 pathway; SIRT3 is a class 3 histone deacetylase, which protects mitochondria from oxidative stress (56-58). In addition, melatonin stimulates the synthesis of other antioxidant enzymes, including glutathione peroxidase, glutathione reductase, γ -glutamyl-cysteine synthetase, glucose-6 phosphate dehydrogenase and catalase (12,13). Experimental sepsis models have demonstrated that melatonin restores glutathione levels (59). Melatonin reduces the levels of malondialdehyde and myeloperoxidase expression in the liver, brain, lung and kidneys and has been demonstrated to reduce hepatic necrosis in septic animals (38). Melatonin's favorable antioxidant properties have been reported in models of cecal ligation and puncture (CLP) induced septic

shock and lipopolysaccharide (LPS) induced liver failure (35,39,59).

Anti-inflammatory properties

The initial phase of sepsis is characterized by an exaggerated pro-inflammatory response leading to organ dysfunction and ultimately death. Melatonin has significant anti-inflammatory and anti-apoptotic properties (13,39,60-63) and in several rodent models has been demonstrated to reduce pro-inflammatory cytokines levels (35,38,64). In a rat model of LPS-induced acute lung injury, melatonin attenuated pulmonary inflammation; this was associated with a reduction of nuclear factor kappa- β p65 (NF- κ B p65) and tumor necrosis factor- α (TNF- α) expression with an increase of the anti-inflammatory cytokine interleukin 10 (IL-10) (65). Melatonin dose-dependently reduced serum TNF- α and interleukin-6 (IL-6) in a murine model of LPS-induced sepsis (66). Attenuation of the cytokine response was also demonstrated in a murine model of sepsis treated with intraperitoneal melatonin, where melatonin significantly improved the survival rate (39). Several *in vitro* models have demonstrated that melatonin switched-off NF- κ B expression (67,68). In a human umbilical vein endothelial cell (HUVEC-C) model of sepsis, melatonin dose-dependently inhibited NF- κ B expression and modulated IL-6 and IL-8 expression (69). These anti-inflammatory effects may be mediated by the modulation of the toll like receptor (TLR) inflammatory cascade (70), the reduction of oxidative stress, NF- κ B inhibition or the prevention of apoptosis (71-74).

Prevention of mitochondrial dysfunction

Mitochondria play a key role in sepsis-related redox dysregulation. Sepsis may be characterized by a reversible bioenergetic failure due to mitochondrial dysfunction which leads to impairments in oxygen consumption and hyperlactatemia (75,76). The post-mortem evaluation of septic patients has indicated mitochondrial injury; cardiomyocytes show mitochondrial loss, collapse and vacuoles and renal cells demonstrate hyalinosis and tubular vacuolization (77). Mitochondrial dysfunction may be due to diminished activity of pyruvate decarboxylation due to thiamine deficiency (78-81), phosphorylation and inactivation of pyruvate dehydrogenase, impaired electron transport chain (ETC), microcirculatory shunting (82,83) and nitric oxide (84) and ROS (85) mediated mitochondrial

damage. The kidney, heart and brain are those organs with the greatest density of mitochondria and are most susceptible to sepsis-induced mitochondrial dysfunction (86). In a murine model of LPS-induced sepsis, melatonin prevented mitochondrial dysfunction through increasing the ATP:O ratio, augmenting complex IV activity and restoring the respiratory control index (RCI)—the ratio of the rate of mitochondrial oxygen consumption (37). Melatonin further proved to normalize the mitochondrial ATP production in septic mice (87), reversing the inhibitory action of LPS on complexes I and IV and restoring the mitochondrial membrane potential (51,69,88). The capacity of melatonin to reverse mitochondrial damage was further investigated by Zhang *et al.* in a murine model of sepsis (66). These authors demonstrated that melatonin restored the mitochondrial membrane potential, reduced the levels of endoplasmic reticulum (ER) stress and inhibited the pro-apoptotic activation of caspase 12. In their study inhibition of B-cell receptor associated protein 31 (BAP31) expression, a regulator of ER mediated cell apoptosis, was reestablished by melatonin, probably through the MAPK/ERK pathway (66). Lastly, melatonin protects mitochondria by blocking the overexpression of inducible nitric oxide synthase (iNOS) and the subsequent production of nitric oxide (NO) (89).

Prevention of hepatic injury

Acute hepatic dysfunction is a serious complication of sepsis leading to coagulopathy, dysregulated metabolic homeostasis, altered mental status and death. The beneficial effect of melatonin is well known in chronic liver disease (90-96). Melatonin has hepatoprotective properties through its widely distributed receptors within the liver and observed in melatonin receptor knockout mice (97). Melatonin protects the liver by reducing the production of NO in a model of endotoxemia (98). Its antioxidant properties reduce lipid peroxidation (38,59), malondialdehyde (MDA) levels and increases superoxide dismutase (SOD) in the liver of rats treated with LPS (99). Melatonin can restore the LPS-induced hepatic downregulation of Pregnane X receptor—a regulator of gene transcription—and CYP3A (100), which similarly to CYP450 is reduced by LPS (101,102). A murine model of sepsis-related hepatic failure showed impaired glucose metabolism, increased transaminases, IL-1 β , TNF- α and IL-6 and inhibitions of silencing information regulator 1 (SIRT1)—a crucial enzyme involved in cell survival, inflammation and metabolism (103,104)—and signal transducer and activator of transcription

3 (STAT3) (105). When treated with melatonin, septic rats showed improvements in insulin resistance and hepatic gluconeogenesis, reduction of liver enzymes, modulation of inflammatory cytokines, increases in SIRT1 and STAT3 and reduced mortality; effects that were antagonized with EX527 a SIRT1 specific inhibitor (105). Finally, melatonin can prevent hepatocyte apoptosis protecting mice from hepatic failure (106).

Preventing septic cardiomyopathy

Myocardial dysfunction in sepsis is closely tied to worse outcomes (107). Septic cardiomyopathy has been labeled a “*junctionopathy*” (77), characterized by mitochondrial damage, ER stress, impairment of actin-myosin coupling culminating in reduced ejection fractions, cardiac output and hemodynamic instability (108). Cardiac myocytes express melatonin receptors and melatonin has been tested in several murine models of LPS-related sepsis. When treated with melatonin, myocytes demonstrate improved mitochondrial membrane potential, reduced levels of ER stress and caspase-12 mediated apoptosis (66). Melatonin was further able to restore BAP31 expression, which can prevent mitochondrial DNA damage (109) and apoptosis through the MAPK/ERK pathway. The inhibition of ERK abolished melatonin mediated upregulation of BAP31, indicating a relationship in preserving mitochondrial function (66). Mitochondrial NO synthase, which leads to mitochondrial dysfunction is counteracted by the administration of melatonin (87,88,110-112). LPS induced septic cardiomyopathy in mice is characterized by reduction of SIRT1 expression, increased CK-MB and apoptosis via caspase-3 activation leading to reduced ejection fractions (113). Treatment with melatonin improved cardiac function, lowered CK-MB levels and restored SIRT1 expression, as seen in models of septic hepatic injury (105). Melatonin treated mice displayed increased autophagy, a mechanism that protects cardiomyocytes during stress (114,115) and improves contraction (116). LPS-induced septic cardiomyopathy studies have highlighted receptor-interacting protein kinase 3 (Ripk3) as a potential mediator of the aberrant inflammatory cascade responsible for the sepsis-induced myocardial dysfunction (117). Melatonin appeared to suppress Ripk3 activity, optimizing mitochondrial bioenergetics, modulating ER oxidative stress, and normalizing cardio-protective signaling cascades (including AKT, AMPK, and ERK). Ripk3, when overexpressed, mitigates the cardioprotective action of melatonin (117).

In vitro cultures of cardiomyocytes exposed to hypoxia/reoxygenation injury displayed inhibition of p21 activated kinase 2 (Pak2), a known primary mediator for ER stress and ERK involvement (118). Melatonin reversed the inverted the hypoxia/reoxygenation injury and through AMPK-Pak2 axis, inhibited caspase 12 and prevented cell death (118).

Inhibiting nitric oxide production

Sepsis results in the increased expression of inducible cytosolic and mitochondrial isoforms of nitric oxide synthase (mtNOS and iNOS) which increase levels of NO and the subsequent mitochondrial damage (88,119,120). In experimental models of sepsis, melatonin inhibits iNOS and mtNOS isoforms (51,88,98). Inhibition of iNOS lowers NO levels, preventing organ failure and death (98). Furthermore, melatonin can increase the activity of complexes I and IV preventing ROS and RNS production and enhancing the ETC (88,121). In addition, melatonin downregulate NOS activity through calmodulin (18,19,122), which impedes the activation of several calcium-dependent enzymes, such as mtNOS and iNOS (88). N-acetyl-5-methoxy Kynurenamine (AMK), a melatonin metabolite, demonstrated an increased ability in binding calmodulin and reducing nNOS expression (123).

Preventing sepsis related brain dysfunction

Altered mental status is one of the cardinal features of sepsis (124). Sepsis associated encephalopathy has a prevalence of approximately 50% in critically ill patients (125,126). The brain's high rate of oxygen consumption and relative antioxidant deficiency renders it disproportionately susceptible to oxidative stress (127). ROS damage disrupts the blood-brain-barrier, alters mitochondrial respiration and alters tubulin arrangements (128). Increased ROS production promotes the release of the excitatory neurotransmitter glutamate, which alters gene expression, accelerates the apoptotic cascade, and impairs neuronal viability (129).

Despite its common occurrence, there are no diagnostic tests or biomarkers which aid in the diagnosis and evaluation of this complication (130). Despite the absence of biomarkers of septic encephalopathy a few studies have evaluated the role of melatonin for limiting septic encephalopathy (36,130). In a CLP mouse model of sepsis, administration of melatonin attenuated blood brain barrier dysfunction and cerebral edema via the SIRT-1 pathway (130). Furthermore,

administration of melatonin was shown to normalize neurobehavioral dysfunction through expression of brain derived neurotrophic factor glial cell-line derived neurotrophic factor within the hippocampus (36).

Immune enhancing properties

Wu and colleagues demonstrated melatonin modulates the immune response after CLP in rats, reducing IL-1 β , diminishing polymorphonuclear infiltration, attenuating oxidative stress and reducing NO levels (35). Melatonin reduces IL-6 production in an LPS model of sepsis (37), switching off inflammasome-dependent cytokine production, preventing mitochondrial dysfunction and inhibiting NF- κ B activation (69).

Regulating circadian rhythm

Sleep disturbances and delirium may complicate up to 60% of patients within the intensive care unit (131). Evidence suggests septic patients' melatonin release is profoundly dysregulated (5) if not completely abolished with loss of the normal diurnal variation (132,133). The precise mechanisms behind these findings remain poorly understood with mRNA expression of circadian master genes Period 2 and cryochrome-1 being reduced in the early stages of sepsis (134). This may affect immune cells which are in part regulated by the circadian rhythm and display diurnal variation in activity (135,136). These cells display time-dependent gene expression which results in altered levels of transcription in a concept termed "circadian-gating" (137,138).

Levels of melatonin in the critically ill

The nocturnal peaks and daytime serum levels have been reported to be severely reduced in critically ill patients with loss of the normal diurnal variation (5,132,139-141).

Pharmacokinetic of melatonin

Oral melatonin is rapidly absorbed from the small intestine by first-order kinetics, with a t_{max} being achieved after approximately 30–45 minutes (142). The bioavailability of oral melatonin is generally low, ranging from 3% to 33%. The low bioavailability is caused by a considerable first-pass metabolism in the liver. The t_{1/2} elimination is about 54 minutes. The C_{max} and area under the curve (AUC) are highly variable, likely attributable to inter-individual

variations in the absorption, distribution, metabolism, and/or excretion of the drug. Patients with cirrhosis demonstrate reduced elimination rates and increased plasma melatonin levels. Healthy volunteers were treated with increasing oral doses of melatonin (20, 30, 50 or 100 mg) without adverse effects (143). Elimination half-life for all doses was 52 minutes. While there is limited pharmacokinetic data in critically ill patients (144,145), a 3 mg oral dose was reported to achieve a peak level at a mean of 16 minutes with a $t_{1/2}$ elimination of 94 minutes. In this study the maximum serum level observed was 11,040 pg/mL. Pharmacological levels were maintained up to 10 hr following administration and no excessive daytime sleepiness was reported in these patients.

Safety of orally administered melatonin

A review of 195 studies (146) evaluating the effects of melatonin supplementation suggested 11 reported adverse effects amongst study patients. These included subjective worsening of symptoms (asthma, headaches, seizures), transient dizziness and headaches, morning drowsiness and abdominal and back pain. In a meta-analysis of 50 studies evaluating the efficacy of oral melatonin supplementation (1 to 20 mg) (147), nearly half reported adverse effects, often transient, associated with daytime dosing and commonly as drowsiness and fatigue. One g/day of orally-administered melatonin over 30-day (148) noted “drowsiness” as a potential adverse effect, with no statistically significant impact on various clinical parameters (blood pressure, heart rate, ECG, serum chemistry, urine analysis). Three separate studies investigating the use of intravenously-administered melatonin (1.25 mg/kg in healthy, epileptic, and Parkinson’s patients (149), 10 mg/kg in preterm infants and septic neonates (150), and 100 mg in healthy subjects (151) did not report adverse side effects. A double-blind, placebo-controlled study evaluating the utility of 5–20 mg of sublingual melatonin in patients undergoing gynecological surgical procedures likewise didn’t report either dose-dependent or dose-independent symptom (152). The lethal dose 50 (LD 50) of melatonin is reported to be infinity; i.e., it is impossible to administer a large enough dose of melatonin to kill an animal. In summary, melatonin is extremely safe being devoid of clinically significant side effects.

Conclusions

Melatonin is a promising adjunctive therapy for sepsis and

with several *in vivo* studies demonstrating the prevention of organ dysfunction and with improvement in outcomes (35-39). Its beneficial effects potentially derive from its free radical scavenging properties, anti-inflammatory action, plausible role in restoring mitochondrial function and protecting from delirium and brain dysfunction. Several clinical trials exploring the use of melatonin in the pediatric population have shown promising results (40-42,150). The safety profile and minimal side effects of oral melatonin should encourage clinicians to consider using melatonin as adjunctive therapy in patients with severe sepsis and septic shock. The optimal dose of melatonin in the treatment of patients with sepsis is unknown. Currently a clinical trial of antioxidant therapy in patients with septic shock is evaluating a 50 mg nighttime dose of melatonin (NCT03557229). Recently, we have included melatonin at a dose of 6 mg (at 9 pm) in our modified hydrocortisone, ascorbic acid and thiamine protocol (mHAT). Clearly, further clinical research is required to evaluate this safe and exceedingly cheap intervention in the management of sepsis.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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