Review

High doses of melatonin as a potential therapeutic tool for the neurologic sequels of covid-19 infection

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ABSTRACT

The therapeutic potential of melatonin as an agent to counteract the consequences of COVID-19 infections is due to its wide-ranging effects as a powerful antioxidant, anti-inflammatory, and immunostimulant, as well as to a possible antiviral action. In view of the recently reported evidence on the occurrence of neurological sequels in COVID-19-infected patients, another putative application of melatonin emerges based on its neuroprotective properties. In this manuscript a brief discussion of melatonin activity in animal models of ischemic and hemorrhagic stroke and the allometric calculations of the possible human equivalent doses are made. Based on the safety of melatonin, and in order to maximize its therapeutic opportunity, doses of 100 - 300 mg p.o. or i.v. are proposed.

Key words: allometry, COVID-19, cytoprotection, inflammation, melatonin, stroke

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1. INTRODUCTION

In light of the public health problem triggered by the spread of COVID-19 and in the face of essentially null options for prevention or treatment presently available, the use of melatonin has been proposed to possibly control the consequences of the disease (1). In severely infected patients with COVID-19, clinical findings indicate that excessive inflammation, a depressed immune system, and activated cytokine storm contribute substantially to pulmonary pathogenesis (2). In addition, in a recently published retrospective consecutive case series of 214 patients from Wuhan, China, with either moderate or severe COVID-19, 36.4% exhibited some nervous system–related clinical finding (3). A report of viral infiltration of the brainstem in pathologic specimens (4) also raises the possibility that some of the crucial pathophysiology behind respiratory failure in COVID-19 may be owing to central nervous system pathology, further expanding the view of which clinical manifestations of the current pandemic are truly neurologic in nature. Moreover, at this time of compulsory and massive isolations or quarantine, patients with symptoms of stroke have higher chances of death or disability.

2. EVIDENCE FOR THE THERAPEUTIC VALUE OF MELATONIN IN STROKE

Stroke is the second leading cause of death and a major cause of disability worldwide and its incidence is increasing because the population ages (5). In addition, more young people are affected by stroke in low- and middle-income countries. Ischemic stroke is more frequent but hemorrhagic stroke is responsible for more deaths and disability-adjusted life-years lost (5).

Melatonin, a methoxyindole present in all forms of life with aerobic respiration and, whose primary function seems to be cytoprotection, has indirect antiviral actions (1, 6) as an anti-inflammatory, antioxidant and immunostimulant effects (7, 8) and a very effective neuroprotective activity (9). In mice with viral encephalitis, the administration of melatonin reduced viremia and viral load, improving the neurological sequelae and death of infected animals (10).

Melatonin exerts anti-inflammatory effects through various pathways. One of them is sirtuin-1, which inhibits the polarization of macrophages towards the proinflammatory type (11, 12). The anti-inflammatory effect of melatonin also includes the suppression of NF-κB activation (13-15). Likewise, the production of Nrf2 is stimulated by melatonin in hepatoprotection and cardioprotection studies (16). Inflammation is commonly associated with elevated production of cytokines and chemokines. Melatonin causes a reduction of proinflammatory cytokines (TNF-α, IL-1β, IL-6, L-8, IL-17) and an elevation in the level of anti-inflammatory cytokines such as IL-10 (11, 17).

In both the cytoplasm and the cell nucleus, melatonin has important antioxidant and scavenging effects on free radicals, which are largely independent of receptors (18). These effects are exerted in three ways: (a) melatonin is a free radical scavenger; (b) melatonin is metabolized to compounds with high antioxidant activity; (c) melatonin is an indirect antioxidant, which stimulates the synthesis of antioxidant enzymes and inhibits that of prooxidant enzymes. Melatonin has a proven superiority to vitamin C and E in protection against oxidative damage and in the elimination of free radicals (19). In addition, melatonin potentiates the effects of other antioxidants, such as vitamin C and Trolox. Several antiapoptotic and cytoprotective effects of melatonin are exerted under conditions of ischemia (unrelated to free radicals) and can be attributed to the stabilizing activity of the mitochondrial membrane (20).

Tables 1 and 2 summarize the effect of melatonin in animal models of hemorrhagic and ischemic stroke. From the doses of melatonin used in the experiment listed in Tables 1 and 2, the human equivalent dose (HED) of melatonin for a 75 kg adult was calculated by allometry. Allometry is an engineering term derived from the Greek *alloios* (meaning different) that defines the study of size and its consequences (21). Allometry applies to properties whose proportions change as a function of size, as opposed to isometry whose relationship to size remains constant. Body surface area, rather than body weight, correlates well across several mammalian species with several parameters of biology, including oxygen utilization, caloric expenditure, basal metabolism, blood volume, circulating plasma proteins, and renal function, and has been advocated as a factor to be used when converting a dose for translation from animals to humans (22). Allometry is commonly used for determining doses for Phase I human clinical drug trials. In clinical medicine, it is feasible to use adult data to predict drug pharmacokinetic parameters in children, which can significantly decrease the occurrences of toxicity and mortality for new drugs used early in children. Noteworthy, theoretical human equivalent doses calculated from Table 1 and 2's results ranged from 2- to 3-orders of magnitude greater than those usually employed in humans.

Table 1. Effect of melatonin on animal models of hemorrhagic stroke. The human equivalent dose (HED) of melatonin for a 75 kg adult is calculated allometrically (22).

Model	Melatonin doses	HED for a 75 kg adult	Melatonin's effects	Ref.
Rat / Model of subarachnoid hemorrhage from cisterna magna.	10 mg / kg, i.p., repeated daily for 2 days.	121 mg	Inhibits lipid peroxidation, restores glutathione levels	(23)
Rat / Model of subarachnoid hemorrhage from Prechiasmatic Cistern.	150 mg / kg, i.p., 2 and 24 h later.	1824 mg	Activates the Nrf2-ARE pathway and increases the expression of detoxifying enzymes and antioxidants	(24)
Rat / Model of subarachnoid hemorrhage by endovascular filament.	150 mg / kg, i.p., 2 and 24 h later.	1824 mg	Reduces the water content in the brain, reduces mortality	(25)
Rat / Model of subarachnoid hemorrhage by endovascular filament.	150 mg / kg, i.p., 2 h later.	1824 mg	Improves autophagy, inhibits mitochondria-dependent apoptosis	(26)
Rat / Model of subarachnoid hemorrhage by endovascular filament.	150 mg / kg, i.p., 2 h later.	1824 mg	Inhibits proinflammatory cytokines, maintains close binding proteins and BBB integrity	(27)
Rat / Model of subarachnoid hemorrhage by endovascular filament.	150 mg / kg, i.p., 2 and 24 h later.	1824 mg	Decreases the expression of mediators related to the TLR4 pathway	(28)
Rabbit / Model of subarachnoid hemorrhage from cisterna magna.	5 mg / kg, i.p., every 12 h for 5 days.	243 mg	Reduces the activity of arterial NF-kB, decreases the vascular levels of IL-1β, IL-6 and TNF-α, improves the antioxidant defense system, and reduces lipid peroxidation	(29)
Rat / collagenase-induced intracerebral hemorrhage model.	15 mg / kg, oral, and every 24 hours thereafter for 7 days.	182 mg	Reduces oxidative stress and improves electrical response capacity	(30)
Rat / collagenase-induced intracerebral hemorrhage model.	15 or 150 mg / kg, i.p., 15 min and 3 h after.	365 or 3650 mg	Decreases lipid peroxidation	(31)
Rat / collagenase-induced intracerebral hemorrhage model.	15 mg / kg, i.p., 1, 24, 48 and 72 h later.	182 mg	Relieves long-term brain atrophy and reverses striatal and cognitive functional deficiency	(32)

Table 2. Effect of melatonin on animal models of ischemic stroke. The human equivalent dose (HED) of melatonin for a 75 kg adult is calculated allometrically (22).

Model	Melatonin doses	HED for a 75 kg adult	Melatonin's effect	Ref.
Rat / middle cerebral artery occlusion.	20 mg / kg p.o. before occlusion and once a day for 11 or 19 days.	243 mg	Improves glial cell survival.	(33)
Rat / middle cerebral artery occlusion.	6.0 mg / kg, p.o.) before occlusion and 1 day after surgery.	73 mg	Reduces ischemia-induced edema.	(34)
Rat / middle cerebral artery occlusion.	5 mg / kg i.v. at the start of reperfusion.	60 mg	Attenuates the stress of the endoplasmic reticulum.	(35)

Rat / transient focal cerebral ischemia.	5 mg / kg i.v. at the start of reperfusion.	60 mg	Ensures the preservation of the blood-brain barrier and the neurovascular unit.	(36)
Rat / transient focal cerebral ischemia.	5 mg / kg i.v. at the start of reperfusion.	60 mg	Inhibits the cellular inflammatory response.	(37)
Rat / brain ischemia injury.	15 mg / kg after the hypoxic-ischemic event and for 2 days.	180 mg	Neuroprotection (reduction of cell death, reactive astrogliosis, and white matter demyelination).	(38)
Rat / transient global cerebral ischemia.	continuous infusion i.v. (10 mg / kg / h for 6 h).	720 mg	Preserves the neural substrate, spatial learning and memory.	(39)
Gerbil / middle cerebral artery occlusion.	10 mg / kg i.p. 30 min before reperfusion and 1, 2 and 6 hours later.	324 mg	Improves survival and decreases neurodegeneration-induced hyperactivity.	(40)
Rat / middle cerebral artery occlusion.	10 mg / kg i.p 15 min before focal ischemia and 6 h and 12 h later.	364 mg	Reduces infarct size and DNA damage.	(41)
Rat / middle cerebral artery occlusion.	5 mg / kg i.p. at 0, 1 or 3 hours after ischemia.	182 mg	Reduces infarct size and improves the antioxidant state in a time-dependent manner.	(42)
Mouse / middle cerebral artery occlusion.	10 mg/kg i.p given twice.	60 mg	Up-regulates SIRT 1, increases antiapoptotic factor, and decreases proapoptotic factor activity.	(43)
Mouse / middle cerebral artery occlusion and oxygen and glucose deprivation.	10 mg / kg i.p 15 min before focal ischemia and 6 h and 12 h later.	180 mg	Decreases oxidative stress and inhibits the release of mitochondrial cytochrome C.	(44)
Mouse / middle cerebral artery occlusion.	5 mg / kg, i.p., 60 min after the onset of ischemia.	30 mg	Attenuates postischemic increase in blood-brain barrier permeability and improves t-PA therapy.	(45)
Mouse / middle cerebral artery occlusion.	5 mg / kg, i.p., 90 min after the onset of ischemia.	30 mg	Negatively regulates post ischemic activation and expression of MMP-9 and improves t-PA therapy.	(46)

3. SAFETY FOR THE CLINICAL USE OF MELATONIN

Melatonin is remarkably non-toxic, and its safety is very high. The lethal dose 50 for intraperitoneal injection of melatonin was determined for rats (1168 mg / kg) and mice (1131 mg / kg), but could not be achieved after oral administration of melatonin (tested up to 3200 mg / kg in rats or subcutaneous injection of melatonin (tested up to 1600 mg / kg in rats and mice) (47). There is evidence in dose escalation experiments of the remarkable lack of toxicity of melatonin in humans up to 100 mg (48, 49). As discussed elsewhere (50), high doses of melatonin have been used in various pathologies without undesirable sequelae, that is, in humans, melatonin has a high safety profile and, in general, is very well tolerated.

4. CONCLUSIONS

Allometric calculations of the HED of Tables 1 and 2 strongly indicate that effective melatonin doses in COVID-19 patients must be in the 100-300 mg / day range. Although there is no report related to the use of melatonin in patients with COVID-19, in subjects with other diseases and a higher level of inflammation, the application of melatonin may show promising results with strong attenuation of circulating cytokine levels. This was documented in patients with diabetes mellitus and periodontitis (51) and severe multiple sclerosis (52). In the acute phase of inflammation, during surgical stress (53), cerebral reperfusion (54) or reperfusion of the coronary artery (55), treatment with melatonin reduced the level of proinflammatory cytokines.

According to the COVID-19 clinical reports, patients with severe infection have an increased risk of sepsis and cardiac arrest (56, 57). The available information indicates that the application of melatonin can improve septic shock through inhibition of the NLRP3 pathway (58). Specifically, melatonin has a preventive effect against sepsis-induced kidney damage, septic cardiomyopathy, and liver damage (59-61). Melatonin has also been reported as beneficial in patients with myocardial infarction, cardiomyopathy, hypertensive heart disease, and pulmonary hypertension, and that it exerts neurological protection by reducing the inflammatory response in the brain, cerebral edema, and hyperpermeability of the blood-brain barrier. In the ICU, deep sedation is associated with increased long-term mortality, and the application of melatonin reduces the use of sedation and the frequency of pain, agitation and anxiety (62, 63) and improves the quality of sleep. Therefore, the rationale for the use of high doses of melatonin in COVID-19 focuses not only on attenuation of infection-induced respiratory disorders, but also on general improvement and prevention of possible complications, like the neurologic ones.

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CONFLICT OF INTEREST

The author declares that there are no commercial or financial relationships that could be construed as a potential conflict of interest.

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