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Review article

The potential use of melatonin to treat protozoan parasitic infections: A review

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ABSTRACT

Melatonin (N-acetyl-5-methoxytryptamine) is a circadian hormone produced in vertebrates by the pineal gland and other organs. Melatonin is believed to influence immune cells leading to modulation of the proliferative response of stimulated lymphocytes as well as cytokine production. Due to the antioxidant and immunomodulatory effects of melatonin, it is suggested that this molecule could be a therapeutic alternative agent to fight bacterial, viral, and parasitic infections by a variety of mechanisms. Herein, we review the effects of melatonin on the cell biology of protozoan parasites and host's immune response. In toxoplasmosis, African trypanosomiasis and Chagas' disease, melatonin enhances host's immune response against the parasite via regulating the secretion of inflammatory mediators. In amoebiasis, melatonin reduces the amoebic lesions as well as increasing the leukophagocytosis and the number of dead amoebae. In giardiasis, serum melatonin levels are elevated in these patients; this suggests a positive correlation between the level of melatonin and phagocytic activity in the *G. duodenalis* infected patients, possibly related to melatonin's immunomodulatory effect. In leishmaniasis, melatonin arrests parasite replication accompanied by releasing mitochondrial Ca^{2+} into the cytosol, increasing the level of mitochondrial nitrites as well as reducing superoxide dismutase (SOD) activity. In malaria, melatonin synchronizes the *Plasmodium* cell cycle via modulating cAMP-PKA and IP3-Ca^{2+} pathways. Thus, simultaneous administration of melatonin agonists or giving pharmacological doses of melatonin may be considered a novel approach for treatment of malarial infection.

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) is an indoleamine synthesized from tryptophan [1]. Tryptophan is taken up from the blood and converted into 5-hydroxytryptophan (5HTP) by tryptophan hydroxylase. 5HTP is decarboxylated by L-aromatic amino acid decarboxylase to form serotonin. Serotonin is subsequently acetylated to N-acetylserotonin (NAS) by arylalkylamine N-acetyltransferase (AANAT). The final step is the O-methylation of NAS to melatonin and involves the action of *N*-acetylserotonin-*O*-methyltransferase (ASMT) [2]. Melatonin is secreted by the pineal gland into both cerebrospinal fluid and into the blood of all mammals [3,4]. Additionally, melatonin is found in other cells, tissues and organs including lymphocytes, bone marrow, thymus, gastrointestinal tract, skin, eyes, etc. [5,6], where it may also be produced.

Circulating melatonin is taken up by liver, where it is hydroxylated in the C6 position by cytochrome P450 monooxygenases. It is subsequently converted to 6-sulphatoxy melatonin; this is the main product of melatonin found in the urine. Under certain conditions such as inflammation, melatonin is metabolized in the brain to kynuramine derivative, namely, *N*1-acetyl-*N*2-formyl-5-methoxy kynuramine (AFMK) and *N*1-acetyl-5-methoxykynuramine (AMK). Interestingly, the

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Table 1
Summary of studies evaluated the role of MLT in protozoan parasites.

Parasite	In vitro	In vivo	Results	Refs.
	Concentration MLT	Dose MLT		
T. gondii	–	Rat, 3 mg/kg/d for 3 wk	There were no differences in $CD3^+$ lymphocyte percentage among all groups. $CD4^+$ and $CD8^+$ ratios in zinc group (GI), MLT group (GII) and MLT + zinc group (GIII) were higher than control groups. The total lymphocyte ratios in GI–III were higher than control groups. The total lymphocyte ratios in group III were significantly higher than groups I and II. The plasma Zn levels in I-III groups were significantly higher than control groups.	[23]
T. gondii	–	Rat, 3 g/kg/day	The highest amount of CD3+, CD4+, CD8+ lymphocytes was detected in choroid and retina in infected + MLT + zinc-treated rats. The least amount of cellular infiltration was observed in Px + zinc-deficient diet-treated rats. Single zinc or MLT treated did not impact on the cellular infiltration in the retina and choroid of Px rats. The supplementation of pharmacological doses of Zn + MLT enhanced cellular immune response to T. gondii eye infection in non-Px rats.	[24]
E. histolytica	100 ng/ml	Hamster, Rat, 15 mg/kg	MLT significantly reduced areas of amoebic necrosis in infected animals. MLT increased the adherence of E. histolytica trophozoites to MN and PMN (The highest rate (80.4%) in MN cells). MLT induced a significant increase in the ingestion of PMN leukocytes :(50.6% in absence and 62% in presence). MLT increased percentage of dead amoebae during leukocyte internalization. MLT treatment showed higher levels of superoxide anion and superoxide dismutase compared to the control group.	[31]
G. lamblia	–	Human	Serum MLT concentration was higher in giardiasis patients (22.9 ± 1.64 pg/mL) in comparison with healthy group (9.2 ± 0.22 pg/Ml).	[37]
L. infantum	MEM, 1, 10, 25, and 50 nM	–	Percentage of parasite inhibition (PPI): 13.9%, 18.9%, 32.9%, and 58.3%, in 1, 10, 25 and 50 nM MLT concentrations respectively. The highest MLT concentrations (25 or 50 nM) stimulated the release of accumulated Ca2+ in all isolated mitochondrial fractions. Level of mitochondrial nitrites was significantly higher in the cultures treated with the highest MLT concentrations (25 or 50 nM). SOD activity was lower in cultures treated with MLT compared to controls. MLT impaired activity of respiratory complexes I, II and III at highest concentrations (25 and 50 mM).	[48]
L. amazonensis	Peritoneal murine macrophage, 3, 10, 30 or 100 nM	Hamsters 30 mg/kg	The parasite load was 80% lower in hamsters infected during the dark phase than in animals infected during the light phase. MLT reduced parasite burden, replication, and development of lesion in animals that were inoculated during the dark phase. MLT treatment reduced macrophage arginine uptake by 40%. MLT did not alter the transcripssion levels of NOS2 or NO production in Leishmania-infected macrophages.	[47]
T. cruzi	LTM, Grace medium, Vero cells, 1, 2, 5 × 10^6 parasites/ ml	–	Light exposure of epimastigotes and metacyclic forms lead to inhibition of the growth and the parasitization ability respectively. Epimastigotes cultured for 7 days under a LD cycle of 2:22 h showed a 55% reduction in MLT content. Light exposure of epirnastigote forms decreased the protein synthesis compared to the darkness. Incubation of epimastigotes with exogenous MLT (1 pM) significantly reduced their transformation into the metacyclic forms.	[87]
T. cruzi	–	Rat, 50 mg/kg/body weight	MLT treatment significantly increased the level of IL-10 and reduced the level of NO and TNF-α produced by cardiomyocytes. MLT treatment decreased heart weight, serum CK-MB levels and inflammatory foci compared to infected animals that didn't receive any treatment.	[88]
T. cruzi	–	Rat, 5 mg/ kg/body weight	MLT treatment reduced the number of blood parasites during the acute phase of infection in comparisone with untreated animals. IL12 level and the numbers of leucocytes increased in MLT treatment group compared to untreated group. In heart tissue, MLT treatment showed a reduced number of smaller amastigote burdens when compared to untreated counterparts. In heart tissue, MLT treatment caused reduction in inflammatory cytokines infiltration, tissue disorganization indicating a reduced parasitism of this tissue.	[56]
T. cruzi	–	Rat, 5 mg/ kg /body weight	Level of IL12, IFN- γ and TNF-α as well as peritoneal macrophage number increased MLT treated groups compared to untreated group. MLT treatment concomitant with the infection was more effective than treatment prior to infection to up-regulate the immune response, with exception of NO.	[58]
T. cruzi	–	Rat, 5 mg/kg/ body weight	The levels of IL-4, IL-10 and TGF-β as well as splenocyte proliferation were reduced in MLT treatment groups (concomitant with the infection or prior to infection) compared to untreated group.	[55]

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