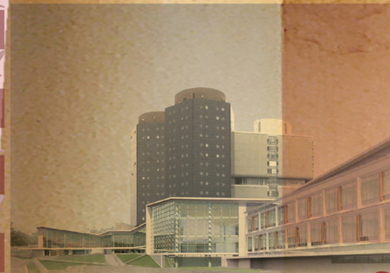

Melatonin, an Anti-Aging Hormone: Current Developments and Future Clinical Implications

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Introduction

Human senescence is characterized by a progressive decline in functional capacity and homeostatic integrity, accompanied by an increase in susceptibility to the acquisition or development of disease and disease related processes and complications. The progressive cumulative stochastic degradation of inherently thermodynamically unstable somatic biomolecules, DNA in particular, has been proposed as an explanation to the phenomena of aging and its associated susceptibility to age related illnesses. This process may be mediated by both endogenously and exogenously generated free radicals. Melatonin is a hormone generated by the pineal gland and other organs which regulates circadian rhythms. The pleiotropic effects of melatonin include its ability to act as a direct free radical scavenger, an inducer of other endogenous antioxidants, a potentially immunomodulatory activator, a modulator of sleep and a regulator of homeostatic processes. Melatonin secretion declines progressively with age. When this secretory wane is taken into consideration within the context of the free radical theory of aging along with the observed disruption of circadian rhythms, the occurrence of age related sleep dysfunction and immunosenescense in the elderly, these age related physiologic observations suggests that melatonin supplementation may have a role in the mitigation of age related diseases.

Objectives

To determine the status of the use of melatonin as an anti-aging agent based on current published literature.

Physiological Systems	Physiological Mechanisms of Melatonin	Effect
Physiological Systems	• Direct free radical scavenger of ONOO- and other reactive biomolecule species • High bioavailability of melatonin to subcellular compartments • Inhibits lipid peroxidation • Enhances GSH synthesis • Potential immune stimulating effects • Potential anti-apoptotic effects • Potential anti-inflammatory effects	Mitigation of age related disease? Effects on longevity?
Mitochondria	• Direct free radical scavenger of ONOO- and other reactive biomolecule species • High bioavailability of melatonin to subcellular compartments • Inhibits lipid peroxidation • Enhances GSH synthesis • Increases transcriptional activity of mitochondrial DNA • Homeostatic effects that improves the efficiency of ATP generating mechanisms leading to the reduction in reactive oxygen generation and leakage	Potential anti-apoptotic effects
Immune system	• Increase in NK cell activity • Enhancement of antigen presentation and phagocytosis • Induction of IL 12 • Effects on cytokine expression • Reduction in NF-κB binding • Regulation of iNOS	Potential immunoenhancing effects Potential anti-inflammatory effects
CNS	• Direct free radical scavenger of ONOO- and other reactive biomolecule species • Neutralization of dopamine autoxidation • Increase in GSH	Potential antiapoptotic effects

Table 1: Proposed Physiological Mechanisms of Melatonin

Methods

A literature search was conducted through Medline for relevant articles on aging and the role of melatonin as an anti-aging hormone during the month of January 2009 and subsequently on March 2009.

In vivo				
Longevity				
Model	**Design**	**Primary Outcome**	**Discussion/Conclusions**	**Citation**
Balb/c female murine model	12 experimental Mel group treated with 10 mg/L of melatonin in night drinking water vs 26 control mice	Effects on mortality: mean increase in 18%	Possible effects on longevity	6
CBA female murine model	50 experimental Mel treated with 20 mg/L of melatonin in night drinking water vs 50 control	Effects on mortality: mean increase of 5% Increased incidence of tumorgenesis	Possible effects on longevity Possible tumorgenic effects	7
Samp 1 female murine model	23 experimental Mel group treated with 20 mg/L of melatonin in night drinking water vs 20 control	Effects on mortality: None No effect on tumorgenesis	Possible lack of effect; perhaps attributed to model or design	8
C3H/Jax female murine model	39 experimental Mel group treated with 20-50 mcg/mouse/day of melatonin drinking water vs 20 control	Effect of tumorgenesis in mammary tumor prone mice: decreased incidence	Possible antitumorgenic effects	9
D. melanogaster (Oregon wild)	D.melanogaster fed mel added nutrient media at conc of 100 ug/ml vs control	Mean increase in 33.2% median life span in experimental group	Possible effects on longevity	10
Immunomodulation				
Model	**Design**	**Primary Outcome**	**Discussion/Conclusions**	**Citation**
Male albino mice	Melatonin subq injected mice exposed to Venezuelan equine encephalomyelitis. Degree of exposure of mel (250ug/kg, 500 ug/kg, 1000 ug/kg) vs mortality.	Mortality rates: (250ug/kg, 500 ug/kg, 1000 ug/kg): 45%, 40% and 16% respectively at day 6 vs 100% in controls	Melatonin demonstrates immunostimulating effects. Suggests potential uses?	1
Male C57 mice	Melatonin fed mice (day 7 and day 14) vs controls (day 7 and day 14)	Immune cell lines spleen/femur marrow compared vs controls	NK and monocyte/macrophages counts significantly higher than control counts	3
Sprague–Dawley rats	Intraperitoneal melatonin (10mg/kg) administered rats vs day exposed rat, dim red night exposed rat, 0.4% alcohol IP	Spleen extracts 60 minutes post intervention assayed for NF-KB activity	Significantly lower NF-KB activity in night exposed rats vs day NF-KB binding affinity inhibited in melatonin treated group vs alcohol treated group Potential immunomodulatory effect	4
Neurodegenerative Model				
Model	**Design**	**Primary Outcome**	**Discussion**	**Citation**
Male Murine Model	MPTP with melatonin IP vs without melatonin IP	Brain analysis for DNA fragmentation and apoptosis demonstrated lower markers for both in mel treated mice	Potential neuroprotective effects	5

In vitro				
Immunomodulation				
Model	**Design**	**Primary Outcome**	**Discussion/Conclusions**	**Citation**
Ring Dove (Streptopelia risoria)	Blood samples drawn were analyzed for effects on non-specific immunity vs melatonin doses of 5, 25, 50, 75 and 100 μM	Phagocytosis enhanced by melatonin Possible chemoattractant at high doses Reduced superoxide levels in a dose dependent manner.	Melatonin may have immunomodulatory effects on non-specific immunity. However high doses were required to elicit such effects in vitro.	2

Results

Current data suggests that melatonin may play a role in the mitigation of age related diseases, particularly those diseases associated with the generation of free radicals. Limited human data exists.

Conclusion

In vitro and in vivo, animal and limited human data, suggests that melatonin may potentially serve a role in the mitigation of age related diseases, particular those with disease related processes that are dependent on the generation of free radicals. However, based on the research data available currently, its supplementation for the prolongation of functional survival through the deceleration of the process of senescent aging or even for the mitigation of age related disease cannot be conclusively determined. Additional human trials are needed to define the safety, toxicity and efficacy profile of melatonin.

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