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Effects of melatonin on oxidative stress, and resistance to bacterial, parasitic, and viral infections: A review

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ABSTRACT

Melatonin, a hormone secreted by the pineal gland, works directly and indirectly as a free radical scavenger. Its other physiological or pharmacological activities could be dependent or independent of receptors located in different cells, organs, and tissues. In addition to its role in promoting sleep and circadian rhythms regulation, it has important immunomodulatory, antioxidant, and neuroprotective effects suggesting that this indole must be considered as a therapeutic alternative against infections. The aim of this review is to describe the effects of melatonin on oxidative stress and the resistance to bacterial (*Klebsiella pneumoniae*, *Helicobacter pylori*, *Mycobacterium tuberculosis*, and *Clostridium perfringens*), viral (Venezuelan equine encephalomyelitis virus and respiratory syncytial virus), and parasitic (*Plasmodium* spp., *Entamoeba histolytica*, *Trypanosoma cruzi*, *Toxoplasma gondii*, and *Opisthorchis viverrini*) infections.

Contents

1. Introduction

Melatonin (N-acetyl-5-methoxytryptamine) (MEL) is a neurohormone secreted primarily by the pineal gland following a circadian rhythm with peak concentrations at night. After its isolation and chemical characterization in 1959 (Lerner et al., 1959), several studies were reported that aimed at clarifying the physiological and behavioral responses exerted by MEL. A growing body of evidence supports the key role of MEL in the entrainment and regulation of circadian rhythms (Reiter, 1991, 1993; Pévet et al., 2002; Arendt, 2005). However, this hormone was also found to be involved in a variety of other pathophysiological processes including the modulation of immune response (Arzt et al., 1988; Arias et al., 2003; Carrillo-Vico et al., 2005), defense against viral infections (Maestroni et al., 1988; Ben-Nathan et al., 1995; Bonilla et al., 1997, 2004), bone formation (Roth et al., 1999), and tumor

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suppression (Lissoni et al., 1993; Jung-Hynes et al., 2010; Park et al., 2010). Melatonin has an important role in antioxidant and neuroprotective processes (Reiter et al., 1995; Reiter, 1997, 2000; Pandi-Perumal et al., 2006, 2008; Lyssenko et al., 2009; Galano et al., 2011). Administration of MEL has been proposed for the treatment of a variety of pathological conditions including sleep disturbances, depression, cancer, stroke, and epilepsy (Sánchez-Barceló et al., 2010). The idea that MEL works as an immune buffer, acting as a stimulant under basal or immunosuppressive conditions or as an anti-inflammatory compound when immune responses are increased, as in acute inflammation, has been recently proposed (Carrillo-Vico et al., 2013).

It has long been known that oxygen is toxic to aerobic organisms when they are exposed to concentrations greater than that of normal air and the main cause of this toxicity is the intracellular reduction of O_2 into highly reactive free radicals (Frank, 1985). In fact, the "free radical theory" proposes that aging is the cumulative result of oxidative damage to the cells and tissues of the body arising primarily as a result of aerobic metabolism (Harman, 1956). However, aging is a complex multifactorial process in which free radical damage provides a very important but not exclusive mechanism of physiological decline (Wickens, 2001). There are other hypotheses, with experimental support. Various nutritional, behavioral, and pharmacological interventions extend the life span in *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Drosophila melanogaster*, mice, rats, and possibly monkeys and humans (Ristow and Schmeisser, 2011).

Although MEL freely diffuses through all biological membranes, its biological activity can be also receptor mediated. The MEL receptors MT1 and MT2 are distinguished by the peculiar sequence motif characteristic of the rhodopsin family, constituted by seven TM-spanning helices connected by three intracellular (ICL1, ICL2, ICL3) and three extracellular (ECL1, ECL2, ECL3) loop segments with the amino terminus located in the extracellular side and the carboxyl terminus on the intracellular side. Spectrum of cell surface membrane receptors of MEL includes MT1 (Mel1a), MT2 (Mel1b), and MT3 (Mel1c) (found in amphibians, avians, and fishes). There are also nuclear receptors of MEL namely, [RZR/RORα and NR1F2 (RZR/RORβ)]. It is believed that the existence of multiple MEL receptor isoforms explains the differential regulation of the receptor expression in different tissues during development and in adult tissues. Furthermore, selective pathways for an intracellular signal transduction have been proposed (Fredriksson et al., 2003; Dubocovich et al., 2010; Li et al., 2013; Pala et al., 2013).

The aim of this review is to describe the effect of MEL on oxidative stress, and resistance to bacterial, viral, and parasitic infections.

2. Effect of melatonin on oxidative stress and inflammation

2.1. Free radicals

Most radicals occurring *in vivo* are reactive oxygen species (ROS) or reactive nitrogen species (RNS). The ROS include the superoxide anion ($O_2^{\bullet -}$), hydroxyl ($OH^{\bullet}$), alkoxyl (RO^-), peroxyl (ROO^-), and hydroperoxyl (HOO^-). The RNS include peroxynitrite ($ONOO^-$), nitric oxide ($NO^{\bullet}$), and nitrogen dioxide ($NO_2^{\bullet}$) (Galano et al., 2011). Aerobic organisms have developed a complex anti-oxidative defense system to combat the destructive effects of O_2 by products. Unfortunately, this defense system is not perfect and some molecular damage always occurs, leading to diseases and aging.

Oxygen (O_2) initially undergoes a single electron reduction to produce the $O_2^{\bullet -}$, which is either dismutated to H_2O_2 or combined with $NO^{\bullet}$ to form $ONOO^-$ which can also degrade into $OH^{\bullet}$ or a similar toxic metabolite. H_2O_2 is converted to $OH^{\bullet}$ in the presence of a transition metal such as iron (Reiter, 2000). $OH^{\bullet}$ is the most electrophilic and reactive of the oxygen radicals, with a half life of approximately 10^{-9} s and can react immediately at the site of their formation damaging almost any molecule in the vicinity. Therefore, $OH^{\bullet}$ is the most dangerous oxygen radical. The reactivity of $NO^{\bullet}$ is rather low, but it reacts with $O_2^{\bullet -}$ yielding $ONOO^-$ which is a potent oxidant able to react with proteins, lipids, and DNA (Galano et al., 2011).

2.2. Characteristics of melatonin as antioxidant

Due to its ability to scavenge ROS and RNS, it has been hypothesized that the main function of MEL is to protect living organisms from oxidative stress (Vijayalaxmi Meltz and Reiter, 1999; Taysi et al., 2003; Zavodnik et al., 2006; Tan et al., 2007; Hardeland et al., 2009; Tapias et al., 2009). Hydrogen and electron transfers have been identified as the main mechanisms involved in the free radical-scavenging activity of MEL, although there are others such as the radical adduct formation (Galano et al., 2011).

Electron spin resonance spectroscopy, pulse radiolysis, and additional indirect methods showed that MEL neutralized the $OH^{\bullet}$ with a high degree of efficiency (Roberts et al., 1998; Stasica et al., 1998; Mahal et al., 1999). It also neutralizes H_2O_2 and others oxidants including singlet oxygen ($^1O_2$), NO, and the $ONOO^-$ (Galano et al., 2011).

Melatonin has been shown to reduce the accumulation of the major products of lipid peroxidation (usually measured as malondialdehyde and 4-hydroxyalkenals) when membranes are exposed to radical-generating agents especially $OH^{\bullet}$ and $ONOO^-$ (Reiter, 2000; Galano et al., 2011). It also reduces the accumulation of DNA adducts induced by carcinogens. The premiere example of melatonin's ability to neutralize free radicals comes from observations in which DNA-damaging agent were utilized (Tan et al., 1998). After surgical removal of the pineal glands of rats, physiological MEL concentrations partially reduce the destruction of DNA by free radicals generated by ionizing radiation and/or radiomimetic agents (Tan et al., 1998). Melatonin has been found capable of repairing the guanosine radical ($G^{\bullet}$) with a high degree of efficiency presumably *via* electron transfer (Pryor and Squadrito, 1995).

The superior antioxidant capacity of MEL is, at least partially, attributed to what is referred to as the cascade reaction when scavenging free radicals (Tan et al., 2000, 2013). The resulting products of the interaction of MEL with ROS and RNS are cyclic 3-hydroxymelatonin (C-3OHM), N1-acetyl-N2-formyl-5-methoxyknuramine (AFMK), and N-acetyl-5-methoxy-knuramine (AMK). These metabolites, like their precursor MEL, also function as radical scavengers (Lopez-Burillo et al., 2003; Ressmeyer et al., 2003; Galano et al., 2013). It is estimated that *via* the cascade reaction, one MEL molecule may scavenge up to 10 free radicals (Tan et al., 2007), which contrasts with the classic antioxidants such as vitamins C and E, and glutathione that detoxify one radical per molecule.

Acting as an indirect antioxidant MEL, at least in pharmacological concentrations, increases mRNA levels and the activities of superoxide dismutase (SOD), glutathione peroxidase, glutathione reductase, and catalase (Reiter, 2000, 1997; Reiter et al., 1997; Emerit et al., 2004). The pro-oxidative enzyme inducible nitric oxide synthase (iNOS) is also inhibited by MEL (Crespo et al., 1999).

It has been proposed that the concentrations of MEL (20–160 pM) required to activate its membrane receptors are in the range of its blood levels (Reiter, 2000). Although MEL is highly lipid soluble, it also displays some aqueous solubility and it is localized virtually in any cellular compartment, including the nucleus (Reiter, 2000).