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Melatonin As A Potent Antioxidant - A Review

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Abstract
Melatonin is an antioxidant which could be the latest supplement to fight against periodontal disease. It is produced predominantly by the pineal gland with a marked circadian rhythm that is governed by the central circadian pacemaker (biological clock) in the suprachiasmatic nuclei of the hypothalamus. Melatonin stimulates the proliferation and synthesis of type 1 collagen and promotes bone formation. This review article surveys the current state of knowledge regarding the physiology and pharmacology of melatonin and discusses the potential uses of melatonin as an antioxidant in periodontal therapy.

Key Words
Melatonin, free radicals ,antioxidants, periodontal disease

Introduction

Periodontal disease is a complex condition that may vary from gingivitis to extreme destruction of tooth-supporting tissue. Although bacterial infection and release of toxic bacterial products triggers a series of processes leading to damage of healthy tissues, a number of actions of the host immune response are also involved. However, the etiopathogenesis and pathophysiology of periodontal disease still remains unclear.

A response of the organism to the periodontal infection includes the production of several intracellular enzymes[1]. Alkaline phosphatase and acid phosphatase are intracellular enzymes present in most tissues and organs, particularly in bones.There is an increase in the activity of these enzymes in periodontitis and a reduction after periodontal therapy. Melatonin, an indoleamine secreted by the pineal gland in a circadian manner is a noteworthy free radical scavenger[2] and also plays an immunomodulatory role[3]. Several studies have shown that melatonin stimulates the proliferation and synthesis of type I collagen and promotes bone formation[4],[5]. Melatonin may have implications in diseases of the oral cavity, limiting tissue damage that is a result of free radicals, stimulating the immune response and reducing the progressive loss of alveolar bone[6],[7].This antioxidant role of melatonin may be of potential use in the pathogenesis of periodontitis[8]. This review summarizes the physiology and pharmacology of melatonin and discusses its potential uses of melatonin in periodontal therapy.

History

Melatonin was originally discovered fifty years ago by the American dermatologist Aaron Lerner and his co-workers as an amphibian skin-lightening factor present in extracts of bovine pineal glands. Lerner named the molecule melatonin because it induces contraction of stellate amphibian melanophores[9]. Subsequently, melatonin was reported to be present in a wide spectrum of organisms, including bacteria, fungi, plants, protozoa, invertebrates[10] and vertebrates including man. The fact that melatonin is an evolutionarily highly conserved molecule speaks in favor of its important physiological roles.

Synthesis , Physiological and pharmacological Role in Humans

Melatonin is a widely occurring neurotransmitter-like compound derived primarily from the pineal gland. It is also produced in a number of other areas, for example the gastrointestinal tract[11].

Melatonin is an indole hormone, widely distributed in both plant and animal sources, such as human milk[12], bananas, beets, cucumbers, and tomatoes[13]. Chemically, melatonin is N-acetyl-5-methoxytryptamine, a derivative of serotonin, which in turn is derived from tryptophan. Melatonin is synthesized from a dietary amino acid precursor, L-tryptophan, via the following pathway:

L-Tryptophan
↓
Tryptophan Hydroxylase (TPH)
↓
5-Hydroxytryptophan
↓
Aromatic Aminoacid Decarboxylase (AADC)
↓
5-Hydroxytryptamine (Serotonin; 5-HT)
↓
Serotonin N-acetyltransferase (arylalkylamin N-acetyltransferase; AANAT)
↓
N-Acetyl-5-hydroxytryptamine
↓
Hydroxyindole-O-methyltransferase (HIOMT)
↓
N-Acetyl-5-methoxytryptamine (melatonin)

The rate of melatonin formation depends on the activity of two enzymes: serotonin N-acetyltransferase (AANAT)[14] and, to a lesser extent, tryptophan hydroxylase (TPH), which controls the availability of serotonin[15]. In addition, it has been demonstrated that some nutritional factors, such as the availability of tryptophan, folate, and vitamin B6, could also influence melatonin production[16]. Melatonin synthesis depends on intact

beta-adrenergic receptor function[17]. Norepinephrine activates the N-acetyltransferase and beta-receptor blockers depress melatonin secretion[18]. The enzymes of melatonin synthesis are activated and depressed, respectively by darkness and light. Release of melatonin follows a circadian (circa: about; dias: a day) rhythm generated by the suprachiasmatic nuclei in response to daylight alterations.

Through melatonin release, the pineal gland maintains the internal clock governing the natural rhythms of body function. This apparent clock-setting property of melatonin has led to the suggestion that it is a "chronobiotic" substance that alters and potentially normalizes biological rhythms and adjusts the timing of other critical processes and biomolecules (hormones, neurotransmitters, etc) that, in turn, exert numerous peripheral actions[19]. Melatonin has been administered in both physiological and pharmacological amounts to humans and animals, and there is widespread agreement that it is a nontoxic molecule[20]. In pregnant rats, the maternal lowest-no-observed-effect level was found to be 200 mg/kg/day, and the developmental no-observed adverse-effect level was > 200 mg/kg/day[21]. Melatonin is easily synthesized in a pharmacologically pure form and is inexpensive and affordable; thus, because of its versatility in protecting against nitrooxidative stress and reducing inflammation, melatonin could have significant potential to improve periodontal health[22]. However the actual therapeutic dosage of melatonin has not been approved as it is still under research.

Melatonin - a versatile antioxidant

Oxidative stressplays a key role in the pathogenesis of periodontal disease[4],[6],[7] therefore, an effective antioxidant therapy would be of great importance in these circumstances. Nutritional, environmental, and chemical factors can induce the overproduction of the superoxide anion radical in both the cytosol and mitochondria. This is the first and key event that leads to the activation of pathways involved in the development of several metabolic diseases that are related to oxidative stress. As oxidation of essential molecules continues, it turns to nitrooxidative stress because of the involvement of nitric oxide in pathogenic processes. Once peroxynitrite (ONOO–) forms, it damages via two distinctive mechanisms. First, it has direct toxic effects leading to lipid peroxidation, protein oxidation, and DNA damage. This mechanism involves the induction of several transcription factors leading to cytokine-induced chronic inflammation. Classic antioxidants, including vitamins A, C, and E, have often failed to exhibit beneficial effects in metabolic diseases and aging.

Melatonin is a multifunctional indolamine that counteracts virtually all pathophysiologic steps and displays significant beneficial actions against peroxynitrite-induced cellular toxicity. This protection is related to melatonin' s antioxidative and antiinflammatory properties. Melatonin has the capability of scavenging both oxygen- and nitrogenbased reactants, including those formed from peroxynitrite, and blocking transcriptional factors, which induce proinflammatory cytokines[23]. Melatonin was associated with improvement in the gingival index and pocket depth, and a rise in salivary concentrations of acid and alkaline phosphatases, osteocalcin and osteopontin. These findings suggest that melatonin may have a favourable effect in slowing osteoclastogenesis, improving the quality of alveolar bone and preventing the progression of periodontal disease[24]. The antioxidant effects of melatonin have been well described[25],[26] and include both direct as well as indirect effects. Melatonin administration leads to increased expression of the antioxidant enzymes superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px).

Melatonin and Free radicals

A very large body of evidence indicates that melatonin is a major scavenger of both oxygen- and nitrogen-based reactive molecules including peroxynitrite (ONOO–)[23]. Melatonin has scavenging actions at both physiologic and pharmacologic concentrations. Not only melatonin but also several of its metabolites can detoxify free radicals and their derivatives. Studies also reveal that melatonin eliminates the decomposition products of peroxynitrite (ONOO–) , including hydroxl (OH•), nitrogen dioxide (NO2•), and the carbonate radical (CO3–) in the presence of physiological carbon dioxide concentrations[23]. Melatonin also supports several intracellular enzymatic antioxidant enzymes, including superoxide dismutases (SOD) and glutathione peroxidase (GSH-Px)[27]. Moreover, melatonin induces the activity of γ-glutamylcysteine synthetase, thereby stimulating the production of another intracellular antioxidant, glutathione (GSH)[23]. A number of studies have shown that melatonin is significantly better than the classic antioxidants in resisting free-radical–based molecular destruction. In these in vivo studies, melatonin was more effective than vitamin E[28], β-carotene[29], and vitamin C, and superior to garlic oil.

Beneficial antioxidant effects of melatonin have been recently shown in clinical settings for several chronic diseases, including patients with rheumatoid arthritis[30], elderly patients with primary essential hypertension[31], and females with infertility[32]. Several antioxidants reportedly preserve the activities of superoxide dismutases (SOD) and/or glutathione peroxidase (GSH-Px). These effects are indirect, however, owing to their ability to scavenge free radicals and protect the protein from damage. Melatonin, on the other hand, possesses genomic actions and regulates the expression of several genes, including those for superoxide dismutases (SOD) and glutathione peroxidase (GSH-Px). Melatonin influences both antioxidant enzyme activity and cellular mRNA levels for these enzymes under physiological conditions and during elevated oxidative stress ,possibly through epigenetic mechanisms[33]. The occurrence of these two features in a single molecule is unique for an antioxidant, and both actions protect against pathologically generated free radicals. Of particular interest is the possible role of melatonin as a bioenergetic agent that can improve and maintain mitochondrial function. The majority of molecular oxygen (O2) inhaled and eventually taken up by cells is processed in the mitochondrial electron transfer chain (ETC), where it is converted to water after its four-electron reduction. During this reductive process, however, partially reduced species of molecular oxygen O2produce reactive oxygen species (ROS).

A specific isoform of nitric oxide synthase (NOS), mitochondrial nitric oxide synthase (NOS), is a constitutively expressed enzyme proposed to exist in mitochondria, where it produces nitric

oxide (NO) within mitochondria. Nitric oxide (NO) is a physiological regulator of respiration and also the rate of ATP synthesis. Elevation of nitric oxide (NO) levels higher than the physiological concentrations may lead to increased formation of superoxide anion radical (O2-) and all downstream oxidants. Consequently, the antioxidant and free-radical–scavenging capacities of melatonin protect proteins of the electron transfer chain (ETC) and mitochondrial DNA(mtDNA) from reactive oxygen species (ROS) induced oxidative damage. This protective effect limits the loss of intramitochondrial glutathione (GSH), improves electron transfer chain (ETC) activity, and reduces mtDNA damage. Melatonin's actions at the mtDNA level also increase the expression of complex IV and the activity of complex I and complex IV of the electron transfer chain (ETC)[34]. Melatonin acts against inducible nitric oxide synthase (iNOS) and peroxynitrite (ONOO–) .In many inflammatory processes, peroxynitrite (ONOO–) rather than other reactive molecules is the predominant molecule that determines the fate of cells. Once formed by the coupling of nitric oxide (NO) and superoxide anion radical (O2?) , peroxynitrite (ONOO–) cannot be removed or scavenged by vitamins E or C, or by other conventional antioxidants. As a multifunctional antioxidant, however, melatonin and its metabolites have unique features not shared by the usual antioxidants, including inducible nitric oxide synthase (iNOS) inhibitory and peroxynitrite (ONOO–) scavenging properties[23].

Melatonin and "The devil's triangle"

Melatonin is the only currently available molecule known to block all aspects of the "devil's triangle" which is formed when both superoxide anion (O2-) and nitric oxide (NO) are generated within a few molecular diameters of each other, they combine spontaneously to form peroxynitrite (ONOO–)in a reaction that occurs at a diffusion-limited rate. Basically, every time nitric oxide (NO) and superoxide anion (O2-) collide, they form peroxynitrite (ONOO–). Nitric oxide (NO) is the only known biological molecule that reacts faster with (O2-)and is produced in such high concentrations that it outcompetes endogenous superoxide dismutases (SOD). Melatonin has been shown to ameliorate inflammation by blocking transcriptional factors and TNF-α[35],[36]. A large body of evidence confirms that these cytokines induce formation of free radicals and promote inducible nitric oxide synthase (iNOS) activity and transcriptional factor activation within cells. These events inevitably induce a vicious cycle of cellular damage. It is now clear that peroxynitrite (ONOO–) induces both apoptosis and necrosis of cells. More highly elevated exposure of this agent is associated with necrosis rather than apoptosis). In this mechanism, activation of the DNA repair enzyme poly(ADP ribose)polymerase- 1 i.e. (PARP-1), a member of poly(ADP ribose)polymerase i.e. (PARP) enzyme family, mediates peroxynitrite (ONOOR09;) induced necrosis. Poly(ADP ribose)polymerase-1 (PARP-1) detects and signals DNA strand breaks induced by a variety of genotoxic insults, including ionizing radiation, alkylating agents, oxidants (essentially hydroxyl OH-and peroxynitrite ONOO–), and free radicals. When strand breaks occur at the time of binding to DNA, poly(ADP ribose)polymerase PARP transfers ADP-ribose units from the respiratory coenzyme nicotinamide adenine dinucleotide (NAD+) to various nuclear proteins. From a physiological viewpoint, poly(ADP ribose)polymerase -1 i.e. (PARP-1) activity are implicated in DNA repair, genomic stability maintenance, gene-transcription regulation and DNA replication. In the case of peroxynitrite (ONOO–) induced DNA damage, poly(ADP ribose) polymerase PARP overactivates in a genome-repair process and consumes nicotinamide adenine dinucleotide (NAD+) as a substrate, causing an energy crisis within cells, leading to their eventual necrosis. Preservation of nicotinamide adenine dinucleotide (NAD+) and cellular energy production may facilitate poly(ADP ribose) polymerase (PARP) to repair the DNA damage rather than blocking PARP; melatonin preserves cellular energy production[23] and protects against DNA damage[37].

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Advantages of melatonin over other antioxidants

A recent, intriguing report suggests that neither tryptophan nor serotonin, but only melatonin, inhibits COX-2 and inducible nitric oxide synthase (iNOS) transcriptional activation. Another advantage of melatonin over classical antioxidants is its lack of prooxidative actions. All classical antioxidants are potential electron donors and they exhibit both reduced and oxidized forms. Once they donate an electron to neutralize a free radical, they are transformed from a reduced to an oxidized state. Usually, the oxidized form will be regenerated to the reduced state through the mechanism known as redox reaction or recycling. In this pathway, the recycling of vitamin C or vitamin E occurs at the expense of glutathione (GSH). In many cases, however, GSH is a better antioxidant than either vitamin C or vitamin E[40] because these antioxidants are electron donors and exhibit redox reactions, their oxidized forms also can oxidize other molecules. Therefore, classical antioxidants are actually prooxidants. Melatonin sacrifices itself and does not participate in redox cycling after scavenging free radicals and thus does not act as a prooxidant. Hence melatonin does not consume cellular glutathione (GSH) and also preserves or even increases the content of GSH in tissues.

Thus, melatonin is classified as a suicidal or terminal antioxidant.[23]

Correlation of melatonin with systemic health

Liver disease such as cirrhosis, which impairs metabolic function, leads to higher than normal plasma concentrations of melatonin. Furthermore, the time of melatonin rise and the time at which melatonin levels peaked were consistently and significantly delayed in patients with liver cirrhosis[41]. Patients with end-stage chronic renal failure showed increased day-time melatonin. An abnormal rhythm of melatonin secretion is a constant feature of Smith-Magenis syndrome, a clinically recognizable rare genetic disease characterized by developmental delay, neurobehavioral abnormalities, and severe sleep disturbances. Very large pineals (~1 g) have been described in a rare genetic syndrome with insulin resistance[42]. Sudden infant death syndrome (SIDS) is associated with small pineals and decreased melatonin production. Melatonin has been extensively measured in psychiatry to assess biological clock status. There is evidence for a decline in the amplitude of the melatonin rhythm in depression associated with an increase in cortisol, and also possibly an increase in mania, although not all studies are consistent .Seasonal affective disorder (SAD) may well relate, at least in some patients, to a delay of the melatonin rhythm, although more complex relationships were recently reported .There is also evidence for abnormal melatonin secretion in patients with pre-menstrual tension. Low melatonin is associated with cardiovascular disease and diabetic autonomic neuropathology. An increased risk of breast cancer has been attributed to lower melatonin; however, the data are inconsistent and in some cases may be interpreted as an altered timing of the melatonin rhythm rather than reduced production[43]. From the above observations it can be interpreted that it seems to have a potential in a large number of disorders of different etiologies.

Conclusion

Melatonin could be the latest supplement to join the fight against periodontal diseases. Not only could it act as a protective function in fighting periodontal infection[44], but also stimulate the proliferation and synthesis of type I collagen and promote bone formation[4]. Studies have suggested decreased salivary melatonin levels as a risk indicator for the severity of periodontal disease[45] and it has been suggested that salivary melatonin levels recovered after periodontal therapy correlated with a decrease of local periodontal inflammation[46]. This may imply that the absence / presence of melatonin in the periodontal tissues may have an influence in the progression of periodontal disease due to its antioxidant properties.

Limitations in the use of melatonin

No definitive guidelines have been formulated for clinical evaluation of patients with low melatonin levels, in large part because a "melatonin deficiency syndrome" has not yet been defined so far as an independent entity. In light of substantial amount of heterogeneity across studies of melatonin for the treatment of periodontitis, more studies are required in this area. It is necessary that the conditions of the studies be clearly defined especially with respect to the amount , formulation and pharmacology of the melatonin product used in these studies. Besides all this even the mechanism by which melatonin is absorbed, distributed, metabolized, and excreted in humans is unclear and further research in this area is required. Very few studies compare the benefits and harms of melatonin in the treatment of periodontitis and more work is required in this field.

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