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Review article

MELATONIN IN ORAL IMPLANTOLOGY: FROM DISCOVERY TO THERAPY

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A B S T R A C T

Melatonin, N-acetyl-5-methoxytryptamine, is a derivative of the essential amino acid tryptophan and is produced primarily in the pineal gland in mammals. Known as a regulator of circadian rhythm, it also has physiologic roles in oral medicine and dentistry. Oral cavity is affected by number of conditions such as periodontitis, mucositis, cancers and cytotoxicity from various drugs or biomaterials. Research has suggested that melatonin is effective in treating the aforementioned pathologies. Furthermore, melatonin has been observed to enhance osseointegration and bone regeneration. The aim of this article is to critically analyze and summarize the research focusing on bone metabolism that promotes bone regeneration around dental implants. Dental implants require surface modifications in order to increase their bioactivity prior to their placement in periodontal bone. However, there are several drawbacks of modified implants such as delamination of the bioactive coating, ion leakage and particle residues. Melatonin has the potential to act as a viable alternative to unstable implant coatings. Melatonin, with its capacity to induce bone cell proliferation and differentiation, could facilitate the process of healing of bone tissue in dental implant surgery, reducing the period of osteointegration and settling of the implant, and therefore, the quality of life of the patient may be improved.

INTRODUCTION

Discovery of an active substance in any component of a living system has never been so exciting as what happened with the isolation, purification, and characterization of an indole compound from extracts of the pineal gland, which has long been considered as a functional relic of the brain[1]. The credit of such breakthrough research goes to a group led by an American dermatologist, Dr. Aaron Bunsen Lerner, in the Yale University School of Medicine, who extracted only a few milligrams of *N*-acetyl-5-methoxy-serotonin from more than 100,000 cattle pineal glands nearly 53 years ago.[2,3]

Role of Melatonin in Bone Metabolism

It is known that melatonin is involved in skeletal development: in particular, increasing evidences from in vitro and in vivo experiments using rodent and chicken have suggested the possible role of melatonin on bone metabolism.[4,5]The structural integrity of mammalian bone is dependent upon a balance between the activity of osteoclasts (the bone-resorptive cells) and osteoblasts (the bone-formative cells).[6,7] The aim of this remodeling process is the renewing of the skeleton while maintaining its anatomical and structural integrity.[8]

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Under normal conditions, bone is constantly degraded and replaced with new bone in cycles in which osteoclasts adhere to bone and subsequently remove it by acidification and proteolytic digestion. After the osteoclasts have left the resorption site, osteoblasts invade the area, and begin the process of forming new bone by secreting osteoid (a matrix of collagen and other proteins), which is eventually mineralized. After bone formation has ceased, the surface of the bone is covered by lining cells, a distinct type of terminally differentiated osteoblasts.[8] Several reports indicate that melatonin is involved in the regulation of calcium homeostasis. The effects of melatonin on calcium metabolism were first studied by Csaba *et al*.,[9,10] who proposed that this hormone could influence the secretion of calcitonin [11]and parathyroid hormone.[9] Indeed, it was demonstrated that suppression of melatonin secretion by white light (at the intensity used to treat hyperbilirubinemia in human infants) in newborn rats or synthesis in adult rats (by administration of the beta-adrenoceptor blocker propranolol) lowered serum calcium concentration.[12] Moreover, in both studies, treatment of rats with melatonin prevented serum calcium decrease.[12-14] The in vitro effect of melatonin on cellular proliferation and differentiation has stimulated interest in its role in bone regeneration. Therefore, the effect of melatonin on bone metabolism was recently examined using different kinds of osteoblastic cell lines. [15,16] Roth *et al*.,26 for instance, examined the direct effect of melatonin on osteoblasts using MC3T3-E1 preosteoblasts and rat osteoblast-like osteosarcoma

17/2.8 cells.[4] Both cell lines in the presence of nanomolar concentrations of melatonin augmented gene expression of bone sialoprotein (an extracellular bone matrix protein that is expressed during osteoblastic cell differentiation and is required for mineralization), as well as several other essential bone marker proteins including alkaline phosphatase, osteocalcin, and osteopontin, and stimulated both osteoblast differentiation and mineralization.[4] This relationship is supported by the fact that the genes of a large portion of bone matrix contain the sequence of bases (RGGTCA) necessary for the nuclear receptor of melatonin to bind with its promoting zone[17]. In these preosteoblastic cell lines, melatonin seems to reduce the period of differentiation into osteoblasts, and this reaction seems to be mediated by the membrane receptors for the indole[18]. Previous studies have shown that melatonin stimulates the synthesis and proliferation of collagen type I fibers in human osteoblasts in vitro[15]. Similar results were reported in clinically relevant human bone cells, in which micromolar concentrations of melatonin significantly increase procollagen type Ic peptide production (a measure of type I collagen synthesis) in a concentration-dependent manner[15]. Some authors reported that the mitogen-activated protein kinase (MAP-K) signal transduction pathway may be responsible for melatonin's effects on osteoblasts differentiation[19-20], even if further studies are needed. In another study, melatonin acted directly on human bone cells (HOB-M) and human osteoblastic cell line (SV-HFO) and dose-dependently increased the proliferation in both cell types by twofolds[15]. Type I collagen synthesis was also elevated in both cell types, but neither alkaline phosphatase activity nor osteocalcin secretion was influenced by melatonin[15]. Furthermore, seems that these effects on osteoblasts are mediated through melatonin transmembrane receptors[22]. Two genes have been isolated for membrane melatonin receptors in mammals including humans: one is the melatonin 1a receptor and [23] the other is the 1b receptor[24].In a recent study, reverse transcription–polymerase chain reaction and Western blot analysis showed that human osteoblasts express the melatonin 1a receptor and that its expression levels decrease gradually with age[25]. In this study, Satomura *et al*. confirm a possible role of melatonin in human bone formation, showing that at pharmacological doses, it is able to enhance proliferation and differentiation of normal human osteoblasts, even if its mechanisms of action remain unclear.

Moreover, to demonstrate the possible utility of melatonin as a pharmaceutical agent to shorten the period of bone regeneration, the effects of this hormone on bone formation in vivo were also tested; in mice, intraperitoneally administered melatonin to mice induced a significant increase in the ratio of new to old bone mass in the cortex of the femur[24]. Collectively, all these findings indicate that melatonin has a promotional action on osteoblasts. The bone complex, therefore, includes osteoblasts, osteoclasts, and the bone matrix. An interaction between osteoclasts and osteoblasts has been recently noted in mammals, and it is necessary to consider both their actions[8,26]. On the whole, osteoclasts are under the control of local modulator factors produced, among other cells, by the osteoblasts. The receptor activator of nuclear factor j B (RANK) and the receptor activator of the nuclear factor j B ligand (RANKL) have been identified in osteoclasts and osteoblasts, respectively[27]. Exposure of osteoblasts to substances such as parathyroid hormone stimulated the expression of osteoclast differentiating factors: in particular, it was found that the bound RANKL to RANK induces multinucleated osteoclasts (active type of osteoclasts)[27] and then can activate bone resorption[28]. Another osteoblastic protein, osteoprotegerin (a soluble member of the superfamily of tumor necrosis factor receptors), on the contrary, can inhibit the differentiation of osteoclasts by binding to osteoclast differentiation factor as a decoy[28].The effect of melatonin on the expression of RANK and osteoprotegerin was investigated in mouse MC3T3-E1 osteoblastic cells[16]. In this study, melatonin at pharmacological doses causes an inhibition of bone resorption and an increase in bone mass by down-regulating RANK-mediated osteoclast formation and activation:[16] The authors observed a significant dose-dependent decrease of RANK mRNA and an increase in both mRNA and protein levels of osteoprotegerin in MC3T3-E1 cells. On the other hand, melatonin is capable of influencing the RANKL system, suppressing its activity[16] and favouring the formation of new bone: this indicates that melatonin may bring about a reduction in bone resorption and an increase in bone mass because of its repression of osteoclast activation by means of RANK[29]. Moreover, in in vivo studies on intact mice, pharmacological doses of melatonin elevated the bone mineral density[16] aside from the trabecular thickness of the vertebra and the cortical thickness of the femur already showed in ovariectomized mice[30]. This treatment significantly reduced the bone resorption parameters (osteoclastic surface and osteoclastic number) but did not increase the histomorphometric bone formation parameters (bone formation rate, mineral apposition rate, and osteoid volume)[16]. So the skeletal effects of melatonin are, presumably, a result of the inhibition of osteoclast activity.

In a recent study, the effects of melatonin on osteoclastic and osteoblastic cells were examined using a culture system of the teleost scale.The teleost scale is a calcified tissue that contains osteoclasts, osteoblasts[31], and also components of the bone matrix;[32,33] hydroxyapatite also exists in the scale[34]. The scales of teleosts contain as much as 20% of the total body calcium and are a functional internal calcium reservoir during periods of increased calcium demand.[35,36] Thus, there are many similarities between the teleost scale and mammalian membrane bone. In this "in vitro assay system," melatonin directly suppressed both tartrate-resistant acid phosphatase and alkaline phosphatase activities, markers of osteoclastic and osteoblastic activity, respectively, by suppressing their growth and differentiation.This was the first report related to the function of melatonin in osteoclasts and on the inhibitory effect of melatonin in osteoblasts when incubated in the presence of osteoclastic cells. Indeed, the authors argued that the previously reported effects of melatonin to stimulate proliferation of mammalian osteoblasts[4] were artifacts because the experiments were conducted with isolated osteoblasts, while in bone formation and metabolism, cell-to-cell contacts between osteoblasts and osteoclasts occur[8].

Moreover, melatonin acts directly on osteoclasts, which use a variety of chemical agents and different mechanisms to resorb the extracellular matrix and degrade bone, including the production of free radicals. Osteoclasts generate high levels of free radicals, superoxide anions, in particular, during bone resorption, which contribute to the degradative process[37]. Thus, melatonin, being an antioxidant and a free radical scavenger at both physiological and pharmacological

concentrations177 may interfere in this function of the osteoclast detoxifying free radicals, which are produced during osteoclastogenesis,[39] leading to an inhibition of reabsorption of the bone[29]. Therefore, the effect of melatonin in preventing osteoclast activity in the bone may depend in part on its free radical scavenging properties. These data point toward an osteogenic effect of melatonin, which may be of clinical importance because it could be used as a therapeutic agent in situations when bone formation would be advantageous, such as in occlusal reconstruction using dental implants.

Melatonin Promotes Bone Regeneration around Dental Implants

All the actions of melatonin on bone metabolism described above are of interest, as it may possible to apply melatonin during endo-osseous dental implant surgery as biomimetic agent[40]. Occlusal reconstruction using dental implants is of importance from the point of view of the quality of life of patients: for this reason, osseointegration should be promptly completed and it should be maintained for as long as possible. So, in order to obtain functional bone as soon as possible, it is critical to enhance at the same time both the proliferation and differentiation of osteogenic cells. The long-term success of many dental implants depends on their ability to become well integrated in bone. Titanium (Ti) is the implant material of choice for use in dental applications, even if the surface properties of this material are not well suited for bonding to bone. Modifications of both surface topography and chemistry have led to significant improvements in the integration of such materials in bone. Several measures have been proposed to improve and accelerate osseous healing using topical treatments. They include the application of platelet-rich plasma, bone morphogenetic proteins, and growth factors (e.g., melatonin)[41]. Tacheki *et al*. focused on the possibility that melatonin may be an effective hormone in the treatment of bone changes around dental implants; its efficiency has been shown when melatonin acts synergistically with fibroblast growth factor 2 (FGF-2) to promote bone formation around titanium implants placed in the tibia of rat by enhancing both the proliferation and differentiation of osteogenic cells[42]. The results of Tacheki *et al*. strongly suggest that these two molecules have the potential to promote osteointegration of titanium implants, even if their exact roles during osteogenesis are not completely understood; FGF-2 is typically thought to control osteoprogenitor cell proliferation, whereas melatonin is more important in osteoblast differentiation. Moreover, in a recent study, it has been stated that topical application of melatonin successfully activated osteogenesis around titanium implants in a canine mandibular model. Considering a possible future application of melatonin in dentistry, the authors of this study thought that it was beneficial to introduce the effects of melatonin in implant treatment and showed that when applied topically, melatonin promotes peri-implant bone formation. A study with experimental beagle dogs was carried out to evaluate the effect of the topical application of melatonin mixed with a very biocompatible collagenized bone substitutes of porcine origin[43,44] on the osteointegration of dental implants. Bone grafts have been usually placed in bone defects or into extraction sockets to facilitate healing, used, for instance, in order to increase the width of the crest or for augmentation of the maxillary sinus floor to enable implant placement[45]. The results of Calvo-Guirado *et al*. showed that melatonin, combined with collagenized porcine bone substitutes, reveals more bone-to-implant contact and less crestal bone resorption than control implants, suggesting a positive role of melatonin in osteointegration around dental implant [46]. As emerged from all these studies, melatonin, with its capacity to induce bone cell proliferation and differentiation, could facilitate the process of healing of bone tissue in dental implant surgery, reducing the period of osteointegration and settling of the implant, and therefore, the quality of life of the patient may be improved.

Melatonin-Mediated Collagen Synthesis in Bone Healing

Bone, like cartilage, is provided structure mostly through its ECM; however, a few key structural differences exist. The matrix is produced by osteocytes rather than chondrocytes and is 60–70% inorganic material, primarily calcium and phosphate. Organic bone ECM is primarily collagen type I, providing most of its tensile strength rather than collagen type II. Bone has excellent blood supply compared to cartilage and contains a relatively higher proportion of cellular material than cartilage. These two facts combined explain why bone heals better than does cartilage when damaged. The bone marrow, the site of synthesis of red and white blood cells, platelets, and stem cells, is also stored within the long bones of the body. Bone contains a wider variety of cells than does cartilage.

Osteoblasts are the bone-forming cells, while osteoclasts break down bone. The balance between these two constitutes bone homeostasis[47,48]. The first studies of melatonin that sparked interest in melatonin's effects on bone were in vitro and revealed a dose-dependent increase in collagen synthesis and cellular proliferation as shown by increased procollagen type 1 c-peptide production, while cellular differentiation remained unaffected[49].

Other early studies showed in vitro potential for melatonin to promote osteoblast differentiation and bone formation[50]. Using luzindole, a melatonin receptor antagonist, they provided a plausible explanation for the mechanism of action through melatonin transmembrane receptors. These investigations spawned much work on melatonin as a regulator of bone metabolism both in vivo and in vitro. Because melatonin steadily decreases in humans as we age, which is even more dramatic in females at menopause[51], researchers have studied melatonin and its role in preventing osteoporosis and increasing bone mass alone and in combination with estrogen therapy[52,53]. Naturally, melatonin became of orthopedic interest for fracture healing and bone fusion.

Interestingly, one group found that long-term studies on pinealectomized rats maintained high levels of melatonin within the bone marrow[54]. Additionally, it was shown that bone marrow cells have the necessary enzymes to create melatonin from serotonin[55]. Together, these studies suggest that melatonin can function as an autacoid with local paracrine function in addition to the effects on bone metabolism that may be realized from systemic pineal melatonin[53]. Other studies showed that melatonin's effects on bone metabolism were related to decreased osteoclast activity secondary to down regulated RANKL expression from osteoblasts[56], providing yet another potential mechanism. Further in vitro research on human osteoblasts from mandibles concluded that melatonin promotes osteoblastic differentiation in a dose-dependent manner. Melatonin receptor expression was confirmed in these human osteoblasts, and significantly more receptors were found within the younger patients' bone

samples. Furthermore, other markers of up-regulation of osteoblasts, including type I collagen, were shown to be significantly increased. In vitro, the effects of melatonin were blocked with the administration of luzindole and other inhibitors of this receptor-mediated pathway[57]. This strengthens the position that melatonin's mechanism of action is based on its receptor-mediated cascade. The same investigators also studied in vivo effects on bone in mice, concluding systemic daily melatonin administration stimulated bone growth by measuring volume of nonhealing bone growth over a 21-day period[57]. The dental community investigated similar local application of melatonin to stimulate osteointegration within dental implants with favorable results[58]. Our laboratory has begun research into the effects of local and systemic melatonin administration on fracture healing in an osteoporotic and nonosteoporotic fracture rat model given these previous findings and the lack of in vivo studies to date. Further studies will be required to elucidate the mechanism of action of melatonin in bone.

CONCLUSIONS

From an accurate analysis of scientific literature, it seems that melatonin, either systemically or locally administered, has some interesting properties that both protect the oral cavity from inflammatory processes or infections and modulate the activity of cells involved in bone metabolism. Nowadays, experimental and clinical evidences are still inconsistent, so further studies are needed to clarify melatonin role in the homeostasis of oral tissues and enable the use of this hormone in the therapy of oral pathologies. Nevertheless, the scientific community believes that assumptions exist to look at this molecule with attention.

Conflict of interest- none

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