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Melatonin: Implications at the oral level

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SUMMARY

The strong relationship between the pineal gland and the immune system continues to establish itself more and more. In situations of a pinealectomy or in those of inhibition of the production of melatonin, a state of immunosuppression is produced which disappears when the patient receives this hormone. Likewise, melatonin counteracts the negative effects that immunosuppressive drug treatments produce over the immunity. It is due to these facts that one postulates the possibility of utilizing melatonin in primary and secondary immunodeficiency states as well as in cancerous immunotherapy. The action of this hormone over the immune system is carried out through the T-helper lymphocytes, lymphokines and also it seems through certain pituitary hormones. On the other hand, lymphokines such as Gamma-Interferon and Interleukin-2, as well as the thymus, can modulate the synthesis of melatonin at the level of the pineal gland. Without doubt, all these actions have important consequences at the time of treatment of our high-risk dental patients who have, in one way or another, an altered immunologic system. The altered immune system has direct implications in primary oral pathologies, or in others derived directly from our dental treatment.

KEY WORDS:

Melatonin, Oral implications.

RÉSUMÉ

Une relation de plus en plus précise s'établit entre la glande pinéale et le système immunitaire. Dans les cas d'une pinéalectomie ou d'une inhibition de la production de mélatonine, un état d'immunodépression apparaît et qui disparaît lorsque le patient reçoit cette hormone. Par ailleurs, la mélatonine contrecarre les effets négatifs des immunodépresseurs sur l'immunité. Il en résulte que l'on peut postuler l'utilisation de la mélatonine dans les états d'immunodéficience primaire et secondaire ainsi qu'au cours de l'immunothérapie cancéreuse. L'action de cette hormone sur le système immunitaire s'exerce au travers des lymphocytes T-helper, des lymphokines et aussi semble-t-il au travers de certaines hormones hypophysaires. De plus, des lymphokines telles que l'Interferon gamma et l'Interleukine 2, aussi bien que le thymus, peuvent moduler la synthèse de la mélatonine au niveau de la glande pinéale. Sans doute, toutes ces actions possèdent d'importantes conséquences lors du traitement en dentisterie, chez nos patients à haut risque souffrant d'une manière ou d'une autre d'une altération de leur système immunitaire.
Le système immunitaire altéré exerce une implication directe dans des pathologies primitives de la bouche ou dans celles qui dérivent directement de notre traitement dentaire.

MOTS CLEFS:

Mélatonine, implications orales.

INTRODUCTION

The quality of dental care received by patients with systemic pathology is on an ever-increasing rise. This improvement helps equally the health care provider as it does the patient. First, this increase in quality leads to an improvement in the criteria used at the time of selecting the required treatment. The treatment strictly related to the type of dental care received is many times not the same as for normal patients. Secondly, by way of medical-dental investigations, the quality of care is improving not only to help the high-risk patient to be in a better state to receive this treatment but also in order to minimize the secondary effects of said treatment. Some years ago the hormone melatonin came rushing forth into this field of the study of patients with systemic pathology; and even though this hormone is still in an investigative phase, many aspects of melatonin are already known which are perfectly applicable in many of our medically compromised dental patients.

Through the post-synaptic activation of the β-adrenergic receptors (defined as biochemical night messengers), melatonin is synthesized and secreted by way of the pineal gland during the night (Deguchi and Axelrod, 1973, Reiter, 1991). This denotation of night messenger is due to the fact that light prevents adrenergic activation of the pineal gland, producing an inhibition in the synthesis of melatonin.

The experimental studies in this regard have demonstrated that rats subjected to constant light, or else treated with propanolol (a β-adrenergic blocker) had a diminution in their capacity to produce antibodies, as well as diminished cellularity equally in the spleen as in the thymus (Maestroni and Pierpaoli, 1981). These inicial studies found, likewise, that the primary response of antibody production was depressed in the afternoon, but not in the morning, after the administration of propanolol, which blocks the synthesis of serotonin. The utilization of exogenous melatonin through the afternoon makes the pharmacologic-induced immunitary altered state disappear (Maestroni, *et al.*, 1987).

These are the inicial studies which already show the implications of melatonin within the complex immunitary map, and which also have been subsequently confirmed in repeated ways (Champney and McMurray, 1991). Thus, in recently published articles utilizing young and old rats, an immunosuppression using cyclophosphamine and/or corticosteroids was carried out in which the utilization of melatonin restored the activity of T-helper lymphocytes as well as the production of Interleukin-2 (Caroleo, *et al.*, 1992).

It is thought that endogenous opioids are mediators in the immunologic action of melatonin. This suspicion comes about by way of the anticonvulsive and analgesic properties which melatonin has demonstrated in the experiments carried out on rats (Maestroni, *et al.*, 1988, Maestroni, *et al.*, 1989), as well as by way of the possibility that a specific opioid antagonist such as naltrexone can abolish all the actions of melatonin linked to the immune system. Thus, it is thought that melatonin can stimulate opioid peptide production through the activation of T-helper lymphocytes.

With respect to natural immunity and melatonin, that is, non-antigen dependent immunity, some authors have found no effect of melatonin over the immune system in the absence of antigenic stimulation (Maestroni, 1993). However, other groups of scientists have reported effects of melatonin over the natural immunity. In this regard, they have shown its action over the activity of natural killers, in the form of depression or stimulation, and also on its action of stimulation over the production of IL-2, lymphocytic blastogeneis, as well as in the relation of T-helper/T-suppressors. It must be pointed out, at the time of evaluating the differences among the various studies, that melatonin apparently has a stimulation action over live animals and humans, and on the contrary an inhibitory action when the study is carried out in vitro (Lewinski, *et al.*, 1989, Lissone, *et al.*, 1990, Caroleo, *et al.*, 1992, Champney and Mc Murray, 1991).

Recently, in a group of voluntary young patients, a 10 mg oral dose of melatonin was administered over a ten (10) day period, in which some received only a placebo. Before and after the treatment, the concentration of IgA was measured in the serum and the in saliva. The results obtained showed a significant rise in the IgA in the saliva at the oral level. This result is interesting from the point of view of the known role played by the salival IgA at both the oral and the upper respiratory tract levels (Maestroni, 1993).

Gamma-Interferon and Interleukin-2 are secreted through T-helper lymphocytes activated by the target-cell antigen over which melatonin then exerts its action. Both lymphokines are well knowned for their stimulatory action, above all, at the NK level. One would think that these lymphokines act as mediators in regards to the actions that melatonin produces over the immunity. If this were so, it

would imply that the action of melatonin depends on the quantity of T-helper lymphocytes that are present which were activated by an antigen. The utilization of IL2 inhibits the production of melatonin during the night in living beings (Lissoni, *et al.,* 1990).

It is known that not only melatonin produces actions over the immunity, but other hormones, such as growth hormone, opioid peptides and prolactin can also have a major or minor influence (Kelley, 1991).

MELETONIN AS AN IMMUNOTHERAPEUTIC AGENT

The use of melatonin as an immunotherapeutic agent appears clear, above all in states of immunodeficiency, as it seems that melatonin is more active in these situations. However, and unfortunately, the studies carried out on patients with AIDS have not been very positive. Thus, studies of eleven [11] patients in different states of infection with HIV were administered oral doses of melatonin in the afternoons for intervals ranging from 56-84 consecutive days. The results of these studies detected an exceptional rise in the peripheral blood of T-lymphocytes and mononuclear cells. However, this fact could be explained by, both the low number of patients studied, as well as the advanced stage of the infection in some of the cases (Maestroni, 1993). Nevertheless, it is considered that melatonin must be seriously taken into account at the time of treatement of these patients.

Likewise, it is considered that melatonin is one of the most important therapeutic promises in the fight against cancer. This pathology has been frequently associated equally with a depression in the secretion as much as in an activation of the immune system (Blask, 1984). Recent advances in cancerous immunotherapy are focused on the natural activation of cytolytic mechanisms. The natural killers and the activated lymphokine killers cripple cells which are either malignant or infected with virus. It is interesting to note, as has been demonstrated repeatedly, that IL2 can potentiate the NK and generate LAK cells of the NK as well as T-cells (Rosenberg and Terry, 1987). However, the anticancerous action of IL2 only appears at high concentrations, which also brings with it significant toxicity. Therefore, it seems that the anticancerous action of IL2 depends on the LAK phenomenon which is no more than a physiologic phenomenon linked to the well-known mechanism of the NK cells. This mechanism constitutes one of the most simple mechanisms that the body can utilize in its fight against cancer. If this is true, other elements can act in a synergistic way on IL2; and this is where the neuroendocrine system can play an important role, and therefore melatonin could share in this important role. This has been studied (Maestroni and Conti, 1993) in patients with pulmonary metastases who were administered melatonin and IL2 in combined form. The results of these experiments showed that melatonin could effectively potentiate the effects of IL2.

In other studies melatonin as been used in the treatment of one of the most severe pains that a patient can suffer, that of migraine headaches. These patients showed the presence of low nocturnal levels of melatonin together with an alteration in immunologic parameters (Martelli *et al.,* 1987). Nine patients were treated with a 5 mg dose of melatonin by mouth for intervals ranging from 10-60 days. After ten days of treatment the NK cells at the peripheral blood level showed a clear rise. The clinical results showed that in one patient there was a moderate improvement in the migraine headaches, in three patients there was no change, and in five patients there was a marked improvement (Maestroni and Conti, 1993). The nocturnal seric concentrations of melatonin were low in the patients who had improvement as well as in those who showed no improvement. These results must be interpreted in relation with the action that melatonin has over the immune system by way of the opioid receptors.

IMPLICATIONS OF MELATONIN IN PSYCHIATRIC PATIENTS

* *Depressive Patients*

For quite some time it has been postulated (Schildkraut, 1965) that in the depressive process there is a noradrenergic deficiency; thus, this has been the basis for study of the secretion of melatonin in patients with depression. As we already know, melatonin is secreted through the night and this secretion is controlled by noradrenergic fibers. Since a deficit of these noradrenergic fibers in depressive patients is already affirmed, it must be assumed that there must also exist a deficit in the secretion of melatonin. This is a fact that has been verified (Beck *et al.,* 1985, Wetterberg *et al.,* 1984), having been detected in patients who are experiencing serious depressive processes. Hereditibility being an important factor in relation to depression in these patients who presented these nocturnal alterations, it has

been postulated that the low nocturnal seric concentrations of melatonin might be a marker of susceptibility to the suffering of depression. However, these affirmatins must be taken with caution due to the fact that the concommitant ingestion of medications can cause the results to vary greatly (Thompson *et al.*, 1988). Therefore, at the present time, there is not sufficient data in clear form that relates the low concentrations of melatonin with depression (Arendt, 1989).

* *Schizophrenic Patients*

In order to open the way in the relationship of melatonin to schizophrenia, a study was carried out on twenty-one (21) chronic schizophrenic patients who had not taken medications for the previous year (Ferrier, 1982). The results showed that the nocturnal levels of melatonin were significantly lower than in those of the controls. These results have been subsequently confirmed by better planned studies in which it was been taken into account that medications can affect the variables of the melatonin (Robinson *et al.*, 1991). The influence of melatonin on the pathophysiology of schizophrenia is still not clear.

FUTURE STUDIES

Although the relation between melatonin and the immune system is clear, it is not clear how the influence over the so-called natural cascade of lymphokines in the immunitary system is carried out (Giordano and Palermo, 1991). Since we consider that the products of lymphocytes are those that act on the immunocompetent cells, we can consider that the MIIO are also lymphokines. The MIIO appear to have a specific function in counteracting the effects of corticosteroids, which can increse their seric concentrations by way of the hypothalamus-pituitary-adrenal gland pathway in response to situations of stress or also to an antigen. It has been suggested that the elevation of adrenal steroids in association with the immune response has a function of control on the expansion of immunocompetent cells with low antigenic affinity. This system of control could serve for trying to avoid the appearance of autoimmune diseases as well as that of lymphoproliferatives (Besedovsky *et al.*, 1988).

An important fact is that of the presence of melatonin receptors at the cellular and organ levels of the immune system. The presence of these receptors has been demonstrated in the membrances of the spleen of different animals along with the presence of opioid receptors in the thymus. This knowledge came about due to the search, also in the thymus, for specific receptors for melatonin, and these findings permit the continued penetrating into the role of this hormone on the immunitary system (Sibinga and Goldstein, 1988, Smith *et al.*, 1985).

By way of all that has been previously expounded, one can say without being excessively optimistic that melatonin is an antineoplasmic agent and an important immunologic agent. In addition, melatonin is a non-toxic substance that can be administered very safely by mouth. Nevertheless, if melatonin is going to be developed as an immunostimulant agent and as an oncologic medication, one must consider, up to what level the immune system or the growing tumor is dependent on melatonin. In this train of thought, it would not be preposterous to carry out periodic preventive therapies of melatonin on high risk patients who suffer from cancer. It would be most interesting to study the effect of melatonin in tumors where the element of risk of the presence or absence of hormonal factors is well known, such as occurs in breast cancer. We mustn't forget that there are other neoplasias of lesser importance that can appear in patients who have received protocols of chemotherapy and/or radiotherapy that produce a high risk of appearance of secondary cancers (Maestroni and Pierpaoli, 1981). The other field of application could be on patients with primary or secondary problems of immunologic deficits. Within this group of patients it would be interesting to obtain results in relation to the periodic utilization of melatonin in those patients with HIV. It seems to be equally true that both melatonin and the HIV virus have the same target-cells, CD4 and T-lymphocytes. Because of this it might perhaps be most interesting to utilize melatonin in the presence of good concentrations of CD4 and T-lymphocytes prior to the development of AIDS. The possibilities of utilizing melatonin must not be restricted only to its aspects relative to tumors or the immune system, but also one must firmly consider its utilization in the presence of situations of stress, surgical interventions, high-risk patients, medically compromised patients and in the elderly.

At the time of carrying out whatever type of study on the action of melatonin on the body, it is necessary to take into accout internal and/or external factors that can alter the synthesis of melatonin, such as: a simple change in one's work schedule, transcontinental flights, chronic exposure to electro-

magnetic fields, treatment with B-adrenergic blockers or naturally a pinealectomy. These investigations must be carried out within the general aspect of the immune system and not within the strict point of view of the phenotypic characterization of the immunocompetent cells, and of course without forgetting the immunomediators of melatonin like the opioid receptors.

IMPLICATIONS AT THE ORAL LEVEL

Although all the investigation at the oral level is yet to be done with relation to melatonin, in light of the contributions achieved by different investigators one can consider that, without doubt, these should be lines of investigation.

From our point of view, the most important implications of melatonin at the oral level lie in the implications that it has on the immune system. Thus, one could pose the utilization of severe measures of prevention and control at the oral level on those patients who are going to be submitted to β-blocking treatments. This utilization could be especially appropriate in hypertension, where it is used more and more, when the treatments are going to be very prolonged and are going to produce a block of the β-receptors through which melatonin is capable of modulating the production of antibodies. As has been repeatedly reported (Nederfors *et al.*, 1994, Maestroni *et al.*, 1987), this fact must make us think that the oral-dental pathology will be augmented.

Another group of patients who could be implicated could be those groups of patients with primary as well as secondary immunodeficiencies. With relation to dental treatment of these patients, it must be planned in an extremely cautious way and it must always be subordinated as much to the immunologic state of the patient as to the colateral effects that the cause of this immunologic state has produced. In view of the studies already carried out, one would expect that the utilization of melatonin prophylactictly at the time of our dental treatments would not only cause an improvement in the immunologic state, with a disminution of the pathologic processes derived from the primary disease which has caused the immunodeficiency, but would also lessen whatever negative effects that might be produced by our protheses, endodontics, surgeries, periodontal treatments, etc.; that is, provided that the immunologic system is in sufficient condition to give a minimum response to the stimulating effect of the melatonin (Caroleo *et al.*, 1992, Maestroni, 1993).

A similar situation to the block of the β-receptors occurs in a pharmacologic way in depressive patients, and in a less clear form in schizophrenic patients. This situation of noradrenergic deficit blocks the normal path of action of melatonin with a consequent undesirable effect on the immunologic system. Thus, in these patients one would expect a greater degree of oral-dental pathology which forces us to consider them high-risk (Ferrier, 1982). This is due not only to the actions that melatonin has on the T-lymphocytes, lymphokines, etc., but also for the action it has directly on the secretion of IgA at the oral level, as much for its increased secretion upon administering exogenous melatonin as for its depression in situations of pineal deficit.

Therefore, at the oral level melatonin opens up for us an extremely interesting pathway. It could be expected that our professional activities will be more secure on those patients with immunologic-deficit alterations; and, we mustn't forget its applications in the natural immunity of geriatric patients in which the aging process has an affect on the capacity of the action of the immune system. Neither should we forget the carrying out of careful studies which might clarify if melatonin is implicated in oral pathologies which have an autoimmune basis. This then is an extraordinary field of study in which there remains much to be done and in which we must focus our efforts.

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