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The Well-Recognized Ability of Melatonin to Potentiate an Equilibrated Immune Response Calls for an Urgent Study about Its Use as an Adjuvant in Anti-SARS-Cov-2 Vaccines

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ABSTRACT

Vaccines are a major weapon to control the present COVID-19 pandemic. To achieve this goal, vaccines should confer a robust and long-lasting immunity against SARS-Cov-2. Breakthrough infections and waning immunity are currently observed in patients that recovered from COVID-19 as well as in the vaccinated people. Therefore, a highly effective vaccine is needed to control the present and future outbreaks. Exogenous N-acetyl-5-methoxy-tryptamine or melatonin (MLT) is well known to potentiate an effective and equilibrated immune response in a variety of situation including viral and bacterial infections and vaccines against different microbial and cancer antigens. In regard to anti-SARS-Cov-2 vaccines, beside stimulating specific IgG production as well as specific CD4+ and CD8+ T cells, exogenous MLT might also enhance specific IgA and secretory IgA in the mucosae; hence, preventing the re-infection and/or asymptomatic transmission of the virus. Thus, a study is urgently proposed to evaluate the effects of MLT administration either before or after vaccination against SARS-Cov-2 to evaluate its effect on strength, quality and duration of the immunity. Las but not least, due to its powerful antioxidant and anti-inflammatory properties, MLT administration might minimize the occurrence of adverse events after the vaccination.

Citation:

INTRODUCTION

Phylogenetically, N-acetyl-5-methoxy-tryptamine or melatonin (MLT) is a very ancient indoleamine, endowed with impressive pleiotropic effects. Its primary role in primitive unicellular organisms is that of a powerful antioxidant. Later during evolution, MLT acquired many other biological functions such as synchronizing the organism in the photoperiod and modulating the immune response in all vertebrates [1]. MLT may be synthesized in virtually any cell type of organisms, including immunocompetent cells. [2]. Nonetheless, the source of plasma MLT is the pineal gland which synthesizes and releases it into the blood during the night darkness hours. This circadian rhythm of secretion is generated by the suprachiasmatic nuclei and entrained by the light/ dark cycle of the day. Light is, in fact, able to inhibit or synchronize MLT synthesis, to adjust the light/dark schedule via the sympathetic nervous system [3]. In contrast, extra-pineal MLT neither circulates nor shows any circadian variation and may exert only autocrine or paracrine effects [2].

In any case, MLT acts via membrane receptors, MT1 (MTNR1A, in humans) and MT2 (MTNR1B in humans). MT1 ;and MT2 may be found in almost all tissues as heterotrimeric Gi/ Go and Gq/11 protein-coupled receptors. Furthermore, MLT might interact at the nuclear level with retinoid orphan receptors/ retinoid Z receptors [4]. MLT receptors mediate an extraordinary number of intracellular events such as modulation of cyclic nucleotides and calcium concentration, triggering of protein kinase C subtypes, displacement of intracellular steroid hormone receptors and modulation of G protein signaling. As for other hormones, MLT receptors are downregulated by the agonist and thus both receptors expression and responses show a circadian variation [5].

The first evidence that MLT could influence the immune response dates back to the eighties of the past century [6, 7]. Today, this MLT property is recognized to the extent that a dysregulation of MLT synthesis has been associated in humans with the pathogenesis of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus and multiple sclerosis [8]. The interplay between Th1, Th17 and Treg cells is unbalanced in autoimmune diseases and MLT has been shown to equilibrate this interplay in favor of Treg cells [9]. On the other hand, MLT may boost the immune and inflammatory

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responses [10], function as a Toll-like receptor inhibitor [11] and/or as a most powerful lipophilic antioxidant [12]. Due to all these properties, MLT has been suggested to work as a buffer of the immune system aimed at optimizing the immune responses [13]. Here, the term "buffer" means that in basal or immunosuppressed states, MLT may function as an immunostimulant, providing the conditions for a more effective immune response against microbial pathogens such as bacteria, viruses and parasites. Meanwhile, in presence of an exaggerated immune response, such as during severe infections or septic shocks, MLT may exert an immune depressing action and could be considered an anti-inflammatory molecule. The relative contribution of the various MLT receptors in these contrasting effects is not yet clear.

Most interestingly, even MLT pretreatment may modify the immune reactivity, that is when administered before any antigenic challenge [14]. This remarkable effect might involve a direct MLT influence on peripheral immunocompetent cells as well as on hematopoiesis [15]. In particular, MLT may stimulate platelets production [16] and rescue bone marrow cells against the toxic effects of anti-cancer drugs [17]. A series of studies even indicated the existence of a physiological immune-pineal axis. In an acute inflammatory response, the transcription factor NFkB switches MLT synthesis from the pineal gland to macrophages/microglia and upon resolution of inflammation back to the pineal gland. Switching the source of MLT production from the pineal gland to immunocompetent cells seems to be involved in the appropriate activation of the immune responses [18]. These complex effects of MLT on immunity results also from its action on monocytes, macrophages, neutrophils, basophils, eosinophils and dendritic cells (i.e., the players of innate immunity) [19]. However, it is in the adaptive phase of the immune response that MLT plays a crucial role, especially on T cells. T cells express both membrane and nuclear MLT receptor and are themselves capable of synthesizing the indoleamine. MLT may enhance IL-2 production and modulate T cell activation and differentiation for Th17, Treg and memory T cells [20].

Because of these important properties, together with the observation that MLT may be of therapeutic value against parasites [21], viral and bacterial infections as well as in sepsis [22], the indoleamine has been widely suggested to exert a protective role against SARS-Cov-2 infection or as a therapeutic agent in COVID-19. Here I quote, just few examples out of 98 articles retrieved in PubMed [23,24,25,26]. It should also be mentioned that COVID-19 is often severe in elderly males, that is in a population in which plasma MLT concentration may be particularly low [27]. Exogenous MLT may act also as an adjuvant in various vaccines and has been shown to enhance the quality and the strength of the immune responses against a variety of microbial and cancer antigens. MLT administered in sheep as an adjuvant for a vaccine against Dichelobacter nodosus could increase specific IgG+ B cells and CD4+ T cells [28]. In a another study in mice, using MLT together with an anti-cancer DNA vaccine increased the generation of specific CD8+ Tcells [29]. Taken together, all these considerations suggest that exogenous MLT might optimize the immune responses also in anti SARS-Cov-2 vaccines by coordinating the antibody response and SARS-Cov-2 specific CD4+ and CD8+ T cells, resulting in increased efficacy and long-lasting immunity against the virus.

Interestingly, coordinated antibody response and SARS-Cov-2 specific CD4+ and CD8+ T cells were associated with milder disease in COVID-19 patients. This coordination was lost in patients over the age of 65 who failed to control the disease [30]. Hence, one could infer that administration of MLT during COVID-19 vaccination might be especially useful for the elderly patients; however, the available evidence does not discriminate among sex and age, as far as its immunological properties are concerned.

In addition, as natural immunity acquired by COVID-19 in certain cases do not protect against the reinfection [31], the possibility to boost and prolong the immunity conferred by vaccines is probably the key to control the pandemic. In fact, waning immunity is currently observed in patients who recovered from COVID-19 and also in the vaccinated people [32]. Last but not least, the immuno-equilibrating and antioxidant properties of MLT may well reduce the incidence of adverse events following anti-SARS-Cov-2 vaccination.

In conclusion, it is suggested to perform a study to assess the effects of MLT administration before and/or after vaccination against SARS-Cov-2 on the strength and quality of the immune response, considering specific IgG production as well as specific CD4+ and CD8+ T cells. In addition, it would be advisable to evaluate also the level of specific IgA and secretory IgA. In fact, a robust IgA production would neutralize the virus at the mucosal surface, preventing the possibility of a vaccine breakthrough infection as well as of becoming asymptomatic carriers of the virus [33]. Interestingly, it has been reported that MLT administration in football players before exercise could minimize oxidative stress and increase the level of mucosal IgA [34]. A reevaluation of the same parameters at 6 and 12 months after the vaccination would check the possibility that MLT might prolong the immunity against SARS-Cov-2. In addition, if the effect of MLT were strong enough, one might consider reducing the vaccination schedule to one injection, at least for the vaccines that are now considered for two doses. This would greatly simplify vaccination strategies in the future as it seems probable that a vaccination campaign will have to be repeated every year.

MLT should be administered orally in the evening at a dose able to ensure a sustained plasma concentration for substantial part of the night for 10 days. MLT displays a short blood half-life, so fast release preparations should be administered at a high dose (several mg per day), while prolonged release preparations can be administered at 2 mg per day. However, no study has addressed the relationship between the pharmacokinetic of exogenous MLT and its effects. These suggestions are extrapolated from previous pharmacological studies and the observation that physiologically, plasma MLT concentration during the night remains elevated for several hours [3]. Therefore, in the case of fast released preparations, I would propose a dose of 6 mg per day divided in two doses of 3 mg with the second dose administered 3 hours after the first one. High supra-pharmacological doses (over 50 mg per day) should be avoided because such doses might over-downregulate MLT receptors and disrupt the endogenous circadian rhythm, resulting in immunosuppression [7]. Ideally, the study should consider four arms: MLT pre-treatment ending the evening before vaccination; MLT treatment after vaccination starting the day of vaccination and a placebo as control for both groups. It is well known that exogenous MLT may produce, if any, only mild adverse effects, mostly related to its ability to alter sleep structures.

Finally, I take the privilege of adding a general comment: current vaccines against SARS-Cov-2 have been designed starting from the observation that the virus S protein is highly immunogenic and that the immune response elicited may confer

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protection against the infection [35]. I believe that the contemporary pandemic has provided an unprecedented occasion to test new vaccine platforms in human beings on the largest possible scale. Perhaps, this is favored by the need of rapidly getting an effective vaccine and, maybe, by the possibility of using the same approach to stimulate the production of other non-antigenic proteins with therapeutic properties in the patients. However, present-day reports tell us about the emergence of new genomic variants of the virus that pose a greater threat to the public health, due to increased transmissibility or infectivity. Hence, the risk that vaccines based on only one viral protein might turn to be ineffective, is real. On the contrary, vaccines based on inactivated or attenuated virus have the advantage of presenting to the immune system an antigenic array, similar to that of the invading virus. I would thus reconsider this approach, with all the necessary precautions, and combine it with exogenous MLT as a possible solution to control the pandemic.

CONFLICT OF INTEREST

The author declares he has no conflict of interests.

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