

Review

## **An urgent proposal for the immediate use of melatonin as an adjuvant to anti- SARS-CoV-2 vaccination**

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### **ABSTRACT**

Competition among pharmaceutical companies to develop safe and effective vaccines against SARS-CoV-2 is high. However, based on the prior experience with the influenza vaccine, up to 50% in lack of effectiveness would be found among healthy adults receiving effective vaccines against SARS-CoV-2. There is growing evidence that insufficient sleep may potentially be a pervasive and prominent factor accounting for this variability. Individuals experiencing total or partial sleep loss exhibit markedly reduced antigen-specific antibodies as compared to healthy sleepers. Besides, pre-vaccination sleep quality is also an important contributing factor. Several meta-analyses and expert consensus reports support the view that the chronobiotic/hypnotic properties of melatonin are useful in patients with primary sleep disorders to decrease sleep onset latency and to increase total sleep time. Hence, the prescription of melatonin for at least 2 weeks prior to vaccination can be a useful approach to improve sleep quality and to ensure that the vaccination is performed at a moment of optimal sleep conditions. Moreover, melatonin enhances the immune response to vaccines by increasing peripheral blood CD4+ T cells and IgG-expressing B cells. Administration of exogenous melatonin could increase the potency of the immune response and the duration of the immunity induced by the vaccine. Besides, melatonin could also prevent adverse effects of the vaccination due to its antioxidant and immunomodulatory properties. Therefore, the administration of melatonin from 2 weeks to at least 4 weeks after vaccination may constitute an effective means to enhance the efficacy of vaccination against SARS-CoV-2.

**Key words:** COVID-19, Sars-CoV-2, adjuvant, chronobiotic, melatonin, insomnia, immunoenhancement, sleep, vaccination.

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## **1. INTRODUCTION**

Competition among pharmaceutical companies to develop safe and effective vaccines against SARS-CoV-2 is high. However, even if such a vaccine is established, an unknown variation in vaccine efficacy can be expected. In this sense, the evidence concerning the

influenza vaccine must be considered. Although the influenza vaccine can be used in the whole population without significant risks, its capacity to produce an adequate immune response varies widely. As shown by a meta-analysis of randomized trials performed in healthy adults (aged 18 to 65 years) the lack of effectiveness of the influenza vaccine attains 33 to 49% (1). The factors causing this variation in immunogenicity are not defined but several lines of evidence point out insufficient sleep as a cause.

Sleep and immunity are intrinsically linked (2, 3). Sleep disruption affects innate and adaptive immune responses and the inflammatory response that follows microbial or viral stimulation of the immune system can disrupt sleep significantly. Normal sleep is associated with reduced infection risk and concerning vaccination, individuals suffering total or partial sleep loss exhibit significant reductions in antigen-specific antibodies as compared to undisturbed sleepers (2, 3). For example, on the 10<sup>th</sup> day post-immunization, a 50% reduction in antibodies was seen in individuals who endured 6 nights of partial sleep restriction as compared to normal sleepers (4). Sleep deprivation during the night after hepatitis A vaccination was associated with lower antibody levels (5, 6) and impaired specific Th cell responses (6). A similar observation was made after hepatitis B vaccination (7). Conversely, a polysomnographically determined increase in slow-wave activity was associated with higher antibody responses (6). In the case of trivalent inactivated influenza vaccines, sleep deprivation (4), but not was sleep duration (8) or obstructive sleep apnea (9), was associated with lower antibody responses. In healthy night workers who received a meningococcal C meningitis vaccine and who showed decreased polysomnographic N3 stage and rapid eye movement sleep, increased inflammatory cytokines, and a weak specific cellular and humoral response to vaccination were found (10).

In addition to the quality of post-vaccination sleep, pre-vaccination sleep quality also deserves consideration. In a recent study carried out on 83 healthy young adults that completed 13 days of sleep diaries and received the trivalent influenza vaccine, measures of self-reported sleep duration, sleep efficiency, and subjective sleep quality was contrasted with antibody levels to the influenza viral strains at baseline and 1 and 4 months following influenza vaccination (11). Shorter sleep duration on the two nights before the vaccination predicted fewer antibodies 1 and 4 months later. Measures of self-reported sleep efficiency and subjective quality were unrelated to antibody responses to influenza vaccination (11). This study indicates that sleep on nights prior to vaccination is critical and thus this deserves careful consideration.

In a recent publication, several interventions that might stimulate innate immunity against (viral) respiratory tract infections were reviewed (12). Interventions included lifestyle-related (exercise, >7 h sleep, forest walking, meditation/mindfulness, vitamin supplementation), nonspecific immune stimulants (letting fever advance, bacterial vaccines, probiotics, dialyzable leukocyte extract, pidotimod), and specific vaccines with heterologous effect (BCG vaccine, mumps-measles-rubeola vaccine). Remarkably, melatonin was not listed among these interventions. However, because of its recognized chronobiotic and immunoregulatory activity melatonin can be very useful in this respect (13).

## **2. MELATONIN AS A CHRONBIOTIC AGENT TARGETED TO IMPROVE SLEEP PRIORLY TO ANTI- SARS-COV-2 VACCINATION**

“Chronobiotic” defines a drug that is capable to modify the circadian rhythms, both in phase and amplitude (14). The magnitude and direction of the phase change depend on the time of day when the chronobiotic is administered (“phase response curve”). Melatonin behaves as chronobiotic since when administered in the morning it delays the phase of circadian rhythms, when administered in the afternoon/early evening it advances the phase of circadian rhythms, while when given during the rest of the day, it does not alter the endogenous clock phase (15).

In the modern 24/7 Society we live in, the time and duration of exposure to ambient light, the most important environmental time-giver (*Zeitgeber*), is altered. For example, the excessive use of screens that emit light rich in the blue spectrum (mobile phones, tablets, computers, TV screens) leads to the suppression of the natural production of melatonin that is maximum during the night. Additionally, exposure to light at night by means of excessive illumination at home and social environments and during work (e.g., night shift) hours contribute to disruption. Activity levels during the day also influence the normal alternation of sleep/wake rhythm, being affected by both a low level of activity (confinement or depression) and strenuous activity (for example, due to stress or work overload) (16, 17).

Alterations in the sleep/wake rhythm physiology such as phase delays or phase advances in sleep onset, frequent nocturnal awakenings, increased latency to sleep onset, reduced sleep efficiency, or due to other primary sleep disorders leading to excessive daytime somnolence, are often the consequence of alterations in the circadian output from the central pacemaker located in the anterior hypothalamic suprachiasmatic nuclei (SCN) (18). Such alterations are corrected by chronotherapy, designed to restore the adequate circadian pattern through adequate sleep hygiene, exposure to programmed light, and the use of chronobiotic medications like melatonin (19).

Melatonin is a powerful chronobiotic with a mild hypnotic capacity. Daily doses of 2-10 mg of melatonin, timed to advance the phase of the internal clock by interaction with MT1 melatonin receptors in the SCN maintains synchronization of the circadian rhythms to a 24-h cycle in sighted persons who are living in conditions likely to induce a free-running rhythm (20). Melatonin synchronizes the rhythm in persons after a short period of free running. In blind subjects with free-running rhythms, it has been possible to stabilize, or entrain, the sleep/wake cycle to a 24-h period by giving melatonin, with resulting improvement in sleep and mood (21).

The phase-shifting effect of melatonin is also sufficient to explain its effectiveness as a treatment for circadian rhythm sleep disorders, such as jet lag or delayed phase sleep syndrome (22, 23). Several meta-analyses support the view that the chronobiotic/hypnotic properties of melatonin are useful in patients with primary sleep disorders to decrease sleep onset latency and to increase total sleep time, with little if any effect on sleep efficiency (24–26). Several expert consensus reports also support a role of melatonin in adult insomnia (27–30)]. Hence, the prescription of melatonin for at least a 2-week period prior to vaccination is an established approach that can improve sleep quality and thus make sure that the vaccination is performed at a time of optimal sleep conditions.

In addition to sleep quality, evidence in literature points out a significant effect of mood on the vaccine response (8). Since influenza vaccination is estimated to only be effective in about half of older adults, multiple patient behaviors and psychological factors have been entertained to act as immune modulators sufficient to influence vaccination outcome. In a prospective, diary-based longitudinal observational cohort study of 138 community-dwelling older adults (65–85 years) IgG responses to vaccination were measured at 4- and 16-weeks post-vaccination.

The positive mood on the day of vaccination was a significant predictor of seroprotection at 16 weeks post-vaccination and IgG responses to vaccination at 4 and 16 weeks post-vaccination (8). Melatonin, besides its chronobiotic activity, displays anxiolytic (24) and antidepressant (25) properties which may complement the increase in sleep quality with mood stabilization and hence augment the efficacy of subsequent vaccination.

### **3. MELATONIN AS AN IMMUNOENHANCEMENT ADJUVANT IN ANTI- SARS-COV-2 VACCINATION**

Maestroni provided the first evidence that melatonin could increase immunoglobulin (Ig) G response and counteract the immunosuppressive effect of corticosteroids or acute stress (26).

Melatonin is very effective in reversing the immunosuppression observed in aging (27, 28). This effect of melatonin could be associated with an increase in CD4 + T lymphocytes (29).

Concerning vaccines, exogenous melatonin acts as an adjuvant enhancing the response of CD8 + T cells in cancer vaccines (30, 31) and vaccines employed against several pathogens in veterinary medicine (32). Melatonin increases the immune response to vaccines by increasing both CD4 + T cells and B cells that express IgG in peripheral blood. In convalescent COVID-19 patients, a vigorous response of CD4 + T cells was found to the spike protein of the SARS-CoV-2 virus, which is the main target of most of the vaccines under investigation, and that this response was correlated with the level of anti-SARS-CoV-2 Ig G and Ig A (33).

The decrease in the number of CD8 + T cells due to the inhibition of the interleukin (IL) - 2 and IL-2 receptor is especially important in patients with COVID-19, particularly in the elderly group. Since melatonin stimulates IL-2 production and in doing so increases CD4 + T cells (34), its use as an adjuvant to anti- SARS-CoV-2 vaccines may enhance the immunity achieved (35). Furthermore, due to its cytoprotective properties and its pleiotropic action on the immune system, melatonin could counteract the adverse effects of the vaccine. Therefore, the administration of melatonin from 2 weeks to at least 4 weeks after vaccination will constitute an effective means to enhance the efficacy of vaccination against SARS-CoV-2.

#### **4. CONCLUSIONS**

Melatonin has been used as a sleep aid for decades without any serious adverse effects being reported (36, 37). Moreover, it has often been used in critically ill patients to improve sleep and wellbeing, both of which would also be beneficial to SARS-CoV-2 infected patients (38). It is a molecule with an uncommonly high safety profile and can be administered via numerous routes including orally. It is inexpensive, stable without refrigeration, and would be particularly useful in underdeveloped countries where access to high-quality health care may be lacking. Thus, a claim for the immediate use of melatonin as an adjuvant to anti- SARS-CoV-2 vaccination is made.

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#### **AUTHORSHIP**

Conceptualization: D.P.C., G.M.B, S.R.P-P. Writing, Original draft: D.P.C. Writing, Review & Editing: D.P.C., G.M.B, S.R.P-P

#### **CONFLICT OF INTEREST**

The authors have read the journal's policy and have the following potential conflicts: SRP is a stockholder and the President and Chief Executive Officer of Somnogen Canada Inc., a Canadian Corporation. He declares that he has no competing interests that might be perceived to influence the content of this article. This does not alter the authors' adherence to all the journal policies. All remaining authors declare that they have no proprietary, financial, professional, nor any other personal interest of any nature or kind in any product or services and/or company that

could be construed or considered to be a potential conflict of interest that might have influenced the views expressed in this manuscript

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