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ROUNDTABLE DISCUSSION

Future of melatonin as a therapeutic agent

Michal Karasek,[1,2] Russel J. Reiter,[3] Daniel P. Cardinali,[4] Marek Pawlikowski[5]

1. Clinic of Endocrinology, Polish Mother's Memorial Hospital – Research Institute, Lodz, Poland.
2. Laboratory of Electron Microscopy, Chair of Pathomorphology, Medical University of Lodz, Lodz, Poland.
3. Department of Cellular and Structural Biology, University of Texas Health Science Center, San Antonio, Texas, USA
4. Department of Physiology, Faculty of Medicine, University of Buenos Aires, Argentina
5. Department of Experimental Endocrinology and Hormone Diagnostics, Institute of Endocrinology, Medical University of Lodz, Poland.

Correspondence to: Prof. Dr. Michal Karasek
Clinic of Endocrinology,
Polish Mother's Memorial Hospital – Research Institute
93-338 Lodz, Rzgowska 281/289, Poland.
TEL: +48 42 271 14 89
FAX: +48 42 271 1343
E-MAIL: karasek@csk.am.lodz.pl

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Abstract

Report of the round table conference summarizing the International Symposium on "Melatonin: Clinical Significance and Therapeutic Applications" is presented in this article. Some sleep disorders and circadian rhythm disturbances are the widely accepted indications for melatonin treatment. However, other possibilities for use of melatonin in the therapy should be also taken into account, including a co-treatment in cancer patients and free radical-related diseases. All aspects of the possible therapeutic use of melatonin as well as its safety, dosage, side effects and contraindications are discussed herein based on the round table conference and they are presented in this paper.

Introduction

A round table discussion on the future of melatonin in the therapy was held at the end of the International Symposium in Polanica Zdroj (Poland) devoted to clinical significance and therapeutic application of melatonin. The authors were the active participants of this conference, and this article summarizes the round table discussion.

Melatonin, the main secretory product of the pineal gland was discovered by Lerner and coworkers [1] in 1958. Although the diversity of functions of melatonin is still under debate, numerous investigations performed since that time brought about significant progress in understanding the relevance of this substance in animals and in humans. Moreover, melatonin has become recently available in some countries (e.g. USA, Argentina, Poland, China) as either an OTC drug or food supplement.

There are some widely accepted indications for therapeutic use of melatonin but also perspectives for its broader use. Both the accepted indications and further perspectives are discussed in this article.

Generally accepted indications for therapeutic use of melatonin

Melatonin in sleep disorders

The promoting effect of melatonin on sleep and sedation has been known for a number of years. In most recent reports melatonin has been shown to significantly improve subjective and/or objective sleep parameters in some individuals. Its administration reduces sleep latency and/or increases sleep efficacy and total sleep time. Such effects are probably the consequence of increasing sleep propensity and of a synchronizing effect on the circadian clock (chronobiotic effect). Melatonin treatment is especially successful in delayed sleep phase insomnia and sleep disorders in advanced age [2–4]. It is also interesting to note that melatonin can effectively facilitate discontinuation of benzodiazepine therapy while maintaining good sleep quality [5]. It should be stressed, however, that melatonin is not a universally effective drug for treatment of insomnia. It may not be helpful in all patients suffering from insomnia.

Melatonin in circadian clock disturbances

Circadian rhythm disorders have been described in the majority blind people, especially in those without light perception and free running (non 24-h) rhythms, with disturbed sleep as a consequence. Melatonin has proven efficacy in phase-shifting of the circadian clock for phase resetting in blind people [6, 7].

Crossing several time zones during transcontinental flights causes many symptoms, including insomnia, lack of concentration, headache, fatigue, and irritability (collectively known as jet-lag). Published evidence indicates that melatonin is useful for ameliorating jet-lag symptoms in air travelers [8–11]. Although a few schemes have been proposed for use of melatonin to avoid jet-lag [6, 9, 10], it seems that it should be taken close to the target bedtime at the destination for a few days. A recent meta-analysis on the efficacy of melatonin to prevent and treat jet-lag indicated that such administration of melatonin decreased effectively jet-lag from flights crossing five or more time zones [11]. Indeed, the jet-lag effect is perhaps the best clinical indication for melatonin use so far demonstrated.

Other possibilities for therapeutic use of melatonin

Melatonin as free radical scavenger

Melatonin is very effective and ubiquitously acting antioxidant. It shows direct free radical scavenging activity, and also stimulates a variety of antioxidative enzymes. Its intracellular distribution seems to be significantly different than some other classic antioxidants. Due in part to its ability to neutralize a variety of different reactive species which are generated at different intracellular sites, melatonin has proven effective in limiting oxidative damage to proteins, DNA, and lipids [12, 13]. Its efficacy as a free radical scavenger and antioxidant has been widely documented in animals and in humans [14–16].

Melatonin in aging and age-related diseases

There is yet little justification for referring specifically to melatonin as an antiaging molecule. The antiaging activity of melatonin, however, is supported by some experimental data. According to Harman's theory, aging is a consequence of accumulated free radical damage [17]. If true, it should be possible to defer signs of aging by antioxidant administration.

Generally, the average age of the world population is increasing. As the consequence, the number of age-related diseases is also increasing. With increased age the frequency of neurodegenerative and other chronic diseases is increased and as a result financial and social resources to care for this individuals are being maximally taxed. There is some evidence to suggest melatonin may defer some of these conditions, so it is possible we may see melatonin's use in aged people afflicted with radical-based degenerative conditions [18–20]. Melatonin may be useful as a co-treatment with specific drugs used in certain diseases. Such beneficial use of melatonin has been recently shown in Alzheimer's disease [20–22] and cancer [23, 24].

Considering a decrease in melatonin concentrations with age, its antioxidant action, beneficial effects on sleep disorders which frequently occur in elderly people, and evidence of helpful effects in age-related diseases, recommendations of melatonin supplementation in advanced age should be considered.

Melatonin in clinical oncology

Two questions arise considering the use of melatonin in clinical oncology. First, does melatonin prevent cancer? Second, is melatonin an anticancer drug?

There are several studies dealing with the administration of melatonin to cancer patients, who failed to respond to standard anticancer therapy, or suffering from advanced cancer, and eligible for supportive care only, and having only short expected survival time. Melatonin administration resulted in stabilization of disease in some cases, and an improvement in performance status [24–26].

We agree with Bartsch et al. [24] that if the above mentioned results are confirmed and verified by independent and controlled replication studies, attempts should be made to administer melatonin to patients with earlier stages of cancer in combination with standard oncological treatment regimens.

Beyond the possible anticancer effect of melatonin its possible use in conjunction with very toxic chemotherapeutic anticancer agents, such as adriamycin, cyclosporine or interleukin-2, which have remarkable cardiac and liver toxicity, should be considered. There are numerous publications showing that toxic effects of chemotherapeutic drugs can be markedly attenuated when they are given in conjunction with melatonin [27, 28]. It has been also shown that in some types of cancer melatonin may amplify the therapeutic efficacy of interleukin-2 or tamoxifen [28, 29].

Although, nowadays melatonin should not recommended as anticancer drug, considering improvement in performance status administration of melatonin may

be beneficial as a additional therapy in patients with advanced cancer.

Melatonin in circulatory system diseases

Although there are some anecdotal data indicating that melatonin may reduce blood pressure in patients with hypertension and may lower cholesterol levels [30], there are no substantial scientific data to prove these effects of melatonin in humans.

In reference to hypertension, however, it should be noted that almost all drugs used to lower blood pressure (e.g. β-blockers, calcium antagonist or calcium channel blockers) reduce melatonin levels. 40% of patients taking β-blockers have sleep disorders which may be easily overcome by giving melatonin.

Currently there are drugs to reduce cholesterol levels – the statins, which however, are not without significant side effects. Probably much of the damage caused by statins is free radical mediated. Therefore, considering the antioxidant action of melatonin clinical trials combining statins and melatonin should be considered.

Safety of melatonin use

Registration of melatonin either as a drug or food additive is important issue. If a molecule is registered as a drug, the purity would be certified by the producing company and strictly verified. That is not case in many compounds registered as food additives. Food additives may contain contaminants, and their control is not as strict as that of drugs.

Toxicity of melatonin is remarkably low. This statement is supported by experimental evidence. It should be noted that it was not possible to determine DL_{50} for melatonin because the highest possible dose (800 mg/kg b.w.; limitation imposed by the solubility of the compound) failed to produce death of the experimental mice [31]. When melatonin was given to the rats on gestation days 6–19 in very large doses (50–200 mg/kg b.w./day; the doses equal to ~ 17.5–70 g/day in humans!) the maternal toxicity NOAEL and LOAEL were 100 and 200 mg/kg/day, respectively, and the developmental toxicity NOAEL was > or = 200 mg/kg/day [32]. No significant negative side effects were observed even following as high doses as 3.0 to 6.6 g administered to 11 individuals for 15 to 35 days (only isolated episodes of cutaneous flushing, abdominal cramps, diarrhea, and headache were observed) [33] or 75 mg/day given to 2000 women [34]. Other studies in humans have also shown melatonin to have little toxicity as well [5, 35–37].

In many preparations of melatonin, it is combined with other substances (e.g. vitamin B6). Although there some data suggesting that vitamin B6 may increase secretion of endogenous melatonin, there seems to be no rationale for combining melatonin with other substances.

Possible side effects of melatonin

In studies performed so far no serious negative side effects of melatonin have been reported. Only occasional individual reactions of a minor and idiosyncratic nature have been reported. Sleepiness (desirable), headache, abdominal pain, and nausea are occasionally mentioned. Moreover, some individuals report nightmares after taking melatonin (although this has never been mentioned in a scientific publication). It is possible that nightmares are simply an effect of deeper sleep promoted by melatonin, and in consequence deeper REM sleep with more vivid dreams.

Melatonin has been administered to a substantial number of people for a long enough periods of time to rule out the possibility that some people may react atypically to the molecule. However, additional, double blind trials on the use of melatonin are warranted. Unfortunately, the financial incentives for such studies are not great.

Contraindications

Generally, contraindications for melatonin use are not known. Some people perhaps should retrain from taking melatonin, or to take only under close supervision of a physician because of possible negative side effects. On the basis of these, purely theoretically possible side effects it seems that melatonin should not be used by:

- pregnant and nursing women (because of unknown risk);

and should be used with caution by:

- people with severe allergies (melatonin may exaggerate an allergic response by stimulation of the immune system);
- people with autoimmune diseases (melatonin could exaggerate an autoimmune response by stimulation of the immune system);
- people with immune-system cancers such as leukemia and lymphoma (melatonin may further stimulate the immune cells).

Concluding remarks

Melatonin is unique universal substance with the molecular structure unchanged throughout the animal and plant kingdom. It is well known fact that molecular structure of many hormones varies greatly among species (e.g. gonadotropins, growth hormone, prolactin, and insulin have different amino acid sequence in different species). Melatonin is always N-acetyl-5-methoxytryptamine, i.e. to put it in the vernacular, melatonin "speaks" without dialects. Moreover, melatonin is present in all living organisms from plants, through animal kingdom to humans. It is soluble both in aqueous and organic media, and therefore easily penetrates cell membranes. Melatonin appears to play a fundamental role in biology of all cells. It is highly probable that not all actions of melatonin have been discovered so far.

There is no doubt that melatonin is useful in some sleep disorders and circadian rhythm disturbances but available data suggest that it also may be beneficial in some other pathologies. For example, it has also been shown to be beneficial in children with sepsis [38] and asphyxia [39]. However, there is a need for extensive studies on larger populations to uncover other therapeutic applications of melatonin.

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