Editorial

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Melatonergic Treatment: Chronobiological Basis and Translational Problems

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Editorial

Melatonin is primarily known as the hormone of the pineal gland, where it is synthesized rhythmically, with a prominent nocturnal peak [1]. It is secreted by this gland into the circulation and also, in relatively higher concentrations, via the pineal recess, into the third ventricle of the brain [2]. Moreover, melatonin is produced in numerous extrapineal sites [3,4]. In these organs, mainly because of amounts produced in the gastrointestinal tract, the total quantities of this compound are by orders of magnitude higher than in the pineal gland or in the circulation [4]. Nevertheless, the extrapineal sites contribute poorly to the circulating levels, with a few exceptions such as the postprandial release from the gut [5,6]. Therefore, melatonin of pineal origin is insofar privileged as is transmits chronobiological information to other organs [1,3]. Melatonin exhibits effects in practically all types of vertebrate cells and has to be understood as a systemically acting, pleiotropic regulator molecule that orchestrates countless functions within the body [3].

The remarkably short half-life of melatonin in the circulation, which is usually in the range of 20 – 30, maximally 45 min, has been one reason for developing longer acting synthetic melatonergic agonists, such as ramelteon, agomelatine, tasimelteon, TIK-301, piromelatine, and various other investigational drugs [7-9]. These compounds do not only differ with regard to their half-life in the blood and other pharmacokinetic parameters, but also in their absolute and relative affinities to the membrane-bound, G protein-coupled melatonin receptors, MT_1 and MT_2. Profound differences exist in their metabolism [8,9]. An exceptional case is that of ramelteon, an agonist with higher affinities than melatonin to both MT_1 and MT_2 receptors, which is converted besides other compounds to a metabolite usually referred to as M-II, which is much more slowly eliminated and attains concentrations 30 or more times higher than the parent compound [10,11]. Because of a moderate receptor affinity, the high levels of M-II contribute to the overall effect of ramelteon.

The synthetic agonists are mentioned here because of applications in mainly three fields of clinical interest. These concern the treatment of (a) insomnia, including circadian rhythm sleep disorders, (b) subtypes of depression and (c) the complex of metabolic syndrome and insulin resistance. Notably, depression is frequently associated with sleep difficulties, which may be even aggravated by several antidepressant drugs [12,13]. Moreover, some subtypes of depression seem to comprise an etiology of circadian dysfunction, as indicated by associations with mutations in genes of the circadian core oscillator and accessory oscillator components [9,14], i.e., in the cellular machinery that generates circadian rhythms in central and peripheral tissues. This relationship is especially documented in Seasonal Affective Disorder (SAD) and Bipolar Disorder (BD), but may also play a role in some subforms of Major Depressive Disorder (MDD), in dysthymia and, perhaps, other neurological disorders, too. The possible usefulness of melatonergic treatment in counteracting or preventing metabolic syndrome and insulin resistance represents an emerging field that is based on (a) an association with polymorphisms of the melatonin receptor gene *MTNR1B*, which encodes the MT_2 receptor protein [14,15] and (b) a number of promising findings in preclinical studies [9,16-21]. Recent evidence even indicates that insulin resistance is an early change leading to low-grade brain inflammation on the route towards neurodegenerative diseases, in particular, Alzheimer's disease [22-24], findings that are of interest to geroprotective actions of melatonin [25,26].

Especially in the three fields mentioned, sleep, depression and metabolic diseases, the conceptual design of experiments and approaches of treatment often reveal an insufficient understanding of the chronobiological basis and rules that have to be followed in the case of melatonin and synthetic melatonergic agonists. These compounds are chronobiotics, i.e., agents capable of phase shifting and otherwise modulating circadian rhythms. The first decision that has to be made concerns the aim of the treatment, in terms of a distinction between either (a) a readjustment of circadian phases and, eventually, period lengths of rhythms or (b) mimicking a youthful melatonin pattern and amplitude that have been lost in the course of aging or because of a melatonin-depressing disease. In the first case, moderate doses of a short-acting drug are entirely sufficient, whereas maintenance of near-physiological high nocturnal levels is desired in the second case. In principle, the latter aim may be achieved either by long-acting drugs or by extended-release formulations. Unfortunately, the currently approved drugs do not yet meet these requirements sufficiently. The longer-acting synthetic compounds exhibit half-lives in the circulation that rarely exceed 2 hours, and prolonged-release formulations of melatonin do not produce near-physiological nocturnal patterns. For this reason, all these agonists and

formulations thereof have remained relatively poor in supporting sleep maintenance [7,9,15]. It should be emphasized that a statistically demonstrable extension of total sleep time (TST) by 15 or 30 minutes may be significant, but is not yet relevant in a patient with TST reductions of several hours. Nevertheless, the successful design of a formulation that mimics a youthful high-amplitude nocturnal pattern of a melatonin or another agonist would be of utmost value for a suitable replacement therapy.

Longer extensions of total sleep time have been reported, but not necessarily in insomniacs. Such data have to be appropriately interpreted. If TST was prolonged by 1 – 2 hours, after a previous time shift of 5 hours, as in the case of tasimelteon [27,28] this merely reflects the chronobiotic potency of the drug, but not a substantial sleep maintenance-promoting property, which was, in fact, not statistically significant in a phase III study in non-shifted insomniacs [27].

Contrary to the poor outcome concerning TST, all melatonergic agonists tested so-far were highly effective in reducing sleep latency [7-9,11,13,15,27,28]. Notably, this action is also present in melatonin, which is a relatively reliable and well-tolerated inducer of sleep onset, in an immediate-release formulation, already at doses as low as 0.1 – 0.3 mg/d [11]. With regard to the much higher recommended, applied or experimentally supported doses of the synthetic drugs, such as 8 or 4 mg of ramelteon, 25 or 50 mg of agomelatine, 5 mg of TIK-301, or 50 mg of tasimelteon, one cannot see any reason for why low doses of the natural compound should not be preferred.

The discrepancies in efficiency concerning sleep onset and sleep maintenance are easily explained by chronobiology. Sleep onset facilitation by melatonin is mediated by its rapid increase at the beginning of night, a phase at which the pineal hormone acts jointly (a) at the Suprachiasmatic Nucleus (SCN), the central nervous circadian master clock, which transmits this information to the hypothalamic sleep switch, and (b) at the thalamus, from which, in a thalamocortical interplay, sleep spindles are induced and the SCN receives additional sleep-promoting information [7]. These effects require only short actions and not a sustained elevation of melatonin.

The necessity of actions of only short duration, as observed in sleep onset, are reminiscent of the requirements for circadian phase shifting. Again, the circadian pacemaker SCN is involved, although additional effects on peripheral circadian oscillators likely exist. The reason for why a chemical signal such as elevated melatonin is already effective at short duration has to be understood on the basis of properties of circadian oscillators and their sensitivity to resetting signals. Contrary to usual pharmacokinetic properties required for efficacy of a drug, the absolute and for a certain period of time maintained level of the drug is not decisive. Instead, the phase-shifting capacity of a signal is determined by the rapid change in its strength [15,29]. This kind of responses of circadian oscillators has become known as the so-called non-parametric resetting, as first described for changes of the light-dark synchronizer [30]. With regard to concentrations of melatonin or synthetic melatonergic agonists, this means that the rapid change in concentration, the non-parametric effect, is decisive rather than a parametric influence by the long-term level or the Area Under Curve (AUC). However, parametric data are not generally unimportant, but relevant for functions that require sustained action over the entire night, such as sleep maintenance, resting metabolism, and antioxidative protection. Nevertheless, this is not a necessity for phase resetting or stable entrainment.

If short-acting melatonergic signals are used for entrainment, which may be desired for treating disorders related to circadian dysfunction, another fundamental chronobiological rule has to be indispensably considered. A synchronizing time cue depends in its effect on the timepoint of treatment. In certain parts of the circadian cycle, it will cause phase delays, but in other parts, the same signal will cause phase advances. Between these sections, two zones exist in which phase shifting is moderate or close to zero, a short one with a rapid transition and a longer one, often called the silent zone, in which phase resetting is poor. This phase dependency of direction and extent of phase changes is described by the so-called Phase Response Curve (PRC). In humans, the PRC for melatonin is known since long [31]. Similar PRCs have to exist for synthetic melatonergic drugs, but should be studied systematically. An improved synchronization is required in circadian rhythms disorders, which may be associated either with deviating period lengths, such as in Delayed Sleep Phase Syndrome (DSPS) and Familial Advanced Sleep Phase Syndrome (FASPS), or with poor or absent photic coupling, such as in blind individuals. In these cases, it is recommendable to first determine the phase position of the endogenous rhythm, preferably by measuring the circadian rise in melatonin concentration, in sighted persons as the Dim Light Melatonin Onset (DLMO) [32]. Moreover, it has to be taken into account that a single phase shift can be easily obtained if the signal is given in the appropriate phase of the PRC, but that a stable entrainment usually requires several well-timed repetitions of the melatonergic drug on consecutive days.

These guidelines for treatment are correspondingly valid in mood disorders with a circadian etiology, as assumed for cases of BP and SAD. If the role of circadian dysfunction is decisive in the individual case, resynchronization by melatonergic treatment, eventually in combination with bright light in the morning, should be considered as a causal and efficient therapy [15]. However, there has been an additional discussion on whether melatonin may have some direct antidepressant properties, too. In the case of agomelatine, the antidepressant actions have been associated with additional properties as a 5-HT_{2C} antagonist [33], but more recent interpretations have assumed an interplay between melatonergic and 5-HT_{2C} antagonizing actions [34]. Similar considerations have been made for TIK-301, which exhibits a similar spectrum of actions [9].

Another general problem related to chronobiology concerns the differences between nocturnally active laboratory rodents and the diurnally active human, a difficulty that can become adverse to translational medicine. First, melatonin and similar

agonists can be easily administered to rats and mice via the drinking water, thereby creating a sustained nocturnal peak of the drug, whereas the compounds can be given to humans only once per day, shortly before sleep time. Second, a fundamental difference exists insofar as melatonin is associated in these rodents with physical exercise, food intake and higher neuronal activity, whereas it is related in humans to rest, sleep and a pause of food consumption. Although sleep research in rodents is meaningful with non-chronobiotic drugs, this is not the case with melatonergic agents. If researchers conclude on soporific effects by melatonergic agonists in nocturnal rodents, this cannot be attributed to physiological sleep, but rather indicates central nervous suppression. The problem of nontranslatable findings may also exist in the emerging field of metabolic syndrome and insulin resistance, because of an inverse relationship to the timing of food. Despite many promising findings of preclinical studies [9,16-21], initial data seem to indicate that melatonin may rather impair glucose tolerance in humans [35]. Although this point requires further clarification, it sheds light on the necessity of caution in translating findings from nocturnal animals to the human.

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