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Mini Review

Entraining Melatonergic Pulses Instead of Long-Acting Drugs: Resynchronization Rules For Depression with Circadian Etiology -

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ABSTRACT

Several types of depression such as bipolar disorder, seasonal affective disorder and subforms of major depressive disorder are known to be associated with deviations in the circadian system, alterations that are crucial to the etiology of these pathologies. Therefore, entrainment of circadian rhythms is regarded as a promising basis for treatment. The rules for successful synchronization by melatonin are outlined. Differences of phase resetting within the phase response curve are emphasized. Moreover, deviations from classic pharmacological thinking are underlined. When appropriately timed, relatively low doses are sufficient for entrainment, whereas increases of doses may reduce rather than improve the success of resynchronization. Immediate-release formulations are sufficient and recommendable, since they generate synchronizing signals that are favorable with regard to their time structure, whereas extended actions as desired in classic pharmacology of antidepressants may prevent successful entrainment. The assessment of circadian deviations prior to the development of an individual therapeutic strategy is of utmost importance for knowing whether phase advances or delays are required and also for avoiding concomitant symptomatic treatment with drugs that cause opposite effects, such as lithium, which extends the circadian period and should not be used in patients who anyway have developed an abnormally long period.

Keywords: Bipolar Disorder; Circadian; Depression; Melatonergic Drugs; Melatonin; Phototherapy; Seasonal Affective Disorder

INTRODUCTION

Depressive disorders are not uniform, but rather represent a number of different pathologies, each with their own specific etiology. Among the major classes, subforms exist that may, again, vary with respect to their causes. Deviations of the circadian system have been identified as one possible basis of depressive symptoms. These are characterized by deviations of circadian period lengths, associated changes in the phase position of awakening and falling asleep, and/or flattening of rhythm amplitudes, changes that are typically associated with sleep disturbances [1]. Moreover, the complexity of the circadian system that is composed of countless cellular oscillators present in numerous central and peripheral tissues [2], bears the possibility of misalignment between oscillators, especially when amplitudes are decreased, changes that are assumed to represent a cause of physiological malcoordination that results in reduced performance and, perhaps, illness [2-4]. Several reasons for circadian malfunction are known. One of them can be based on polymorphisms of circadian oscillator genes. Associations of clock gene variants with Bipolar Disorder (BP), Seasonal Affective Disorder (SAD), subforms of Major Depressive Disorder (MDD) and other neurological pathologies have been described, as summarized elsewhere [2]. As always in gene expression, epigenetic mechanisms may change the levels of circadian oscillator components as well. While epigenetics is an emerging field in depressive disorders [5], the specific relationship to circadian malfunction is still in its infancy and has been only occasionally addressed [6]. Nevertheless, numerous epigenetic influences on circadian rhythms have been reported [7] and receive increasing attention. A further cause of circadian deviations that can lead to depressive symptoms is aging. Again, several reasons may be responsible for these changes. In particular, aging-related epigenetic changes including reductions of sirtuin 1 (SIRT1) expression can reduce circadian amplitudes, in both the circadian master clock, the Suprachiasmatic Nucleus (SCN) [8], and in peripheral oscillators [9]. The role of epigenetics in aging clocks may be also deduced from findings in rats, in which some oscillators were shown to be damped, sometimes down to arrhythmicity, whereas others maintained a substantial amplitude [10]. Some of these oscillators were re-activatable, which indicates a previous lack of sufficiently strong rhythmic inputs [10]. Another cause of circadian dysfunction may be assumed to be related to the aging-associated decrease in melatonin. The pineal hormone depends in its rhythmic synthesis on the SCN, but also feeds back to the master clock and also influences peripheral oscillators [2]. Therefore, reduced melatonin secretion leads to a decrease in the strength of the feedback, an effect that should also be present in various disorders and diseases that additionally reduce melatonin secretion [11,12].

On the background of these considerations, the correction of circadian malfunction in depressive disorders appears as a promising procedure of treatment. The aim of such a therapy has to be the resynchronization of the previously deviating rhythms. However, as will be outlined in this article, several rules have to be followed which differ from that what pharmacologists are accustomed to apply.

DEVIATION ASSESSMENT

As usual, a diagnosis has to precede the therapy. In this field, it may not be necessary to identify, in the first run, the eventual genetic deviations, such as clock gene mutations. It seems much more important to determine the deviations of the actual endogenous circadian period length. This is important as subforms of depression can be associated with either shortened or lengthened periods [13-16]. In cases in which Circadian Rhythm Sleep Disorders (CRSDs) have been previously diagnosed, such as Familial Advanced Sleep Phase Syndrome (FASPS) or Delayed Sleep Phase Syndrome (DSPS), this can be taken as a good reason for trying a treatment of enforced circadian entrainment [16]. In other cases, the deviation remains to be identified. Although a precise determination of the period length would require analysis under isolation of the patient, a preliminary guess on whether the period is substantially longer or shorter than normal can be obtained by comparing time points of awakening and sleep onset in the patient, since period length under free-running condition and phase position of an entrained rhythm are correlated [17,18]. The result of the period determination has to be considered in the selection of a phase of treatment according to the phase response curve (cf. respective section below).

However, one has to be aware that strong deviations from a normal period may impede a successful synchronization, which is only possible within a so-called range of entrainment, i.e., a range of period lengths that allows synchronization. From a fundamental point of view, this question is more complicated, because the free-running human circadian rhythms can already substantially deviate within a human individual, as observed during internal desynchronization [19]. In the extreme, the free-running period of the body temperature rhythm may remain close to 25 hours, whereas that of sleep/wakefulness can exceed 33 hours. However, in practice, this complication should first be ignored, although the internal misalignment is presumably of substantial relevance to DSPS and the development of associated psychiatric symptoms under conditions of circadian malfunction [20-22].

Nevertheless, there may be cases in which synchronization is impossible for more fundamental reasons. This may not only be caused by a period outside the range of entrainment, but may result from mutations in oscillator genes or degenerative processes in the SCN or its neuronal connections. However, this situation is relatively rare and should not keep a physician from trying an entrainment therapy.

COUNTERPRODUCTIVE MEDICATION

Psychiatrists may have the tendency to first apply a symptomatic treatment with antidepressants. This may be entirely justified if symptoms are severe. However, this may be counterproductive if the antidepressive therapy interferes with the chronotherapy. A frequent side effect of many antidepressants is sleep disturbance, which may be a cause of inconvenience in patients who suffer anyway from depression-associated sleep difficulties [23-25].

Although sleep and the circadian system can mutually influence each other [26], this problem may still be a minor one relative to the disregard of circadian influences of lithium. Lithium is known since long to lengthen the circadian period. Therefore, the use of lithium should be strictly avoided in the subgroups of patients with an anyway lengthened period [15, 16]. The initial assessment of circadian deviations is, thus, meaningful for developing a suitable strategy, regardless of whether this will be a conventional symptomatic treatment or a causal chronotherapy.

EFFECTIVE SYNCHRONIZING SIGNALS

The basis of circadian entrainment is phase shifting. Under normal conditions, this process is used for re-adjusting the endogenous circadian rhythm, which deviates from 24 hours, to the length of the solar day. Importantly, the main action of a synchronizing time cue can be described as a nonparametric effect [27]. In other words, the decisive property of the entraining signal is the rapid change in the respective value, which has to have, of course, a certain extent. This contrasts with a parametric effect that depends on an enduring elevated level of the parameter rather than on the change. Parametric effects do also exist in chronobiology, such as that by light intensity during the photophase, which influences the length of the spontaneous period and, under synchronized conditions, the phase position relative to an entraining cycle, as described by Aschoff's rule [28, 29]. Therefore, the efficacy of an entraining signal depends on its time structure, i.e., the rapid increase, eventually followed by a soon decline. The importance of the decline seems to be particularly important for endocrine parameters in relation to the dependence of direction and extent of changes on the time point of treatment, as will be outlined next. Nonparametric and parametric effects, which had been originally worked out for synchronization by light signals, also have some validity for other entraining time cues, such as changes in melatonin levels [11,12]. The consequence is of fundamental importance, since it leads to a profound difference from classic pharmacokinetic considerations that are taken as granted by many pharmacologists. This means especially that an improvement of an action is not achieved by extending the duration of action. Synthetic melatonergic agonists have been specifically developed for purposes of increasing the duration of action on sleep. The short half-life of melatonin in the circulation, which is usually in the range of 20- 30 min and maximally attains 45 min, was believed to be insufficient for a prolonged action with the aim of supporting sleep maintenance [30]. Apart from the fact that the extension of total sleep time remained rather moderate [30,31], the rules for direct sleep promotion and for circadian entrainment are not identical. Of course, this difference also refers to the indirect effects of melatonin or its synthetic analogs on sleep, as far as their actions are achieved by correcting circadian malfunction.

A basic rule concerning entrainment by phase shifting consists in the adherence to the phase response curve (PRC). The PRC describes the extent and direction of phase changes in their dependence on the phase of treatment. A typical PRC is composed of three sections, (1) several hours in which no phase change is induced, the so-called silent zone, (2) a delay part and (3) an advance part. This is also the case in the PRC for melatonin [32,33], also schematically depicted and explained in ref. [31]. A most surprising property of the PRC for melatonin concerns the temporal position of the dim-light melatonin onset (DLMO), a phase that is often, and with good reason, taken as circadian marker. This time point of the DLMO is found close to the onset of darkness in a normal light/dark cycle. For purposes of sleep induction, melatonin or its synthetic analogs are typically given at or near this time. However, with regard to the PRC, the DLMO is still located in the silent zone! In other words, moderate doses melatonin given around this time will not (!) phase shift the circadian rhythm. As melatonin is rapidly decaying in the circulation, only higher doses of melatonin may spill over into the subsequent delay part of the PRC. The poor entraining efficacy of melatonin at the DLMO contrasts with other effects of the pineal hormone, especially as it is very effective at that time in reducing sleep-onset latency [31]. Therefore, the low synchronizing potential at the DLMO is not a matter of receptor availability or other types of reduced melatonergic signaling, but instead reflects properties of the circadian oscillator.

In the melatonin PRC, the silent zone is followed by the delay part, in which maximal shifts are obtained in the second half of the night [31,32]. Thereafter, the phase-shifting activity declines and, via a transition phase, changes over into an advance part that may become maximal around noon. The positions of the delay and advance parts have, of course, consequences to treatments aiming at re-entrainment of deviating circadian rhythms. Treatment in the second half of night may result in some inconvenience and, importantly, should not be accompanied by exposure to light, which would counteract the melatonergic effects [34]. Treatment with melatonin, in case that phase advances are desired, is easier, but this is, again, complicated by eventual counteractions by light, and melatonin during the photophase may also be inconvenient if a normal all-day-functioning is required, since melatonin interferes with alertness. Nevertheless, in a clinical setting, this treatment should be feasible. If this is not possible, the use of other entraining time cues should be preferred, such as well-timed exposure to light.

If delays are required, e.g., in cases of a shortened circadian period associated with an advanced phase position, melatonin or other melatonergic drugs should be administered later than at DLMO, to induce effects in the delay part of the PRC. It may be possible to use somewhat higher doses than the minimally required ones, in order to attain sufficient levels in the delay section.

However, it is not recommendable to elevate the dose too much. In part, the reason for this is related to the aforementioned deviation from classic pharmacokinetics. As outlined above, a prolonged presence of the synchronizing agent does not conform to the necessity of generating a pulse-like signal that acts according to nonparametric effects. Moreover, higher doses of melatonin, already

those in the range of commercial pills, may transiently generate strongly elevated, supraphysiological levels of circulating melatonin [35]. Sometimes, high doses of melatonin have been observed to induce fragmented sleep [36]. Again, one should keep in mind the deviations of synchronization rules from classic pharmacokinetics. An increase in dose does not warrant a more profound effect. In fact, surprisingly low doses of melatonin are sufficient for inducing phase shifts and entraining human circadian rhythms. Immediate-release formulations of 0.25, 0.3 or 0.5 mg were found to efficiently synchronize circadian rhythms in humans, whereas higher doses such as 10 mg failed to entrain [32,37-39].

CONSEQUENCES OF THE PHASE RESPONSE CURVE

The normal advice for sleep improvements by melatonin or its synthetic analogs is to take the drug about half an hour before bed time. This is usually close to the DLMO and, thus, will not entrain the circadian system, although effects on sleep onset are typically obtained. If the treatment strategy does not adhere to the rules of the PRC, a melatonergic therapy for entrainment will fail. This may result in an unjustified conclusion on inefficacy. Moreover, attempts of improving an apparently insufficient effect by enhancing the dose will not necessarily be successful, as outlined above.

Another cause of failure may result from a missing deviation assessment before treatment. Although it is not always easy to precisely identify the deviating positions of delay and advance parts, the previous determination of circadian markers, such as time of awaking, sleep onset, DLMO, maximum or minimum of core body temperature can help to roughly estimate optimal phases of treatment. This should be possible in many patients who are exposed to the environmental 24-hour cycle. If patients exhibit circadian rhythms that deviate from 24 hours in the presence of environmental time cues that would normally entrain the circadian system, the incompletely synchronized or, in the extreme, free-running rhythms have to be more closely characterized and phases for treatment identified. With regard to these procedures, experience exists for totally blind subjects, which were successfully entrained by low doses of melatonin [33, 37, 38].

Finally, the physician has to be aware that successful entrainment is typically not yet achieved by a single administration of melatonin. In the optimal case, the first dose may change the phase position by 1 or 2 hours. Further appropriately timed administrations, which consider the respective previous phase shifts, will be required to achieve full synchronization. This may take a number of days and the treatment may, as soon as the entrainment has been accomplished, require continuation to avoid return to the previous unfavorable state. With regard to the good tolerability of melatonin, this is usually unproblematic from a toxicological point of view, except for patients that should be excluded from melatonergic treatment, because of pregnancy, diseases or interfering medications [30].

NONRESPONDERS

The absence of a response to melatonergic treatment may result from missing consideration of the above-mentioned rules. This may not only be caused by selecting inappropriate phases of treatment, but can also be the consequence of elevated doses that reduce the success of entrainment [37]. Longer-acting synthetic melatonergic drugs may, in this regard, be less recommendable, especially if they generate a signal with a shape that is unfavorable for nonparametric effects, such as slow increase and delayed decline in the circulation. If the treatment is conceived with disregard of the chronobiological efficacy, an elevated number of nonresponders will be observed, many of whom are, however, mistakenly classified.

Other subjects may represent real nonresponders to melatonergic therapy. This may have two possible reasons. First, dysfunctional melatonin receptor variants may prevent normal signaling. This would especially concern the MT_1 receptor, which is the prevailing melatonin receptor in the human SCN [40]. However, as the two melatonin receptors can often, though not always, substitute for each other, a total loss of melatonergic effects is rather unlikely. According to current evidence, the cause of deficient melatonergic signaling seems to be rare.

The other possibility of nonresponsiveness is based on severe circadian malfunction, which may be associated with non-entrainable rhythms, because of extremely long or extremely short period lengths or, alternately, defective connections between the SCN and its output pathways. By contrast, defective input pathways from the retina, including total blindness, only results in a lack of synchronization by photic signals, but retains the possibility of entrainment by melatonin. Again, these possible causes of nonresponsiveness seem to be rare.

MELATONERGIC AND/OR LIGHT TREATMENT

With the exception of blindness including missing photoreception by melanopsin-containing retinal ganglion cells, an alternative to melatonergic treatment can be entrainment by light. Again, a deviation assessment is required for developing a promising strategy. Whether phototherapy will be successful in resynchronizing rhythms, depends on the deviations. In many cases, patients have been exposed to bright light in the morning. Mostly, bright light in the early morning causes phase advances, whereas delays are achieved in the evening. As the photic information towards the SCN mainly depends on the melanopsin-containing retinal ganglion cells, which strongly absorb in the blue range, blue light has also been used and was shown to induce similar phase shifts as bright light does [41,42]. Nevertheless, this type of phototherapy has yielded positive results in numerous cases of SAD and BP, as summarized elsewhere [16]. Even in several cases of MDD, bright light therapy has been reported to be successful, however, with a highly variable degree of success [16, 43-46], which is not surprising with regard to the divergent etiologies of MDD subforms, among which only a minor section is based on circadian malfunction. Studies and meta-analyses often disregard the etiological complexity of MDD.

On the one hand, phototherapy has the advantage of a nonpharmacological treatment and should be devoid of drug-related side effects. However, light exposure can be a source of discomfort [16]. Especially blue light has been shown to exert undesired reductions of photosensitivity [47]. For the application of blue blocking glasses, of other chronotherapies including dawn simulation and sleep deprivation, and the use of light treatment as an adjunctive therapy to conventional antidepressants see ref. [16].

Generally, it is also possible to combine the actions of light and melatonin for more efficiently entraining circadian rhythms [12,16], however, under the condition of avoiding interfering actions, such as light in the late evening, which suppresses endogenous melatonin secretion and may cause chronodisruption.

A LOOK AT SYNTHETIC MELATONERGIC DRUGS

Two different properties of melatonergic agonists have to be distinguished, (1) that of re-entraining circadian rhythms and, thereby, counteracting a cause of depression, as far as it is related to an etiology of circadian malfunction; and (2) direct antidepressive actions that have been also reported for some agonists. This article is focused on the first of these aspects, whereas direct antidepressive effects will be only briefly mentioned with regard to actual discussions.

Direct antidepressive actions have been particularly described for agomelatine, a drug that combines properties of a melatonergic agonist at MT_1 and MT_2 receptors and of a serotonergic antagonist at the $5\text{-}HT_{2C}$ receptor [23-26]. Although the affinity to $5\text{-}HT_{2C}$ is rather moderate, the actual state of the discussion has been to assume an interplay of melatonergic agonism and $5\text{-}HT_{2C}$ inhibition as the antidepressive mechanism [48,49]. As recently summarized [16], several studies have reported a superiority of agomelatine over other drugs in BP, SAD, and sometimes even MDD by acting as an antidepressant with additional sleep-promoting properties. However, as also stated there [16], other reports arrived at variable conclusions, which included poor efficacy and biased publication [50-52]. In the latter paper [52], agomelatine was very negatively judged as being ineffective in depression and an unnecessarily dangerous drug. Although this conclusion may have gone somewhat too far, concerns related to hepatotoxicity are well-founded and may be caused by formation of oxidotoxic metabolites [53]. As direct antidepressant properties have been sometimes claimed for other melatonergic agonists and melatonin, too, it should be briefly mentioned, without in-depth discussion of details, that antidepressive effects in the proper sense may be easily mistaken for anxiolytic and sedating actions [40], even when using established models.

Concerning the indirect antidepressive actions by correcting circadian malfunction, any agonist with sufficient affinity to the melatonin receptors should be able to phase shift circadian rhythms, as far as the chronobiological rules outlined above are followed. However, in terms of resetting, it has to be remembered that short-acting drugs are sufficient and that relatively low amounts of melatonin are capable of causing entrainment. In this regard, the recommended doses of the synthetic agonists, which have been defined on the basis of sleep promotion or direct antidepressant properties, but not in resetting studies, are typically unnecessarily high. For instance, recommended doses for ramelteon, which displays higher affinities than melatonin to MT_1 and MT_2 receptors [12,24,30], amount to 4 or 8 mg, those for agomelatine to 25 or 50 mg, and the effective dose of tasimelteon has been found to be 50 mg [54]. These high doses have been selected despite longer persistence in the circulation than melatonin. In the case of ramelteon, an additional problem exists insofar, as one of its metabolites, usually referred to as M-II, has a considerably longer half-life in the blood than the parent compound and retains about one tenth of the receptor affinities. Because of its long persistence, it attains levels between 20 and 100 times (mean: 30 times) higher than ramelteon [55] and certainly contributes to the overall action of the drug. In the light of the requirements for an efficient resetting signal, the long half-life and the high recommended doses are not in favor of a successful entrainment. Moreover, it is rather illogical to use high doses of synthetic drugs, while the natural hormone, melatonin, is an effective entraining agent at much lower doses and anyway known for its extremely good tolerability [12].

SYMPTOMATIC TREATMENT AND ADJUNCTIVE THERAPY

It may be a matter of care about patients to not only try to entrain perturbed circadian rhythms, but also to seek a rather soon relief by symptomatic treatment with classic antidepressants. While the combination of antidepressants with light therapy has been explored several times [16,56,57], similar studies concerning combinations of antidepressants with melatonin are still a demand. However, it will be important to avoid interference of direct antidepressants with melatonin's actions or with the circadian system. The unsuitability of lithium in cases of extended spontaneous circadian periods has already mentioned above and can serve as an example.

The combination of melatonin and light therapy is principally possible, as long as the circadian phases of the respective treatments are well-selected, in order to avoid phase shifts into different directions by the two treatments. For optimal phasing by combinations of melatonin and light see ref. [58]. This strategy has been used for correcting the Delayed Sleep Phase Syndrome (DSPS) [59,60], and also in attempts of improving cognitive functions in elderly subjects [61] and disturbed activity/rest patterns in patients with Alzheimer's disease [62]. Systematic studies on a combined melatonin and bright or blue light therapy in subforms of depression should be welcome.

CONCLUSION

Circadian malfunction is one of the possible causes for BP, SAD and, presumably, some subforms of MDD. The responsible circadian deviations may result from gene polymorphisms, epigenetic changes related to lifestyle or aging, and may be associated with comorbidities. Subclinical and clinical neurodegenerative processes, typically in conjunction with low-grade neuroinflammation, seem to play a particular role in the development of depressive disorders [16]. Notably, changes in the circadian system are already observed in midlife, but become more pronounced with advanced age. They comprise flattening of rhythms, deviations of period length, internal misalignment and, additionally, concern decreases in melatonin secretion that weaken the feedback to the SCN and the stimulatory input into peripheral oscillators [2,9,12]. Under these perspectives, the readjustment of the circadian system by entraining and internally coupling the periodicities to the environmental cycle represents a therapeutic objective for forms of depression with a circadian etiology.

This mini review has focused on the action of melatonin as an entraining signal. In this context, the most important insights concern the shape of a synchronizing signal that should be suitable for accomplishing the requirements of nonparametric resetting, the relatively low doses needed for synchronization and the chronobiological rules of entrainment according to a phase response curve. Moreover, it is important to be aware of the pharmacological differences between successful resetting and customary concepts based on duration of action and dose/effect relationships in classic pharmacokinetics. Disregard of these differences can easily lead to inappropriate therapeutic concepts and to false conclusions on inefficacy.

An important demand for successful treatment of depression with an etiology of deviating circadian rhythms is the assessment of these deviations prior to the development of an individual concept for treatment. Such an assessment leads to the decision of whether entrainment should be tried by phase delays or advances.

Moreover, knowledge of the endogenous period length should provide information on the suitability or inappropriateness of other, additionally applied symptomatic treatments, as exemplified by the case of lithium, which lengthens the circadian period and, thus, is counterproductive in the subgroup of patients with anyway extended periods.

If appropriately timed, a dual treatment with melatonin and bright or blue-enriched light, in the respective suitable phases can be recommendable. These procedures, which have been applied for correcting rhythms for purposes other than antidepressive treatment, should be extensively tested in the future in BP, SAD and, in case of circadian deviations, in forms of MDD. Both melatonin and light treatments have the advantage of excellent tolerability.

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