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Melatonin in Psychiatric Disorders: A Review on the Melatonin Involvement in Psychiatry

Claudia Pacchierotti, Sonia Iapichino, Letizia Bossini, Fulvio Pieraccini, and Paolo Castrogiovanni

Department of Psychiatry, University of Siena, Viale Bracci-26, 1-53100 Siena Italy

In normal subjects, the secretion of melatonin, the pineal hormone that regulates the rhythm of many functions, exhibits a circadian pattern synchronized with the day–night cycle. An alteration of this secretory pattern has been found in various psychiatric disorders (seasonal affective disorder, bipolar disorder, unipolar depression, bulimia, anorexia, schizophrenia, panic disorder, obsessive compulsive disorder). At present, it is not known if such alterations have an etiological role or are secondary to the dysfunctions underlying the different disorders. In addition, we do not know if the involvement of melatonin in several disorders has the same significance in the pathophysiology of each disorder. An understanding of the role of the pineal hormone and of its alterations in psychiatric diseases could help to identify the biological mechanisms underlying such disorders. KEY WORDS: melatonin; pineal; psychiatry; light; season.

INTRODUCTION

The function of the pineal gland and its main hormonal product, melatonin, have been undervalued by clinicians. Although the physiological role of melatonin in humans has not been defined, a characteristic periodicity of serum melatonin has been found in humans (115, 119, 124). The synthesis and secretion of melatonin is controlled by a circadian clock in the hypothalamus (the suprachiasmatic nucleus; SCN) and is synchronized by the light/dark cycle (93, 115).

Production of the pineal hormone is inhibited by daylight (65) and occurs during darkness, and neural mechanisms under sympathetic control are responsible for melatonin release (1, 7). Norepinephrine stimulation regulates the synthesis of melatonin from the precursor serotonin (110).

The levels of melatonin are modulated by a transcription factor. The molecular mechanisms of the rhythmic synthesis of melatonin involve a c-AMP response element on the modulatory gene. This gene is rhythmically expressed and participates in a transcriptional autoregulatory loop that also controls the amplitude of oscillations of 5-HT-*N*-acetyltransferase, the rate-limiting enzyme of melatonin synthesis (41). However, melatonin receptor binding in the

Address correspondence and reprint requests to Claudia Pacchierotti. Fax: +39 577 263451.

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SCN exhibits a diurnal rhythm, with significant increases during daylight (11). Neu and Niles reported the first evidence of a significant diurnal variation in melatonin ML1A receptor mRNA levels within the SNC; this mRNA expression occurs approximately 3 h prior to, but is correlated to, the diurnal rhythm in melatonin binding in the SNC (85). Preliminary data reported by Dubocovich *et al.* indicated that melatonin phase advances circadian rhythms by activation of a membrane-bound melatonin receptor, the MT2 (Mel1b) melatonin receptor subtype, within the circadian timing system (33). Plasma levels begin to rise after sunset, peak at around 2 AM, and decline markedly by morning (65). Factors other than the light–dark cycle, such as genetic regulation (41, 112), age of the subject (48), diet (50), and the season of the year (5) have also been shown to modulate serum melatonin levels in humans.

In the last 3 decades, there have been numerous advances in the knowledge of the biochemistry and physiology of the pineal gland and its main hormonal product, melatonin. It is now evident that the gland affects many organs and functions.

There are reports that the rhythm of melatonin secretion may be impaired in various disorders, including neoplasia (43), neurological disorders, migraine (21), dizziness (42), epilepsy (35), and Alzheimer's Disease (23).

It is also abnormal in circadian phase disorders, e.g., shift-work syndrome (62), jet-lag maladaptation (113), and sleep disturbances (22).

After an alteration of the melatonin rhythm was demonstrated in seasonal affective disorder, almost all psychiatric disorders have been explored, and alterations of the pattern of pineal secretion have been reported in some of them. Therefore, we wondered if a generalized role of melatonin in psychiatric disorders could be identified.

It is necessary to point out that, in some studies reported, the authors do not specify whether their patients are drug-free or under treatment with psychopharmaceuticals; this is a limit, because many of the treatments of psychiatric disease alter norepinephrinergic and other neurotransmitter systems which are important in the regulation of pineal secretion (28, 44, 47, 89, 107).

SEASONAL AFFECTIVE DISORDER

In 1984, Rosenthal *et al.* presented the first description of seasonal affective disorder (SAD), an affective illness with recurrent depressive episodes in winter and hyperthymic periods in spring–summer (97). About 90% of SAD patients also meet the criteria of the Diagnostic and Statistical Manual of Mental Disorders (DSM) for bipolar disorder II (34, 118).

Alterations of endogenous rhythms have been reported in patients with SAD, particularly a dysfunction of the activity–rest rhythm, with an advance of at least 2 h with respect to healthy controls (105). The authors agree with the hypothesis of a supersensitivity to light variation in SAD, which may cause circadian rhythm alterations. In fact, the onset of depressive symptoms in September–October coincides with the fastest variation of light (intensity, spectrum, and photoperiod) at the beginning of autumn, on September 21 (16, 73, 80, 97). The depressive

symptoms progressively worsen during the winter along with the decrease in photoperiod (71). In addition, epidemiological studies have reported a greater incidence of SAD in countries at higher latitudes (16, 68).

The photosensitivity in SAD seems to be secondary to a pineal dysfunction. In fact, the patients with SAD present biological markers like maniac–depressive illness but, unlike unipolar depression (105, 116), for the melatonin circadian cycle. Terman *et al.* have reported that the decrease of plasma melatonin levels, normally occurring in the early morning, seems delayed by around 2 h (106). Other findings suggest a direct link between melatonin alterations and SAD: for example, the administration of high doses of melatonin to healthy subjects induces drowsiness, decreased attention, and prolonged reaction times, and melatonin administration to SAD patients induces a worsening of the depressive symptoms (91). It is not known if SAD is caused by an excessive quantity of melatonin or by a too prolonged secretion or if these alterations are merely an epiphenomenon of other factors, such as increased retinal photosensitivity (86) or neurotransmitter dysfunction. According to Depue *et al.* (31, 32), in SAD there is a state-dependent reduction of dopaminergic transmission. A disregulation of the serotoninergic system has also been proposed (87), and in this regard, the seasonal fluctuations of serotonin metabolism, also present in normal subjects, are of greater magnitude in subjects with SAD (102).

The importance of the circadian rhythm of melatonin in the determination of SAD is confirmed by the fact that the treatment of choice is light therapy, which would act by inducing a phase advance of the circadian rhythms (63, 64).

UNIPOLAR DEPRESSION

Several authors have reported altered circadian rhythms of the neuroendocrine system (hypothalamic–pituitary–adrenal axis, hypothalamic–pituitary–thyroid axis, GH, PRL, etc.) in depressive disorder (77, 103).

Recently, investigators have theorized that these dysfunctions could be based on an altered rhythm of melatonin, since this hormone regulates some endogenous rhythms. There are consistent findings of reduced daily secretion of melatonin in depressed patients, with anomalous diurnal peaks and a reduced and phase-advanced nocturnal peak (10, 20, 120).

Some authors have considered these findings a trait marker of depressive disorder, since they are also present in remission phases (10, 20, 26, 84), while Souetre *et al.* (103) have found that circadian profiles of plasma melatonin in patients endogenously depressed were restored after recovery; according to the authors, the normal features of the circadian rhythms observed in remission may be associated with effects of antidepressant drug.

Other authors disagree because they have observed the same alteration in schizophrenic patients (38). In the study of Beck-Friis (10), the altered pattern of melatonin secretion was independent of the subject's gender, the duration of the depressive episode, a positive family history of depression, and the symptomatological subtype (melancholic, dysthymic, cyclothymic, endogenous, or reactive depression). In contrast, Brown (20) observed a greater reduction of

the nocturnal peak in melancholic patients. An altered rhythm of nocturnal melatonin secretion in depression seems to be related to an emotional trauma before the age of 17 years (10).

Most authors identify a serotoninergic and norepinephrinergic deficit as the primary cause of pineal dysfunction. In particular, a limited availability of L-tryptophan, the precursor of serotonin and thus of melatonin, or an inadequate norepinephrinergic stimulation of the pineal gland has been hypothesized. The norepinephrinergic system could have a primary deficit or could be hyperactive, thus inducing a desensitization of the pineal beta receptors, making them refractory to normal norepinephrinergic stimulation (20).

The alteration of the melatonin rhythm is associated with variations of cortisol, temperature, and sleep rhythms. Some authors have reported a reduced nocturnal peak of pineal secretion only in depressed patients with alterations of the dexamethasone suppression test. It is possible that melatonin or another pineal factor inhibits CRF in subjects with depressive disorder (10, 120). Melatonin, cortisol, temperature, and sleep are all regulated by the same hypothalamic clock, which has melatonin receptors (27, 123).

However Branchey *et al.* (18) observed a dissociation of melatonin and cortisol secretory patterns in depressed patients in whom the two hormones were determined simultaneously, suggesting that the melatonin and cortisol rhythms may be controlled by different mechanisms.

Some reports disagree with the findings of a decrease of pineal function in unipolar depression. In the study of Rubin *et al.* (99), the depressed patients showed a trend toward a significantly elevated average nocturnal melatonin concentration.

The American Psychiatric Association's DSM-IV categorized the premenstrual dysphoric disorder (PMDD), what historically has been referred to as premenstrual syndrome, as a depressive mood disorder, based on studies of its phenomenology and course. With regard to it, recent findings support low serotonin and melatonin metabolism in PMDD compared with healthy control subjects (90).

BIPOLAR DISORDER

Lewy *et al.* showed that, in response to light, nocturnal plasma melatonin concentrations fell twice as much in both acutely ill (66) and euthymic drug-free (61, 64) patients with bipolar disorder. They proposed that supersensitivity to light may be a trait marker for bipolar affective disorder, thus explaining the variation of circadian rhythms in patients with affective illness (117). Their previous studies showed that plasma melatonin levels of bipolar patients are higher in the manic than the depressive phase, perhaps suggesting that the amount of melatonin production reflects state-dependent changes in adrenergic function (59, 60).

Kennedy *et al.* tested nine bipolar patients during manic, depressed, and euthymic states. In all cases serum melatonin levels were lower than those in control subjects. The authors maintain that decreased serum melatonin is a

trait but not a state marker in bipolar affective disorder (51). Moreover, supersensitivity of the pineal to light in bipolar illness was not confirmed by Whalley *et al.* (114).

SUICIDAL BEHAVIOR

A relationship between suicidal behaviors and variations of photoperiod has been reported in several studies. Some authors have investigated the biochemical and metabolic processes underlying the seasonal pattern of violent suicide. An inverse correlation was found between violent suicide and some physiological variables, such as melatonin, whose nadir coincides with about the third day of May (72). Moreover, nonspecific cytological modifications have been observed in the pineal gland of the victims of violent suicide (pinealocytes in a lobular disposition, arborization of the connective tissue and the glia, reduction of the volume of the cell nucleus, irregular dissemination of astrocytes, and the formation of "acervuli"). These morphological alterations are an expression of the functional activation of the pineal gland, which leads to an increase of melatonin secretion (78). Probably the pineal gland makes an attempt to compensate in the presuicide period, an hypothesis that is confirmed by the increased level of plasma melatonin in subjects who have attempted suicide (122).

The involvement of melatonin in the increased risk of suicide can be related to more accredited etiopathogenetic hypotheses, such as a dysfunction of the hypothalamus–pituitary–adrenal axis or the serotoninergic or norepinephrinergic systems. The hyperactivity of the adrenocortical system observed in subjects with suicidal behavior, leading to increased basal levels of plasma cortisol (54), could be caused by a lack of modulation of adrenal function by melatonin. Moreover, the pineal dysfunction could be an expression of altered serotonin metabolism in suicidal subjects (6), since serotonin and melatonin have the same precursor (L-tryptophan). Finally, the reduction of norepinephrinergic activity occurring in suicidal subjects (88) indicates a decreased stimulation of the pineal gland, since norepinephrine is the main positive regulator of melatonin synthesis (78). In fact, Stanley and Brown reported a decreased content of melatonin in the pineal glands of suicide victims (104).

Some authors disagree with the findings of an altered norepinephrinergic function which contribute to decreased pineal secretion in suicidal subjects; in fact, in the study of Little *et al.* (69) no differences in concentration of pineal β-adrenergic receptors were detected between subjects who committed suicide and suffered from major depression and matched controls.

BULIMIA

Bulimia exhibits a seasonal pattern (19, 39, 46, 56, 57), which is more evident than that of anorexia (40, 57). Bulimic behaviors seem to occur in winter (with a peak in December) in 35% of patients, in summer in 20%, and

in spring in 3% (57). The winter peak is confirmed by several studies (15, 39, 52). In addition, hypersomnia, hyperphagia, and weight increase, which are frequent in bulimia, become worse in the winter months, as in seasonal affective disorder (15, 30, 46, 56, 98). This seasonal pattern of bulimic symptoms is independent of the seasonality of mood variations; in fact, in patients with bulimia, depression is more frequent in spring (15, 57, 58). The winter pattern of the craving for carbohydrates, as in SAD, is probably due to the negative peak of serotonin metabolism (125). The increased synthesis of serotonin, secondary to the consumption of carbohydrates, must be related to the higher plasma melatonin concentration during the bulimic behaviors. The melatonin levels are increased only during daylight hours, in which the bulimic behaviors are more frequent (125). At night instead, the melatonin concentration is normal, except in bulimic patients with comorbid depression in whom the melatonin peak is flattened (50). It is not known if this dysfunction of the melatonin rhythm is completely secondary to the serotonin alterations or if it depends on climatic–environmental variables, such as light; for example, the bulimic behaviors seem to be inversely proportional to the photoperiod (15).

Other authors have found no significant decrease of nocturnal melatonin secretion in bulimic, albeit amenorrheic, patients (83).

ANOREXIA

Several authors have found higher diurnal and nocturnal mean plasma melatonin concentrations in patients with untreated anorexia nervosa, without differences in the time peak for nocturnal melatonin secretion (3, 36, 37, 108).

Brambilla *et al*. (17) confirmed the findings of an increase of pineal secretion in anorexia, but they reported phase-advanced nocturnal rises and abnormal diurnal peacks.

The lower blood volume, leading to hemoconcentration, or an impaired metabolic capacity might explain the higher levels of plasma melatonin in subjects with anorexia nervosa (108). However, a more likely hypothesis is that increased concentrations of plasma melatonin are related to hypothalamic hypogonadism. In fact, in anorexia nervosa there is a hypogonadotropic hypogonadism of hypothalamic origin (9, 45, 111) and higher nocturnal levels of circulating melatonin have also been reported in patients with hypothalamic amenorrhea (12) or anorchia (109).

Inhibition of hypothalamic GnRH pulsatility by melatonin has been demonstrated in several studies (14, 96, 126). Moreover, androgen and estrogen receptors are present in the rat pineal gland (24) and melatonin binding sites have been cloned in the hypothalamus (25, 94, 95). Finally, woman experiencing long dark winters in high-latitude countries have greater melatonin secretion and decreased ovarian and androgenic activities (49).

Therefore, in anorexia nervosa a primary disregulation of the hypothalamic control of GnRH activity may be followed by enhanced melatonin synthesis

and secretion as a result of the impaired gonadal steroid input to the pineal. The action of the higher circulating melatonin concentrations on the hypothalamus may potentiate the hypogonadal situation.

Birau *et al.* (13) found significantly reduced melatonin levels in anorexia, perhaps because of the inclusion in the sample of patients with comorbid depression, while a few studies have reported unaltered pineal melatonin secretion in women with anorexia nervosa (29, 83, 101).

SCHIZOPHRENIA

The hypothesis of an involvement of melatonin in schizophrenia derives from the structural similarity between this hormone and some hallucinogenic substances (e.g., harmine) (76) and from the observation that intravenous administration of melatonin to schizophrenic patients in remission causes a worsening of psychotic symptoms which persists even after the treatment is interrupted (2).

Harmine and other agents (e.g., cocaine, amphetamine) induce the activation of the enzyme hydroxy-*O*-methyltransferase, which controls melatonin synthesis in the pineal gland (53, 70).

Little information is available concerning circadian rhythms of hormones in schizophrenia and the studies of the relationship between melatonin and schizophrenia have yielded contradictory results: Wetterberg (121) and Mills (79) found a leveling of nocturnal secretion.

The study of Sandik *et al.* (100) suggested that a subnormal plasma melatonin level may be a marker of a subgroup of schizophrenia characterized by cerebral atrophy and ventricular enlargement, negative symptoms, impaired cognitive and psychosexual development, onset at pubescence, poor response to neuroleptic medication, and possible increased risk of extrapyramidal symptoms.

Monteleone *et al.* (82) found that the nocturnal increase in plasma melatonin levels of drug-free schizophrenics was significantly blunted and that chronic treatment with antipsychotic drugs, which significantly improved the psychotic symptomatology, did not change the secretory pattern of melatonin. The biosynthetic activity of the pineal gland must be impaired in chronic schizophrenia and successful treatment with antipsychotic drugs does not induce changes in the production of melatonin.

The study of Rao *et al.* (92) indicated a significant phase-advance of tryptophan, prolactin, and melatonin concentrations in the blood of 90 drug-free schizophrenics and 25 neuroleptic-treated schizophrenic patients.

PANIC DISORDER

The first studies of melatonin in panic disorder reported significantly reduced nocturnal melatonin concentrations (20, 74). However, the reliability of these results is limited since panic subjects were under treatment with anti-

depressant medications. The use of antidepressants and benzodiazepine modifies the sensitivity of β receptors and suppresses nocturnal melatonin secretion (28, 47, 89, 107).

In a more recent study, McIntyre (75) reexamined the plasma melatonin concentrations in drug-free patients and reported opposite results: significantly greater melatonin levels than those in healthy subjects in the second part of the night (from 4:00 to 7:00 AM) and a phase delay of around 2 h. According to the authors, the excess melatonin in panic disorder patients could represent an attempt to reduce the anxiety state. Exogenous melatonin in healthy subjects produces a state of sedation, drowsiness, and decreased alertness, perhaps sensitizing the CNS to sleep-inducing factors (4, 67, 125). Alternatively, this melatonin alteration could be secondary to the impairment of neurotransmission reported in panic disorder.

Nevertheless, Bandelow *et al.* (8) recently reported normal melatonin levels in panic disorder. The pattern of nocturnal levels of melatonin in the urine was studied in a male with untreated panic disorder over two periods of five consecutive nights. The melatonin levels did not differ between panic patients and controls. The measurements were repeated after 4 weeks and once again no differences were found.

OBSESSIVE COMPULSIVE DISORDER

Some authors have found lower diurnal and nocturnal plasma melatonin concentrations in drug-free patients with obsessive compulsive (OC) disorder, with a delay of 2 h in the peak time of nocturnal melatonin secretion (81). These alterations were significantly correlated with the severity of the OC symptoms, particularly with obsessions, but not with concomitant depressive symptoms, if present. A primary dysfunction of the noradrenergic system could be followed by a disregulation of melatonin synthesis and secretion and by enhanced cortisol synthesis.

DISCUSSION

As mentioned above, an altered rhythm of melatonin secretion has been reported in many psychiatric disorders. Nevertheless, it is very difficult to find a common pattern for these data and for their significance, particularly in light of their often contradictory nature.

In seasonal affective disorder, in which the evidence of an altered synchronization between pineal secretion and sunlight is more constant (and according to some authors has etiological importance), it is still not clear if the alteration is primary or secondary to neurotransmitter or retinal dysfunctions.

Different mechanisms have been hypothesized in other disorders, all related to the principal characteristics of the disease (e.g., alterations of the sexual

hormones in anorexia or the presence of eating binges in bulimia). More often, the alteration of the melatonin rhythm has been considered (like other alterations of circadian rhythms) an epiphenomenon of the neurotransmitter dysfunctions underlying the disorders, since (as mentioned above) pineal secretion is controlled by various neurotransmitters.

Nevertheless, we would like to emphasize that in mood disorders the depressive phase is accompanied by reduced melatonin secretion and by a phase advance, whereas the opposite occurs in the maniac or hyperthymic phases (bipolar disorder, seasonal affective disorder).

It is interesting that increased diurnal melatonin secretion is also found in the phases of other disorders in which one finds some kinds of activation: the presuicidal decisional phase, the phase of increased physical activity in eating disorders, the psychotic phases, and perhaps panic disorder.

A correlate can be seen in studies showing that intense stress in animals can increase daytime pineal melatonin synthesis (89). There are also reports that intense daytime exercise can increase melatonin in humans (55). Alternatively, endogenous melatonin might be produced at higher concentrations by the body in an attempt to stabilize the patient with anxiety or agitation. Exogenous melatonin administered at pharmacological doses produces some sedation in normal subjects (4, 67). It has been proposed that melatonin can induce sleepiness, decreased alertness, and slow reaction time, perhaps sensitizing the brain to sleep-inducing factors (125).

Therefore, it would be interesting to study in more detail this transnosographic view of anticipated and increased melatonin secretion as a possible state marker of excitatory phases of various psychiatric disorders.

CONCLUSION

The characteristic rhythm of melatonin secretion appears to be altered in various psychiatric disorders. Further investigation is necessary to assess whether, and in which of them, this alteration has etiological importance or whether it is simply an epiphenomenon of primary alterations underlying the different disorders.

Knowledge and clarification of the role of melatonin in psychiatry could help to further our understanding of the biological bases of various psychiatric disorders (especially the chronobiological aspect) and to define the potential for light therapy in their treatment.

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