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Chronobiological mechanisms in seasonal affective disorder

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15.1 Introduction

Seasonal changes in behaviour and physiology have been recognised since ancient times and their relevance to psychiatry was described at least as early as in the middle of the last century. The degree to which seasonal changes affect criteria such as mood, energy, sleep length, appetite, food preference, or the wish to socialise with other people can be called seasonality. Two characteristic syndromes of seasonal mood changes have been reported in the literature: recurrent depressions in autumn and winter, termed seasonal affective disorder (SAD) by Rosenthal *et al.* (1984); and the opposite pattern, recurrent depressions in the summer, described by Wehr *et al.* (1987) and Boyce and Parker (1988). Kasper *et al*. (1989) reported winter difficulties in individuals who neither met criteria for major affective disorder nor were seeking treatment for their difficulties but who nevertheless experienced mild dysfunction and vegetative changes similar to those found in SAD. This group has been termed sub-syndromal SAD (S-SAD). More recently, there has been described a subgroup of depressed patients with brief recurrent depressive episodes during winter, termed recurrent brief SAD (Kasper *et al*., 1992). Whereas the winter depressive symptoms of patients with SAD and S-SAD respond well to light therapy (Neumeister *et al*., 1999), a successful nonpharmacological treatment for summer depression has not yet been developed.

15.2 Diagnosis of SAD and light therapy

The diagnostic concept of SAD was first included in the *Diagnostic and Statistical Manual of Mental Disorders*, Revised Third Edition (DSM-III-R) and has been updated in the DSM-IV (APA, 1994) as 'seasonal pattern', an adjectival modifier of any form of seasonally recurrent mood

disorder. The combination of depressed mood and a characteristic cluster of vegetative symptoms, together with the occurrence of depressive episodes during autumn and winter with full remission or hypomanic episodes during spring and summer, distinguishes SAD and its sub-syndromal form from other mood disorders. The demographic and clinical characteristics of patients with SAD are given in Table 15.1.

The characteristic neurovegetative symptoms in patients with SAD include abnormalities in eating behaviour and food preference (Rosenthal *et al.*, 1984). Hyperphagia and carbohydrate craving are typical symptoms of SAD and have also been described in patients suffering from atypical depression. These patients differ from anorectic depressive patients by being more often female and more mildly depressed.

Table 15.1 Demographic and clinical characteristics of female and male patients with seasonal affective disorder in Bonn and Vienna

n	610
Age (years)	41.1 ± 12.9
Diagnosis (%)	
UP	77.0
BP-II	21.7
BP-I	1.3
GSS	15.4 ± 3.5
Age at onset (years)	29.8 ± 13.1
Psychiatric comorbidity (%)	37.4
Family history (%)	
Depression	40.0
Alcohol dependency	6.9
Schizophrenia	2.1
Affect (%)	
Depressed	93.0
Irritable	75.1
Anxious	65.6
Loss of Energy (%)	98.4
Appetite (%)	
Increased	64.6
Reduced	18.4
Carbohydrate craving	66.5
Sleep (%)	
Hypersomnia	72.2
Daytime drowsiness	93.7
Loss of libido (%)	74.3
Difficulties at workplace	69.2

UP, unipolar depression; BP-II, bipolar-II affective disorder; BP-I, bipolar-I affective disorder; GSS, global seasonality score.

Moreover, these atypical depressed patients show a more pronounced reduction in sexual interest. These clinical features are also observed in patients with SAD. Interestingly, in SAD hyperphagia often correlates with increasing severity of depression. SAD patients have also been shown to demonstrate a significant increase in their well-being after intake of carbohydrates. It has been postulated (Wurtman, 1981) that carbohydrate craving may reflect a functional serotonin (5-HT) deficiency and that carbohydrate craving in SAD patients during autumn and winter may represent a behavioural–biochemical feedback loop for raising the availability of brain 5-HT (Fernstrom and Hirsch, 1977).

Another characteristic symptom of SAD is hypersomnia. It has been speculated (Kupfer *et al*., 1972) that hypersomnic and hyposomnic depressed patients constitute two biologically distinct groups. 5-HT has been implicated in regulation of sleep (Jouvet, 1969). Several investigators have studied the relationship between diet and sleep and have shown that changes in diet may induce changes in total sleep time, delta sleep and REM sleep. It can be hypothesised that some of the changes in sleep observed in SAD patients during winter episodes of depressed mood may be related to changes in diet and weight, and that serotonergic mechanisms may be involved.

There is agreement in the literature that light therapy is the first-line treatment for patients with SAD. This is based on numerous studies showing efficacy and safety, including randomised, controlled trials (Eastman *et al*., 1998; Terman *et al*., 1998) and meta-analyses (Lee and Chan, 1999; Terman *et al*., 1989). Such studies have shown that administration of light therapy in the morning is more effective than at any other time of the day (see Figure 15.1).

It was noted in the first large controlled trial of the effects of light therapy in SAD (Rosenthal *et al*., 1984) that light therapy is not only an effective treatment for the condition but may also serve as a research tool for exploring further the pathophysiology of the disorder. Since then, the study of the pathophysiology of SAD has been intimately linked to investigations into the mechanisms of action of light therapy. In 1980, Lewy *et al*. demonstrated that melatonin secretion in humans can be suppressed with artificial bright light (Lewy *et al*., 1980). Based on this finding, artificial light was used to treat a patient with winter depression (Lewy *et al*., 1982), subsequently stimulating the first systematic studies on the effects of light therapy in SAD (Rosenthal *et al*., 1985). Light therapy has also been found useful in nonseasonal depression, when combined with other treatment modalities, e.g. sleep deprivation (Neumeister *et al*., 1996) or pharmacotherapy (Kripke, 1998). This

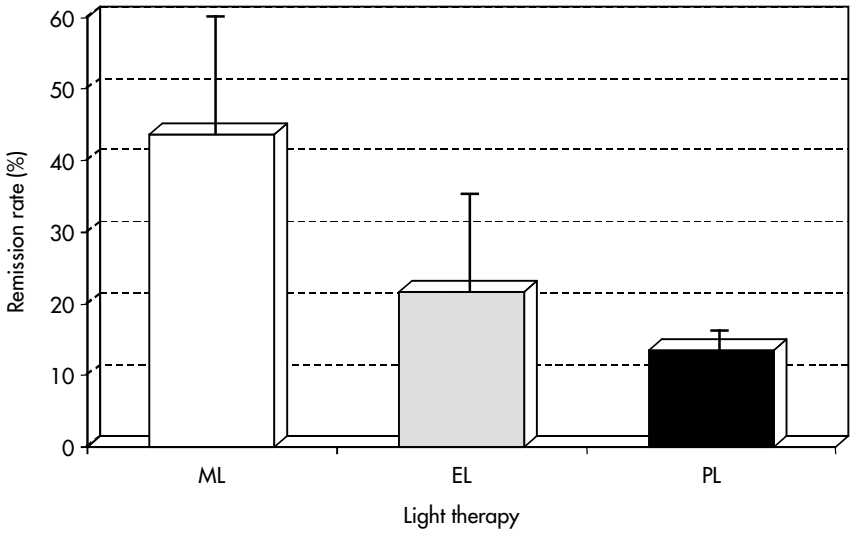

Figure 15.1 Comparison of morning and evening light therapy in the treatment of patients with SAD. The data from three controlled, randomised trials provide evidence for the superiority of morning light therapy (ML) over evening light therapy (EL) and placebo (PL). Data are derived from Terman *et al.* (1998), Eastman *et al.* (1998) and Lewy *et al.* (1998b).

chapter reviews the major biological hypotheses for SAD and light therapy, specifically focusing on circadian rhythms and neurotransmitter function.

15.3 Biological rhythms in SAD

Neurotransmitters have been postulated as playing a key role in the pathogenesis of SAD and also in the mechanisms of action of light therapy. Two neurotransmitter systems have been the main focus of interest during the past decade: serotonin (5-HT) and catecholamines, particularly noradrenaline (norepinephrine). Evidence is published in the literature for the role of each of these; however, it seems likely that the two transmitter systems interact and play important roles, in either different areas or different neurobiological systems of the brain.

15.3.1 Seasonality and brain serotonin function

There is considerable evidence in the literature that there exists a seasonal variation in several phenomena, such as mood and feeding

behaviour, and that these variations may be related to changes in central and peripheral 5-HT function (Maes *et al*., 1995). Changes in 5-HT function have been postulated also to be involved in the pathogenesis of SAD. Thus, it is pertinent to ask whether possible seasonal fluctuations in 5-HT function exist only in SAD patients or whether these fluctuations are also found in healthy controls.

Several studies have described seasonal variations in central and peripheral 5-HT function in healthy subjects and nonpsychiatric patients. Studies in humans can be divided in terms of whether measures are static (e.g. biochemical levels in body fluids or blood elements) or dynamic (e.g. neuroendocrine responses to pharmacological challenges). Several lines of evidence based on static measures support the hypothesis of seasonal fluctuations of 5-HT function in humans.

1. Hypothalamic 5-HT concentrations in human postmortem brain specimens are decreased in winter after values peak in autumn (Carlsson *et al*., 1980).
2. Levels of plasma tryptophan, the precursor of 5-HT, show a bimodal seasonal pattern (Maes *et al*., 1995).
3. Platelet 5-HT uptake and [^{3}H]imipramine binding show a seasonal pattern, albeit with some differences in seasonal peaks and troughs (Arora and Meltzer, 1988; DeMet *et al*., 1989; Tang and Morris, 1985; Whitaker *et al*., 1984).
4. Levels of 5-HT and its metabolites in cerebrospinal fluid show seasonal fluctuations, varying with latitude and population studied (Asberg *et al*., 1980; Brewerton *et al*., 1988).
5. Serum melatonin concentrations demonstrate summer and winter peaks in healthy males (Arendt *et al*., 1977).
6. Neumeister *et al*. (2000) have reported *in vivo* a significantly reduced availability of hypothalamic 5-HT transporter sites in winter compared with summer in healthy female subjects (Figure 15.2).

There are only a few reports in the literature about seasonal variations in 5-HT function using dynamic measures. Joseph-Vanderpool *et al*. (1993) reported a seasonal variation in behavioural responses to the administration of *m*-chlorophenylpiperazine (m-CPP) in patients with SAD, with higher 'activation/euphoria' scores in SAD patients during winter compared with summer or after successful light therapy. More recently, Cappiello *et al*. (1996) demonstrated a seasonal variation in neuroendocrine (prolactin) response to intravenous tryptophan administration in unipolar, nonmelancholic depressed patients. Interestingly,

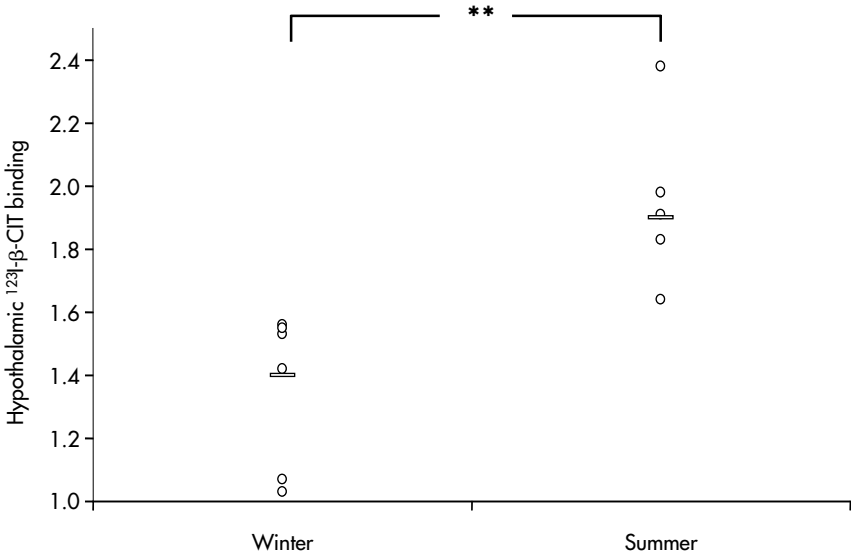

Figure 15.2 Hypothalamic serotonin transporter availability is significantly reduced in winter compared with summer in healthy female controls, as studied *in vivo* using ^{123}I-β-CIT (2β-carbomethoxy-3β-(4-iodophenyl)tropane) single-photon emission computed tomography (SPECT).$^{**}p < 0.01$, Mann-Whitney *U*-test, 2-tailed. Reproduced from Neumeister *et al*. (2000).

seasonality was more pronounced in female than in male patients. No such seasonal variability was found in bipolar, melancholic or psychotic patients or in healthy controls.

It is clear from the above that there is substantial evidence arguing for a seasonal variation of central and peripheral 5-HT function in patients suffering from SAD and also in healthy controls. Thus, it can be hypothesised that seasonality of brain 5-HT function is physiological and may possibly represent a predisposing factor for nonseasonal depression and for seasonal depressions. Interestingly, seasonality was more pronounced in females than in males. However, it has to be acknowledged that this finding is preliminary and requires further study. Also, it has to be said that the variability in the specific seasonal peaks and nadirs reported by different researchers reflects the use of different study designs, methodologies, sample sizes and measures of 5-HT function. Consequently, further studies are needed to clarify the role of seasonal variations in central and peripheral 5-HT function in the regulation of human behaviour and in the pathogenesis of affective disorders, in particular of SAD.

15.3.2 Photoperiod and melatonin secretion

Early epidemiological studies suggested that the prevalence of SAD increases with increasing latitude, where the photoperiod is shorter in winter (Potkin *et al*., 1986; Rosen *et al*., 1990). On the basis of some of these earlier studies it was suggested that symptoms of SAD develop because of the shorter photoperiod (Rosenthal *et al*., 1984). Treatment studies were designed to extend the daily photoperiod by administering light therapy for 3 h per day between 06.00 and 09.00 and between 16.00 to 19.00 (Rosenthal *et al*., 1984). In support of this original hypothesis, the condition of most patients improved. However, subsequent studies have shown that photoperiod extension alone does not explain the therapeutic effects of light (Winton *et al*., 1989). Moreover, it was shown that single daily pulses of light were as effective as the morning plus evening photoperiod extension. Also, more recent epidemiological studies suggest that the association between photoperiod and SAD is smaller than originally suspected (Blazer *et al*., 1998; Mersch *et al*., 1999). The photoperiod hypothesis of SAD has received renewed attention. It has been shown that the nocturnal duration of melatonin secretion reflects changes in the photoperiod of humans (Wehr, 1991). Healthy control subjects in normal living conditions did not show seasonal changes in melatonin profiles, suggesting that artificial indoor light may suppress the melatonin response to seasonal changes in photoperiod (Wehr *et al*., 1995). In contrast, patients with SAD showed a significant seasonal variation in melatonin response to photoperiod, with a longer nocturnal melatonin duration in SAD than in controls. This agrees with findings from a study that used propranolol to block melatonin secretion, showing that truncation of the early-morning melatonin secretion normalises the melatonin profile in patients with SAD (Schlager, 1994). It has also been shown that photoperiod may be important in the onset of the atypical vegetative symptoms that reflect key symptoms in SAD (Young *et al*., 1991, 1997).

The melatonin hypothesis has received substantial attention since it was shown that in many animals the photoperiod signal is mediated by the duration of nocturnal melatonin secretion, that light suppresses melatonin secretion, and that patients with bipolar mood disorders are supersensitive to light (Lewy *et al*., 1985a). The sensitivity of melatonin to light suppression has been shown to depend on light intensity (Bojkowski *et al*., 1987; McIntyre *et al*., 1989b) and timing (McIntyre *et al*., 1989a). Suppression was greater in bipolar disorder relative to normal controls (Lewy *et al*., 1981, 1985a), but no difference

was found between unipolar depressed subjects and healthy controls (Cummings *et al*., 1989). However, no significant differences in 24 h melatonin rhythm were found between SAD patients and controls, and melatonin rhythm was not affected by light therapy (Checkley *et al*., 1993; Partonen *et al*., 1996). The therapeutic effects of light therapy are not explained by suppression of melatonin secretion (Wehr *et al*., 1986). Drugs suppressing melatonin secretion, such as short-acting β-adrenoreceptor antagonists, have been found to be useful in the treatment of SAD (Schlager, 1994), possibly by truncating the early-morning melatonin secretion curve. However, atenolol, a long-acting β-adrenoreceptor antagonist, was not effective in SAD (Rosenthal *et al*., 1988). Thus, it can be speculated that the suppression of melatonin secretion per se is not critical in achieving an antidepressant effects in SAD, but rather that the appropriate time point of melatonin suppression is crucial.

Administration of exogenous melatonin has also been tested for its potential antidepressant effect in SAD. One study, administering 5 mg melatonin, did not show beneficial effects in SAD (Wirtz-Justice *et al*., 1990). Studies that used melatonin in more physiological doses at a specific time of day to induce a circadian phase advance in patients with SAD were found to be effective (Lewy *et al*., 1998a), and it was also shown that the clinical response was correlated with the degree of phase advance.

15.3.3 Circadian phase shift

Several researchers have advanced hypotheses implicating abnormalities of circadian rhythms in the pathophysiology of SAD. Lewy *et al*. (1987b) suggested that patients with SAD have delayed circadian rhythms, whereas Czeisler and Kronauer (Czeisler *et al*., 1987) suggested that the amplitude of the circadian rhythm is reduced in patients with SAD. According to these hypotheses, light therapy exerts its beneficial effects by restoring circadian rhythms to their normal phase position or amplitude.

In humans, the circadian pacemaker can be entrained and phase-shifted by light (Czeisler *et al*., 1986; Minors *et al*., 1991) and by administration of exogenous melatonin (Arendt and Broadway, 1987; Lewy *et al*., 1992; Zaidan *et al*., 1994) or melatonin receptor agonists (Krauchi *et al*., 1997). The timing of light exposure relative to the circadian cycle dictates the direction and magnitude of circadian rhythm phase shifts.

On the basis of work done in patients with nonseasonal depressions (Kripke *et al*., 1978; Wehr *et al*., 1979), researchers have developed a phase-delay hypothesis for SAD (Lewy *et al*., 1985b, 1988). The hypothesis is built on the assumption that SAD results from internal circadian rhythms that are phase-delayed relative to the external clock and to other rhythms, e.g. the sleep–wake cycle, and that light therapy mediates its antidepressant effects by correcting the abnormal phase delay. On this assumption, morning light therapy results in a corrective phase advance, while evening light exposure further phase-delays the circadian phase. Consequently, according to the phase-delay hypothesis, morning light therapy would be expected to be superior to mid-day or evening light therapy. Light therapy in the middle of the day generally has no effect on circadian rhythms, and thus would be presumed to exert no antidepressant effects. Most, but not all, studies support such an assumption, showing the superiority of morning light therapy over mid-day and evening light therapy (for an overview see Neumeister *et al*., 1999). In one study directly comparing morning versus evening light therapy for SAD, the phase position of 6-sulfatoxymelatonin, the urinary metabolite of melatonin, was also assessed, and most patients exhibited a phase delay (Wirtz-Justice *et al*., 1993). However, the phase position did not predict whether a patient would respond better to morning or evening light therapy. Similarly, no association was found between phase advance of nocturnal salivary melatonin secretion and treatment response to light therapy (Rice *et al*., 1995).

One area of interest in circadian rhythms research in SAD involves the time at which melatonin begins to be secreted by the pineal gland during controlled, dim light conditions, called dim light melatonin onset (DLMO). Patients with SAD were found to have phase-delayed DLMO relative to healthy control subjects (Lewy *et al*., 1987a, 1998b; Sack *et al*., 1990). Light therapy induced a phase shift, with morning light exposure resulting in a phase advance and evening light exposure resulting in a phase delay. All studies consistently showed that morning light therapy was more effective than evening light therapy.

Further evidence for abnormal biological rhythms in SAD comes from studies showing delayed melatonin rhythms in SAD (Terman *et al*., 1988). In this study the melatonin cycle phase-advanced with morning light therapy, and also during a combination of morning and evening light therapy. Another parameter that has been shown to be phase-delayed in SAD is the circadian activity–rest cycle (Glod *et al*., 1997); light therapy phase-advanced cortisol, temperature and melatonin, although the sleep–wake cycle also advanced. To control for environmental factors,

such as sleep, light exposure, activity or feeding, researchers used the constant-routine method, in which subjects are studied for 36 h in a controlled setting to unmask endogenous circadian rhythms. Such studies confirmed phase delays of the DLMO, core body temperature and cortisol rhythm (Avery *et al*., 1997; Dahl *et al*., 1993). Light therapy improved depression scores, but the magnitude of changes was not associated with the magnitude of phase advance.

The results of other studies do not agree with these findings and raise the question whether circadian phases are the biological basis of SAD. The 24 h circadian profiles of various hormones, including cortisol, prolactin and thyrotrophin in plasma (Oren *et al*., 1996) and the 24 h core body temperature profile (Rosenthal *et al*., 1990) did not differ between patients with SAD and healthy controls and were not affected by light therapy. Most notably, one study reported significant phase delays of temperature in SAD patients during summer compared with the winter, effects opposite to the phase advances found after light therapy in winter (Levendosky *et al*., 1991). Another study also showed no difference in core body temperature between patients with SAD and controls (Eastman *et al*., 1993). The authors report that morning light therapy advanced the phase of temperature rhythm more in SAD patients than in controls; however, the relation between phase changes and improvement in depression scores was opposite to that predicted by the phase-delay hypothesis.

The interpretation of the findings of these studies is often limited by small sample sizes and by sample selections. It is reasonable to assume that patients with hypersomnia differ from patients with hyposomnia, but both groups of subjects have been studied together in the past. Another factor that has to be considered is that group mean data do not necessarily represent individual circadian responses. The magnitude of light-induced phase shifts may vary considerably between subjects. Terman *et al*. (1988) found no relation between clinical response to light therapy and whether patients were initially phase-delayed or phase-advanced (as measured by DLMO). However, the magnitude of individual phase advances was significantly correlated with the degree of clinical improvement (Terman *et al*., 2001). It has also to be considered that any correlation between clinical response to light therapy and phase advance does not necessarily mean that they are causally related. Other factors associated with morning light therapy, such as better compliance with the treatment or greater sensitivity to light, may affect the outcome. However, these assumptions require further study.

15.4 Conclusion

In summary, studies using the most reliable measures of endogenous circadian phase, such as DLMO or constant routine, provide substantial evidence for circadian phase delays in SAD. Such an assumption is supported by the evidence for the superiority of morning light therapy over evening or mid-day light therapy. There is also evidence that the clinical response to light therapy and melatonin is related to the degree of corrective phase advances, although these findings do not necessarily reflect causality. However, it has also been shown that a subgroup of patients with SAD do not show abnormal phase-delayed circadian rhythms nor do they exhibit phase shifts of their biological rhythms in response to light but they still respond to light therapy with clinical improvement. This indicates that mechanisms other than circadian phase abnormalities play a role in the pathophysiology of SAD and the mechanisms of light therapy.

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