Pathophysiology of seasonal affective disorder: a review

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The study of the pathophysiology of seasonal affective disorder (SAD, also known as winter depression) has historically been intimately linked to investigations into the mechanisms of action of light therapy. This paper reviews the studies on the pathophysiology of SAD with emphasis on circadian, neurotransmitter, and genetic hypotheses. There is substantial evidence for circadian phase shift and serotonergic hypotheses, but conflicting results may indicate that SAD is a biologically heterogeneous condition. Recent progress in defining the molecular mechanisms of the human circadian clock and retinal phototransduction of light will provide important new directions for future studies of the etiology and pathophysiology of SAD.

L'étude de la pathophysiologie du trouble affectif saisonnier (TAS) (aussi appelé dépression hivernale) a toujours été reliée intimement aux études sur les modes d'action de la photothérapie. Dans ce document, les auteurs passent en revue des études réalisées sur la pathophysiologie du TAS et mettent l'accent sur des hypothèses reliées au rythme circadien, aux neurotransmetteurs et à la génétique. D'importantes données probantes appuient les hypothèses relatives au déphasage du rythme circadien et à la dépression sérotoninergique, mais les résultats contradictoires peuvent indiquer que le TAS est un problème hétérogène sur le plan biologique. Les progrès réalisés récemment dans la définition des mécanismes moléculaires de l'horloge biologique humaine et de la phototransduction rétinienne de la lumière établiront d'importantes orientations nouvelles pour des études à venir sur l'étiologie et la pathophysiologie du TAS.

Seasonal affective disorder (SAD), or recurrent winter depression,[1] is considered a clinical subtype of major depression. The criteria for "winter seasonal pattern" in the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, which are similar to other definitions of SAD, specify a recurrent pattern of major depressive episodes during winter and remission of symptoms during summer, in the absence of seasonal psychosocial stressors. Using these criteria, the prevalence of SAD has been estimated at less than 1% in the US[2] and at 1% to 3% in Canada.[3] Much of the interest in SAD has been sparked by its response to exposure to bright, artificial light, known as light therapy or phototherapy. Clinical consensus guidelines have recommended light therapy as a first-line treatment for SAD,[4] based on the evidence of numerous studies showing efficacy, including large

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randomized controlled trials[5,6] and meta-analyses.[7,8]

SAD and light therapy were identified from basic studies of circadian and seasonal rhythms in animals. Kripke et al[9,10] had proposed circadian-rhythm hypotheses for nonseasonal depression and first published reports showing that bright light exposure could improve mood in patients with depression. Many seasonal rhythms are mediated through changes in melatonin, a neurohormone secreted by the pineal gland during the subjective night. Melatonin secretion is controlled by the endogenous circadian clock, but it can also be suppressed by exposure to light. In 1980, Lewy et al[11] demonstrated that melatonin suppression required brighter light in humans than in animals. This finding led to the use of bright light in the treatment of a patient with winter depression[12] and to the first systematic studies involving patients with SAD.[13] Thus, the theories of the pathophysiology of SAD are intimately tied to the mechanisms of light therapy. This paper reviews the major biological hypotheses for SAD and light therapy, focusing on circadian rhythms, neurotransmitter function, and genetics, and defines important future directions for research.

Circadian rhythms in SAD

Photoperiod and melatonin

One of first hypotheses about SAD was that the shorter winter photoperiod (light–dark cycle) led to depressive symptoms.[1] This seemed consistent with early studies showing that the prevalence of SAD increases with more northerly latitude, where the photoperiod is shorter in winter.[14,15] Therefore, bright light exposure at the beginning and end of the winter day should simulate a summer photoperiod and restore summer behaviours. The first light therapy studies in SAD used 3 hours of light exposure given at 6:00 am to 9:00 am and 4:00 pm to 7 pm.[1] This photoperiod extension method led to significant improvement. However, subsequent treatment studies showed that photoperiod extension alone was not effective for SAD,[16] and that single daily pulses of light were as effective as the morning plus evening pulses of photoperiod extension (summarized by Terman et al[7]). Subsequent prevalence studies of SAD showed little or no effect of latitude,[2,3] indicating that the correlation between photoperiod and SAD is smaller than previously believed.[17]

Attention also focused on a melatonin hypothesis for SAD because, in many animals, the photoperiod signal is mediated by the duration of nocturnal melatonin secretion, and light suppresses melatonin secretion. However, the 24-hour melatonin rhythm in winter was no different between SAD patients and controls, and did not change with light treatment.[18,19] Melatonin suppression alone is also not enough to produce a therapeutic response.[20] Atenolol, a long-acting β-blocker that suppresses melatonin secretion, was not effective for SAD.[21] However, a study using a short-acting β-blocker, propranolol, to truncate the melatonin secretion curve in the early morning (an effect similar to that of morning bright light exposure) found beneficial effects for SAD.[22]

Melatonin has also been investigated as a treatment for SAD. In one study, a 5-mg dose of melatonin, given in the morning or the evening, was not effective against SAD.[23] In contrast, studies of melatonin given in smaller, more physiological doses at a specific time to produce a circadian phase-shift in patients found evidence of effectiveness (see next section).[24]

Recent studies, however, have revived the photoperiod hypothesis. The nocturnal duration of melatonin secretion reflects changes in the photoperiod in humans.[25] In normal subjects in naturalistic living conditions, no changes in melatonin profiles were found between summer and winter, suggesting that artificial indoor light may suppress the melatonin response to seasonal changes in photoperiod.[26] In a study comparing patients with SAD with normal controls, only those with SAD had a significant seasonal variation in their dim-light nocturnal melatonin profile. This finding suggests that the patients with SAD, but not the control subjects, respond to seasonal photoperiodic signals (T.A. Wehr: personal communication, February 2000). A longer nocturnal melatonin duration in SAD is consistent with the findings from the propranolol treatment study,[22] because the truncation of the early-morning melatonin secretion would "normalize" the melatonin profile. Photoperiod may also be more important in the onset of the vegetative symptoms found in SAD.[27,28] These findings suggest that the photoperiod hypothesis is worth pursuing.

Circadian phase shift

Light is the most potent zeitgeber (synchronizer) of the circadian pacemaker, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and bright light exposure can reliably shift the phase of the circadian

rhythm in humans. The timing of light exposure relative to the circadian cycle dictates the direction and magnitude of circadian rhythm phase shifts. Building on circadian and phase-advance hypotheses for nonseasonal depression,[9,29,30] Lewy et al[31,32] proposed a phase-delay hypothesis for SAD. Their theory is that SAD results from internal circadian rhythms that are phase-delayed relative to the external clock or to other rhythms such as the sleep–wake cycle, and that light therapy exerts its therapeutic effect by correcting the abnormal phase delay. In a phase-delay hypothesis, morning light therapy is predicted to be superior to evening light because morning light exposure results in a corrective phase-advance, while evening light exposure should further delay the circadian phase. Light exposure in the middle of the day generally has no effect on circadian rhythms, and hence should have no therapeutic effect.

Initial studies used the dim-light melatonin onset (DLMO, the time that melatonin begins to be secreted by the pineal gland during controlled, dim-light conditions) as a marker of circadian phase because it is relatively free of masking effects. Patients with SAD were found to have phase-delayed DLMO compared with control subjects; furthermore, morning light exposure resulted in phase advances, while evening light exposure resulted in phase delays, and only the morning exposure led to clinical improvement.[33] A subsequent study found only a trend to phase-delayed DLMO in the patients with SAD at baseline, but greater phase advances with morning light exposure in the patients with SAD than in the controls.[34] Again, morning light exposure was superior to evening light (which did not result in significant phase-delays relative to baseline in the patients with SAD) in the therapeutic response. A larger study of morning versus evening bright-light exposure (51 patients with SAD and 49 controls) confirmed that morning light therapy was superior to evening light.[35] However, the DLMO was significantly delayed relative to controls in only 2 of 3 time points (pre-baseline and withdrawal), but not at baseline.

Another study found that patients with SAD had significantly delayed melatonin rhythms, and the melatonin cycle phase advanced with both morning light alone and morning light in combination with evening light.[36] Morning bright light also significantly phase-advanced cortisol, temperature, and melatonin rhythms in patients with SAD, although the sleep–wake cycle also advanced.[37] The circadian activity–rest cycle was also found to be significantly delayed in patients with SAD.[38]

The study of circadian rhythms is complicated by masking effects of environmental factors, including sleep, light exposure, activity, feeding, etc. One method to control for these factors is the "constant routine" technique, in which subjects are studied for 36 hours in a controlled setting to unmask endogenous circadian rhythms. In a constant routine study of 6 patients with SAD compared with 6 control subjects, the patients with SAD had phase delays of the DLMO, core temperature rhythm and cortisol rhythm.[39,40] Light therapy advanced the circadian rhythms in the patients with SAD, but improvement in depression scores was not correlated with the magnitude of the phase advance.

The phase-shift hypothesis predicts that other stimuli that affect phase, e.g., medications or sleep changes, would also be effective for SAD. Preliminary studies indicate that low-dose melatonin, when appropriately timed to achieve a circadian phase advance, has therapeutic effects in SAD,[24] and that clinical response is correlated to the degree of phase advance.[41]

Other studies, however, have not supported circadian phase abnormalities in SAD. The circadian rhythm of core body temperature was no more phase-delayed in patients with SAD than in normal controls.[42] Although morning light exposure advanced the phase of temperature rhythm more in the patients than in controls, the relation between phase changes and improvement in depression was opposite to that predicted by the phase-delay hypothesis. No phase differences between patients with SAD and controls were found in the 24-hour core body temperature profile before and after light therapy in winter.[43] Both groups had significant phase-delays of temperature in the summer compared with the winter, effects opposite to the phase-advances found after light therapy in the winter.[44] The 24-hour circadian profiles of various hormones in plasma, including cortisol, prolactin and thyrotropin, did not differ between patients with SAD and control subjects before and after light therapy.[45]

In the phase-delay hypothesis, evening or mid-day light exposure should not have significant antidepressant effects in SAD. Although morning light is usually statistically superior to evening light in controlled comparisons[6,35] and in most[7,46] but not all[47] meta-analyses, there are large individual studies showing that evening light is more effective than placebo[6] and as effective as morning light.[5,48] In a morning–evening comparison study, the phase position of 6-sulphatoxymelatonin, the

urinary metabolite of melatonin, was also determined, and most patients with SAD showed evidence of phase-delay.[48] However, the phase position did not predict preferential response to morning or evening timing of light therapy. Similarly, a phase advance of nocturnal salivary melatonin secretion was not associated with response to light therapy.[49]

In a constant routine study of female patients with SAD and controls, no phase changes were found in most parameters of core body temperature, but mid-day light exposure did result in some phase advances of the temperature rhythm.[50] However, no differences were found in melatonin onset or duration (by salivary melatonin assay), either between groups or before and after light treatment.

The conflicting results from these circadian studies are likely due to several factors. Most studies have small sample sizes, so that the study populations may not be comparable. For example, some studies specifically selected hypersomnic patients, who may be more likely to show phase-delayed circadian rhythms; although the majority of patients with SAD display hypersomnia, they still may not be representative of all patients with SAD. Ambulatory measurements of core body temperature may not be indicative of endogenous circadian rhythms because of the masking effect of environmental factors such as sleep and activity, whereas the constant routine studies control for those factors. Similarly, 24-hour sampling of melatonin rhythms can be masked by external light exposure. Most light therapy studies are done in ambulatory patients over a week or two; hence, nonphotic zeitgebers (e.g., activity, social cues) may confound the circadian effects of bright light exposure.

Another confounding factor is that group mean data may not represent individual circadian responses. For example, light exposure at a constant clock time (as given in most light treatment studies) may vary according to individual circadian time through a range of 5 hours.[51] This means that the magnitude of light-induced phase shift varies considerably for an individual patient. In a study of morning versus evening light in SAD, Terman et al[51] found that there was no relation between clinical response and whether patients had a phase advance or a phase delay (as measured by DLMO). However, the magnitude of individual phase advances was significantly correlated with the degree of clinical improvement.[52] Hence, studies that do not include measurements of individual circadian phase may be prone to negative findings.

It should also be noted that any positive relation between clinical response and phase-advance does not necessarily mean that they are causally related. Other factors that affect morning light exposure (sitting closer to the light, better compliance with light exposure, greater retinal sensitivity to light) may lead to greater improvement and greater phase advance, even if phase advance had nothing to do with the treatment response. A more rigorous test of the phase-delay hypothesis would be to reverse or prevent the therapeutic effect of morning light therapy, which presumably works through a corrective phase advance, by providing melatonin at a circadian time that produces a counteractive phase delay.

In summary, studies involving the most reliable measures of endogenous circadian phase (using DLMO or constant routine) have shown evidence for circadian phase delays in SAD. There is also some evidence that clinical response to light therapy and melatonin is related to the degree of corrective phase advances, although these findings do not necessarily imply causality. However, there remains a subset of patients with SAD who do not have demonstrable phase-delayed circadian rhythms or who do not require a phase shift for response to light therapy or both. Hence, circadian mechanisms may not be the only explanation for SAD.

Neurotransmitter function in SAD

In reviewing the contributions of individual neurotransmitter systems to SAD, several methodological issues must be considered. The major monoamine transmitters implicated in mood disorders (i.e., serotonin, dopamine and norepinephrine) are functionally linked at many levels, making it unlikely that an isolated abnormality in a single transmitter system is responsible for a given disorder. Related to this, while abnormal results on a variety of challenge tests have been found in SAD and other psychiatric disorders, it is not known whether the observed abnormalities are mediated at the transmitter system under investigation, or proximally or distally to it. It must also be considered that, in humans, certain neurotransmitters are more easily investigated than are others; for example, the risk of inducing psychosis or addiction greatly limits our ability to directly examine the dopamine system in patients. Hence, there is much more data available for the serotonin system than for the dopamine system in the literature on depression.

Notwithstanding these limitations, there is considerable evidence from converging areas of research pointing to a major role of monoamine neurotransmitter systems in the pathophysiology of SAD.

Serotonin

While there has been an explosion of research on serotonergic functioning in all mood disorders over the past decade, there is a unique rationale for hypothesizing that serotonergic dysfunction plays a major role in SAD in particular. In animals and normal humans, various measures of serotonin (5-hydroxytryptamine, 5-HT) activity fluctuate markedly across the seasons. The serotonin content in the hypothalamus in human post mortem samples has a marked seasonal variation, with the lowest levels found during the winter months of December and January.[53] Given the role of hypothalamic serotonin in satiety and feeding regulation, this could explain the tendency of patients with SAD to crave carbohydrates and gain weight during winter depressive episodes. 5-HIAA is the major metabolite of serotonin, and cerebrospinal fluid (CSF) 5-HIAA levels are derived from several factors, including serotonin synthesis and turnover, the firing rate of serotonin neurons, and the acid transport system responsible for 5-HIAA excretion. The finding of low CSF 5-HIAA levels in springtime is relatively robust,[54,55] and may (or may not) reflect the cumulative effect of low brain serotonergic activity over the winter. Seasonal fluctuations in other monoamine metabolites have been described as well, but the magnitude of these changes is greatest for the serotonin system.[54]

L-tryptophan is the amino acid precursor of serotonin, and various measures of tryptophan metabolism and availability have been compared across seasons. In a longitudinal study that measured free and total tryptophan levels in normal controls, the highest levels were found in April and May, whereas levels dipped significantly in the late summer/early fall.[56] Another study also found higher plasma levels of free tryptophan in the spring, with lower levels in both the early summer and winter periods.[57] These findings were not simply attributable to dietary fluctuations; however, their overall significance remains unclear in that several other factors, such as protein intake, influence the degree to which plasma tryptophan crosses the blood–brain barrier. Furthermore, the fact that tryptophan levels are highest when 5-HIAA levels are lowest is difficult to rationalize using a singular model of serotonin activity.

Patients with SAD report increased activation following high-carbohydrate meals, whereas normal controls feel more sedated;[58] this may be consistent with altered tryptophan and serotonin metabolism in patients with SAD, since dietary carbohydrates are believed to enhance serotonin synthesis and transmission via increased tryptophan uptake into the brain.[59,60]

In more recent studies, a tryptophan depletion protocol has been used to examine a possible vulnerability factor for SAD related to the serotonergic system. Plasma tryptophan levels can be reduced to 20% of normal within 5 hours by administering an oral tryptophan-free mixture of large, neutral amino-acids.[61] Positron-emission tomographic studies have shown that serotonin synthesis is reduced markedly in response to this depletion protocol.[62] Two separate studies have shown that patients with SAD in remission after light therapy experience a clear relapse of depressive symptoms with tryptophan depletion.[63,64] In the latter study, "atypical" symptoms such as carbohydrate craving were especially sensitive to the depletion protocol, suggesting an important role for serotonergic mediation of this symptom cluster in particular. These results also point to a serotonergic mechanism for light therapy in SAD. The effects of tryptophan depletion during summer remission, however, are less consistent: one report showed relapse,[65] while another did not.[66] Taken as a whole, tryptophan-depletion studies offer significant evidence that serotonin plays a role in SAD. However, the fact that patients with nonseasonal depression also show sensitivity to tryptophan depletion[67] calls into question the specificity of these results to SAD.

Another line of research has studied tryptophan as a potential treatment for SAD. Two studies compared light therapy with tryptophan in a repeated-measures crossover design, finding similar efficacy for the 2 treatments.[68,69] There was some evidence that relapse after withdrawal from treatment was slower following tryptophan discontinuation.[69] In one sample of patients with SAD that was either partially or completely nonresponsive to light therapy, adding tryptophan (3 g per day) produced a robust response in nine of 14 patients (64%).[70] Given the role of tryptophan in brain serotonin activity, these results support the hypothesis that serotonin plays a role in the pathophysiological features of SAD.

Other medications that enhance serotonin function by different mechanisms also have beneficial effects in SAD. D-fenfluramine, a serotonin-releasing medication, was found to be effective in small double-blind con-

trolled studies.[71] Larger studies indicate that the serotonin reuptake inhibitors fluoxetine[72] and sertraline[73] are effective in SAD.

Neuroendocrine studies of SAD have shown relatively robust findings to date. Serotonergic neurons play an intrinsic role in release of prolactin, growth hormone, corticotropin (ACTH) and cortisol and are likely to play a role in mediating subjective responses to serotonergic agonists. Studies found abnormal responses to the non-selective 5-HT agonists 5-hydroxytryptophan[74] and D,L-fenfluramine,[75] although an earlier study with D,L-fenfluramine was negative.[76] Double-blind, placebo-controlled studies indicate that, compared with normal controls, patients with SAD had blunted hormonal responses, and experienced increased subjective activation/euphoria responses, following administration of the postsynaptic 5-HT_{2C} agonist m-chlorophenylpiperazine (m-CPP),[77,78] thereby confirming results from previous non-placebo-controlled studies.[79–81] There was a normalization of the subjective responses following successful light therapy, suggesting that activation/euphoria in response to a post-synaptic serotonergic agent may be a state marker for winter depression, mediated by an alteration in the sensitivity of post-synaptic serotonin receptors.[77] These various findings may be relatively specific for SAD, in that patients with major depression do not show altered responses to m-CPP challenge.[82] m-CPP also has some affinity for other receptors, including 5-HT_{1A} and 5-HT_7; however, no behavioural or neuroendocrine effects were found in a challenge study with ipsapirone, a selective 5-HT_{1A} receptor agonist.[83] Blunted growth hormone responses to the 5-HT_{1D} agonist sumatriptan were also reported in SAD, with normalization after light therapy.[84]

In summary, there are consistent, replicated studies of abnormal neuroendocrine and behavioural responses to serotonergic agents that indicate dysfunction at, or downstream to, 5-HT receptors in SAD. Most of the evidence implicates 5-HT_{2C} or 5-HT_7 receptors, although other receptors such as 5-HT_{1D} may be involved.

Norepinephrine

To determine whether serotonin dysfunction alone can explain the pathophysiology of SAD, Neumeister et al[85] administered both tryptophan depletion and catecholamine depletion protocols, in random order, to patients with SAD in remission after light therapy. Sham depletions were also included in the protocol. Both active depletions caused a temporary relapse of depressive symptoms, demonstrating that catecholamines, in addition to serotonin, likely play a role in SAD.

Clinically, patients with SAD frequently present with core symptoms of hypersomnia and increased eating, in contrast to patients with classic melancholic depression, who exhibit insomnia and weight loss when depressed. One possible interpretation of this difference is that patients with SAD are in a state of central hypo-arousal, while those with melancholic depression are in a state of central hyper-arousal. Several research findings are consistent with this hypothesis. Untreated patients with SAD tended to have lower baseline norepinephrine concentrations than normal controls, and than after light treatment.[77] In this same study, patients with SAD had blunted norepinephrine responses to the serotonin and α_2-noradrenergic agonist m-CPP, both with and without light therapy treatment. Other studies have found an increase in both plasma norepinephrine levels[86] and in turnover of norepinephrine[87] following light therapy. An inverse relation between resting cerebrospinal fluid levels of norepinephrine metabolites and depression scores in patients with SAD has also been reported.[88]

These various lines of evidence may be consistent with decreased basal sympathetic tone or decreased activation of norepinephrine-associated arousal systems in patients with SAD. More work is needed to confirm and extend these preliminary findings, and to determine which components of the norepinephrine system may play a role in the clinical features of SAD.

Dopamine

Few studies have directly examined dopamine functioning in patients with SAD; however, several lines of indirect evidence point to dopaminergic involvement in this disorder. Low resting prolactin levels have been interpreted as reflecting low functional activity of dopamine, with compensatory up-regulation of D_2 receptors, in patients with SAD.[89,90] This decrease was evident across seasons and was unaffected by subtype of depression (bipolar II versus unipolar) , suggesting that it may be a trait marker for the disorder.[90] This same group has found decreased eye blink rates, which may reflect low dopamine activity, in subjects with SAD,[91] although other groups have not replicated this finding.[92] Additional evidence for dopamine dysfunction in SAD comes from studies that have examined thermoregula-

tory heat loss. Compared with controls, patients with SAD exhibit blunted thermoregulatory heat loss in the winter, a finding that normalized after light therapy, and in the euthymic summer state.[93,94] Both light treatment and summer may facilitate central dopamine functioning and normalize thermoregulatory heat loss in patients with SAD.

Dopamine is the major retinal transmitter involved in the light response. Oren[95] has speculated that light therapy might work in SAD by stimulating the production of retinal dopamine. There is some evidence from retinal electrophysiological studies for subtle reductions in retinal light sensitivity, which can be reversed with light therapy, in patients with SAD compared with controls.[96–99] In contrast, another study using a dark adaptation threshold procedure has shown supersensitivity to light in winter in patients with SAD compared with control subjects.[100] Still other studies using different electrophysiological methods have not found changes in retinal or ophthalmic function.[101,102] Hence, there is not yet consistent evidence of retinal dopamine or other retinal dysfunction in SAD.

Furthermore, a treatment test of the dopamine hypothesis, via a double-blind, placebo-controlled trial of L-dopa combined with carbidopa, found no significant response overall in SAD.[103] Of note, however, was that premenopausal women showed the greatest responses to L-dopa in this study, consistent with findings in past studies that premenopausal women were also more likely to show abnormalities in dopamine function.

It has recently been reported that adults with residual attention-deficit disorder, particularly women with impulsive characteristics, have very high seasonality scores.[104] One of the classic models of attention-deficit disorder proposes that, in particular, the impulsive subtype of this disorder is mediated by a state of central under-arousal; this would explain the robust therapeutic effects of psychostimulants (primarily dopaminergic drugs) in attention-deficit disorder.[105] It has also been speculated that the core symptoms of SAD may reflect a state of low central arousal.[106] It is thus interesting to speculate whether patients with "seasonal" attention-deficit disorder might be in a state of chronic under-arousal mediated by low dopamine activity, compounded by light-deprivation and a further decrease in dopamine activity in the fall/winter months. Interestingly, recent neuroimaging studies have found global decreases in cerebral metabolism in both attention-deficit disorder[107] and in SAD[108] that are consistent with such a model.

Genetics in SAD

There is emerging evidence that one or more genetic factors establish vulnerability to, or protection from, seasonality and SAD. One line of study has sought to determine whether genetic selection within the Icelandic population over centuries might have played a role in their adaptation to the long arctic winter.[109,110] These authors studied rates of seasonal depression in native Icelanders and in a group of adults in Manitoba, Canada, who were wholly descended from Icelandic emigrants. Both native Icelanders and emigrated Icelandic descendants were found to have much lower rates of SAD than populations along the east coast of the US, despite living at more northerly latitudes. This is consistent with a genetic model of seasonality and suggests possible genetic protective factors in the Icelandic population.

The largest study of possible genetic factors in SAD used univariate and multivariate genetic analysis of 4639 adult twin pairs from a volunteer-based registry in Australia.[111] Genetic effects accounted for 29% of the variance in seasonality (as assessed using a self-report questionnaire) in this nonclinical sample. Overall, genetic predisposition to seasonality was associated with so-called "atypical" vegetative symptoms of depression, such as increased food intake, weight gain and increased sleep, compatible with treatment studies showing these symptoms to be the best predictors of a good response to light therapy.[112,113]

Sex factors have been studied in the relative importance of genetic versus environmental influences in seasonal mood change. Using a seasonality questionnaire in 339 twin pairs, one study found that genetics accounted for 69% of the variance in seasonality scores in men and 45% in women.[114] Changes in sleep patterns, social activity, mood, appetite and energy were accounted for primarily by additive genetic effects in both sexes, although genotype analyses suggested that the genetic factors mediating seasonality in men may be different from those in women.

From a genetic point of view, mood disorders such as SAD are best thought of as complex phenotypes or "spectrum" disorders. Traditional family-linkage studies, which follow the segregation of marker alleles in multiplex pedigrees with several affected members, are

of limited value when studying complex traits. Genetic association studies test whether polymorphic DNA markers in candidate genes contribute to the disease phenotype, and are more suited to genetic studies of complex disorders such as SAD.

Genetic association studies of SAD have begun to emerge. An association between the short allele of the serotonin transporter promoter gene and the trait of seasonality was reported in a sample of 97 patients with SAD and 71 controls.[115] In a similar study, an association was found between SAD (but not seasonality *per se*) and the 5-HT_{2a} promoter polymorphism –1438G/A.[116] An association between the 218C allele of tryptophan hydroxylase and SAD in a small sample of female patients with increased eating behaviour was also found.[117] In contrast, Ozaki et al reported a lack of association between SAD and naturally occurring amino acid polymorphisms of the serotonin 5-HT_{2A} gene[118] and other 5-HT receptor candidate genes.[119]

Overall, while this early work has been encouraging, each of these studies must be considered preliminary and needs to be replicated in much larger samples before firmer conclusions can be drawn. Nuclear family controls, as opposed to population-based controls, will also be needed to avoid false-positive findings attributable to population stratification effects.

Future directions

Important progress has been made in defining the pathophysiological mechanisms in SAD and the mode of action of light therapy. However, the conflicting results of studies indicate that there is likely substantial heterogeneity in the etiology and pathophysiology of SAD. This may be due in part to diagnostic issues. There is increasing evidence that seasonality, as a dimensional factor, is a more valid construct than the DSM-IV diagnosis of SAD/seasonal pattern.[120] A dual-vulnerability hypothesis, in which SAD results from separate seasonality and depression factors (each of which may have different pathophysiological mechanisms), has been proposed to explain the heterogeneity found in SAD studies.[27,121]

The major hypotheses proposed for SAD include phase-shifted circadian rhythms, serotonergic dysfunction, and genetic vulnerability. It should be recognized, however, that these hypotheses may not be mutually exclusive. Recent findings have highlighted important relations between serotonin and circadian rhythms. Direct and indirect serotonergic projections from the midbrain raphe nuclei are involved in the nonphotic signalling to the SCN,[122] and 5-HT agonists can modulate photic responses of SCN cells.[123] Systemic administration of 5-HT agonists may also shift circadian rhythms,[124] but these effects may occur at the level of the raphe nuclei and may be mediated by other neurotransmitters (such as γ-aminobutyric acid) in the SCN.[125] Serotonergic pathways are also likely involved in SCN projections to effector systems, including the hypothalamus, where regulation of neuroendocrine and sleep–wake functions occur. Further studies to link serotonergic dysfunction with dysregulated circadian rhythms in SAD will likely be informative.

What will also shape future studies of the circadian basis for SAD are results from recent intense and remarkable research activity into the molecular mechanisms of circadian regulation, including the identification of the first mammalian clock genes *clock*, *per* and *tim*.[126–128] There are already preliminary indications that alterations in these genes affect human circadian rhythms. For example, a polymorphism of the human *clock* gene is associated with diurnal preference as measured by a morning-eveningness questionnaire.[129] Similar genetic association studies will be important in SAD. Other recent findings suggest that there is a dedicated retinal pathway for circadian signalling that is separate from the visual pathways, and that the ocular photoreceptors of this circadian pathway do not involve rod or cone cells.[130] Cryptochromes, which are photoactive protein pigments in the mammalian retina, are potential candidates for the circadian photoreceptive component.[131,132] Although it now appears that cryptochromes have a more complex role in regulation of circadian rhythm,[133,134] and they are likely not the only photopigments involved in processing the light signal,[135] cryptochromes will likely be another fruitful area for SAD and circadian research.

In an elegant closing of the circle, basic studies of mammalian circadian rhythms gave rise to the study of SAD and light therapy; a decade and a half later, basic molecular science will offer sophisticated new circadian hypotheses to be tested. However, attention should also focus on the noncircadian effects of bright light. Further study of noncircadian effects is particularly important, since light therapy is being investigated for other psychiatric disorders that may not involve circadian mechanisms, including nonseasonal depression,[136] premenstrual depressive disorder[137] and bulimia nervosa.[138,139]

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