Commentary

Aetiology and pathogenesis of mood disorders

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Introduction

Seasonal affective disorder (SAD) was originally described as a syndrome in which depression developed during autumn or winter and remitted the following spring or summer.\(^1,2\) Since then two subtypes of SAD have been defined in the scientific literature: winter SAD and summer SAD, the former being by far the more frequent.\(^2,3\) Most winter SAD patients have ‘atypical’ depressive symptoms such as increased sleep duration, increased appetite and weight, and carbohydrate craving. Patients with winter SAD may experience a reversal of their winter symptoms in summer: mild hypomania, elevated mood, increased libido, social activity and energy, and decreased sleep requirements, appetite and weight. Seasonality, the tendency to experience seasonal changes in mood and behaviour, can be viewed as a dimension, ranging from those who show no seasonal changes to those who show more extreme changes with the seasons. Seasonal changes of mood and behaviour are common throughout the population.\(^4–6\) A survey in the Washington area found that approximately 4% of the population have winter SAD and over 10% more have subsyndromal winter SAD.\(^6\) Some 27% of respondents reported that changes with the seasons were a problem for them. Another survey, in New York City, indicated approximately 6% with potential clinical severity, 18% reporting milder symptoms that were bothersome, and 35% noting symptoms but without complaint.\(^6\) Thus, many people experience mild analogues of winter SAD. A considerable number of studies by researchers around the world have demonstrated that light therapy (daily scheduled exposure to artificial light) is an effective treatment for winter SAD.\(^1,6–10\)

Circadian rhythms, SAD, and non-seasonal mood disorders

An internal pacemaker that matches internal rhythms to the 24-h day drives circadian rhythms.\(^9–13\) In humans, the master circadian pacemaker is the bilaterally paired suprachiasmatic nuclei (SCN) in the anterior hypothalamus. The SCN is composed of multiple single-cell oscillators that must synchronize to each other and the environmental light schedule. Consistent with their circadian function, these cells rhythmically release certain neurochemical substances, such as brain-derived neurotropic factor (BDNF) and arginine vasopressin. These neurochemical substances, in turn, may act on different brain regions or peripheral organs, generating different circadian rhythms.

Several lines of evidence suggest that abnormalities in circadian rhythms are involved in the aetiology/pathogenesis of winter SAD. The photoperiod hypothesis of winter SAD suggests that elongation of the light part of the day-night cycle is the means by which light treatment improves winter SAD.\(^7,9,10,14,15\) This hypothesis has been proposed because winter SAD usually begins in the autumn, when the photoperiod is diminishing in time, and because the first successful treatments of patients...
with winter SAD were performed by extending the photoperiod. Early studies supported this hypothesis, finding a correlation between higher prevalence of winter SAD with higher latitudes, where the photoperiod is shorter in winter. More recent prevalence studies of winter SAD demonstrated little effect of latitude. However, it is important to note that genetic vulnerability may influence the prevalence of SAD.

Changes in the duration of melatonin secretion controlled by the length of the day are triggers for seasonal changes in behaviour in mammals. Considerable evidence suggests that duration of melatonin secretion may be the signal for seasonal changes in mood and behaviour in humans. In healthy individuals 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. However, a recent study has demonstrated that patients with winter SAD generate a biological signal of change in season that is absent in healthy volunteers. Patients with winter SAD had a significant seasonal variation in their dim-light nocturnal melatonin profile: the duration of the nocturnal period of active melatonin secretion was longer in winter than in summer. A longer nocturnal melatonin duration in winter SAD is consistent with the finding that the short-acting β-blocker propranolol, which truncates the melatonin secretion curve in the early morning (an effect similar to that of morning bright light exposure), has beneficial effects in winter SAD. The balance of evidence is in favour of the hypothesis that photoperiod changes influence the onset and clinical course of winter SAD.

The phase-shift hypothesis of winter SAD is another aetiological hypothesis. ‘Phase shifting’ refers to advancing rhythms (the internal cycle shifts to an earlier clock time) or delaying rhythms (the internal cycle shifts to a later clock time). The phase shift, or phase-delay, hypothesis postulates that some components of circadian rhythms are phase delayed relative to sleep in winter depression. Several studies have demonstrated evidence of phase delay in several rhythms in winter SAD patients. The observation that morning exposure to bright light was more effective than afternoon or evening exposure in winter SAD has been the main argument for the phase-delay shift hypothesis for winter SAD. However, some studies have not supported circadian phase abnormalities in winter SAD. For example, the 24-h circadian profiles of different hormones in plasma, including cortisol, prolactin, and thyroid-stimulating hormone, did not differ between patients with winter SAD and control subjects before and after light therapy.

Some scientists have suggested that the pathophysiology of winter SAD is related to the strength or precision of circadian rhythms. Czeisler et al. suggested that weaker circadian rhythms during the winter might induce weaker rhythms and induce depression in vulnerable individuals. The authors proposed that light therapy for winter SAD might act by increasing an abnormally low circadian amplitude in patients with SAD. Teicher et al. showed that circadian rhythms were not only phase-delayed in winter SAD, but also poorly entrained to the 24-h day. Interdaily stability, an index of coupling between the circadian rhythm and its zeitgeber, was reduced in winter SAD. Compared with controls, patients with winter SAD had best-fit circadian periods that were significantly more deviated from 24 h, and daily acrophase (time of the peak of the fit circadian rhythm) times that were significantly more variable between days. Thompson et al. suggested that instability of circadian rhythms in winter SAD was due to a high-amplitude phase-response curve, rather than a fixed phase abnormality.

The endogenous circadian system is most likely involved in the pathogenesis of winter SAD. Neurotransmitters such as serotonin may play an important role in the regulation of the sleep-wake cycle and circadian system. Abnormalities of circadian rhythm have also been implicated in the aetiopathogenesis of non-seasonal mood disorders. The temporal distribution of rapid eye movement sleep (REM) earlier in the night in depressed patients could be the result of a phase advance of circadian rhythms. According to the ‘internal coincidence model,’ the circadian system is advanced relative to the sleep schedule such that sleep occurs at critical circadian phases at the end of the night. In vulnerable individuals, sleep would exert a depressogenic effect during these phases.

A number of clinical features of bipolar disorder, such as diurnal mood variation, early morning awakening, and the cyclical pattern of relapse, might also be associated with circadian disruption. At least three types of circadian rhythm abnormalities have been described in patients with bipolar disorder: blunting of circadian rhythm amplitudes, advanced position (or non-entrainment) of circadian rhythm phases, and doubling of the length of the sleep-wake cycle from 24 to 48 h. Several types of experiments indicate that alterations in the timing of sleep and wakefulness relative to other circadian rhythms may trigger the onset or offset of episodes of depression and mania.
Developmental alcohol exposure and circadian rhythms

Alcohol exposure during rapid brain growth causes cell loss, alters connections between brain regions, and lowers the production of brain chemicals responsible for the communication among neurons. Thus, it is reasonable to suggest that alcohol may also adversely affect SCN development. Such alcohol-induced insults during the period of rapid brain growth could produce cell loss and/or structural alterations in the SCN that could result in subsequent disturbances of the circadian timekeeping function. It is not likely that the damage to the SCN would be severe enough to cause complete loss of circadian rhythmicity. However, subtle disturbances may occur. For example, it is possible that developmental alcohol exposure could lead to permanent reductions in rhythm amplitude, changes in circadian period, and modulation of the SCN clock’s responses to light.

Earnest et al. suggests that developmental alcohol exposure may affect the circadian clock and its function at two levels. Firstly, prenatal ethanol exposure can damage the SCN clock by affecting the structure or function of cells in the SCN. The changes in circadian function would reflect either a global loss of SCN cells or alterations in the rhythmic expression of specific genes that are essential for normal timekeeping function of the SCN. Secondly, developmental alcohol exposure may affect the SCN output signals, e.g. brain-derived neurotropic factor (BDNF), and circadian rhythms throughout the body that are controlled by these signals, e.g. sleep-wake cycles. Adult rats exposed to alcohol during the early postnatal period, a critical period of brain development, exhibited a shortened circadian sleep-wake cycle. The activity of these rats was more fragmented, with frequent alternation between short intervals of sleep and waking. Other experimental studies have reported that prenatal exposure to alcohol results in sleep abnormalities.

The hypothesis that developmental alcohol exposure may alter circadian rhythms can be supported by the observation that heavy maternal alcohol consumption during human pregnancy is associated with a disturbance of sleep-wake distribution in infants. Continued heavy alcohol use throughout pregnancy is associated with lower total time spent sleeping, more quiet sleep period interrupted by indeterminate sleep, and greater restlessness with more frequent major body movements. Another research group has observed that, compared with healthy controls, infants of women with alcoholism had more difficulty reaching quiet sleep and were more easily disturbed. Disturbances in neonatal sleep cycling in children of drinking women have also been reported by other clinicians. Thus, developmental alcohol exposure may affect the circadian timekeeping function, and consequently cause SAD. This suggestion can be supported by the observation by Allen et al. that 41% of winter SAD patients have first-degree relatives with alcoholism, compared with only 18% of non-SAD depressed patients. Avery et al. found that the incidence of alcoholism among first-degree relatives of patients with winter SAD (even those without a personal history of alcohol abuse) was greater than the incidence among blood relatives of controls (20% vs. 7.2%). Higher prevalence of alcoholism in families of winter SAD patients indicates higher chances that the patients could be affected by developmental alcohol exposure. Circadian rhythm abnormalities related to prenatal alcohol exposure may also contribute to the aetiologicalogenesis of non-seasonal mood disorders.

Conclusion

The harmful effect of alcohol on the developing fetus can manifest in different ways, the most extreme of which is a condition termed fetal alcohol syndrome, characterized by mental and physical retardation, and other symptoms including craniofacial and joint abnormalities. Animal studies indicate a multifactorial mechanism of the teratogenicity of alcohol, resulting from nutrient deficiencies, fetal hypoxia and alterations in enzyme activities and cell function important in cell division and membrane integrity. Circadian rhythm abnormalities are one of many deleterious effects of prenatal alcohol exposure. Individuals prenatally exposed to ethanol can suffer from psychiatric illnesses and cognitive deficits. Developmental alcohol exposure may thus produce subtle abnormalities in circadian rhythms that may contribute to the development of seasonal and non-seasonal mood disorders. Although this hypothesis is speculative, I hope that it will stimulate new ideas and research.

A large and compelling experimental and clinical literature has documented the adverse impact of prenatal alcohol exposure on developing brain. However, many obstetrical textbooks, including those published recently, fail to consistently and unequivocally recommend that pregnant women abstain from drinking alcohol. Alcohol consumption among pregnant women remains one of the
leading preventable causes of birth defects and developmental disabilities. Abstinence during pregnancy is a major health objective.

References


