ORIGINAL ARTICLE

A Circadian Signal of Change of Season in Patients With Seasonal Affective Disorder

Thomas A. Wehr, MD; Wallace C. Duncan, Jr, PhD; Leo Sher, MD; Daniel Aeschbach, PhD; Paul J. Schwartz, MD; Erick H. Turner, MD; Teodor T. Postolache, MD; Norman E. Rosenthal, MD

Background: In animals, the circadian pacemaker regulates seasonal changes in behavior by transmitting a signal of day length to other sites in the organism. The signal is expressed reciprocally in the duration of nocturnal melatonin secretion, which is longer in winter than in summer. We investigated whether such a signal could mediate the effects of change of season on patients with seasonal affective disorder.

Methods: The duration of melatonin secretion in constant dim light was measured in winter and in summer in 55 patients and 55 matched healthy volunteers. Levels of melatonin were measured in plasma samples that were obtained every 30 minutes for 24 hours in each season.

Results: Patients and volunteers responded differently to change of season. In patients, the duration of the nocturnal period of active melatonin secretion was longer in winter than in summer (9.0±1.3 vs 8.4±1.3 hours; $P=.001$) but in healthy volunteers there was no change (9.0±1.6 vs 8.9±1.2 hours; $P=.5$).

Conclusions: The results show that patients with seasonal affective disorder generate a biological signal of change of season that is absent in healthy volunteers and that is similar to the signal that mammals use to regulate seasonal changes in their behavior. While not proving causality, this finding is consistent with the hypothesis that neural circuits that mediate the effects of seasonal changes in day length on mammalian behavior mediate effects of season and light treatment on seasonal affective disorder.

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From the Section on Biological Rhythms, Mood and Anxiety Disorders Program, Intramural Research Program, National Institute of Mental Health, Bethesda, Md (Drs Wehr, Duncan, Aeschbach, Turner, Postolache, and Rosenthal); Psychiatric Institute, Columbia University, New York, NY (Dr Sher); and the Veterans Administration Medical Center, Cincinnati, Ohio (Dr Schwartz). Dr Turner is currently affiliated with the Mood Disorders Program, Portland VA Medical Center, Portland, Ore.

SEASONAL AFFECTIVE disorder (SAD), characterized by recurrent episodes of winter depression, is a common problem and a significant source of distress for those living in temperate and boreal regions.[1,2] Symptoms of SAD, which include weight gain, increased sleep, decreased activity, and loss of interest in sex, resemble seasonal changes that occur in other mammals. Such changes in mammals have been shown to occur in response to seasonal changes in sunlight.[3] The same seems to be true of SAD inasmuch as it responds to treatment with light.[4-8]

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How do changes in sunlight regulate behavior? Many mammals have neural circuits that detect changes in day length and use this information to control the timing of seasonal behavior. A central component of these circuits is the circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus (**Figure 1**).[9] Neurons in the SCN increase their firing rate abruptly near dawn and decrease it abruptly near dusk.[10] During the course of the year, the SCN tracks the changing times of dawn and dusk via the retinohypothalamic tract and makes parallel adjustments in the timing of transitions between its periods of high and low neuronal firing. In this way, seasonal changes in the length of the day are encoded as changes in the duration of the diurnal period of increased firing of SCN neurons.

Through efferent projections, the SCN inhibits the firing of neurons in the paraventricular nucleus of the hypothalamus. When not inhibited, neurons of the paraventricular nucleus act through a multisynaptic pathway to stimulate the secretion of melatonin by the pineal gland.[9] Through these connections, the SCN's signal of day length and time of year is expressed reciprocally in the nocturnal period of melatonin secretion, which becomes shorter in summer and longer in winter. Sites distal to the pineal gland that regulate seasonal behavior read and respond to the durational melatonin signal.[11,12]

SUBJECTS AND METHODS

SUBJECTS

Subjects were recruited through local media and were screened with the Structured Clinical Interview of the *DSM III-R* and *DSM-IV* by a trained psychiatric social worker and psychiatric nurse.[24,25] Patients met the criteria of Rosenthal et al[5] for SAD and *DSM III-R* and *DSM-IV* criteria for major depressive episode with a seasonal pattern for the current episode, and they were free of other Axis I disorders. Healthy volunteers matched with patients by age and sex showed no evidence in their Structured Clinical Interviews of current or past Axis I psychiatric disorders and had no first-degree relatives with histories of psychiatric illnesses.

Subjects were nonsmokers and had normal results of physical examinations and routine laboratory tests, including thyroid hormone determinations. Individuals with histories of significant medical illnesses were excluded. Two patients were taking birth control pills as were their respective controls. Otherwise, subjects were free of medications throughout the study and they refrained from using light treatment prior to winter assessments. They were instructed to refrain from using over-the-counter medications and alcohol and to restrict their use of caffeine for at least 2 weeks prior to blood sampling.

Premenopausal women were studied in the follicular or luteal phase of the menstrual cycle but each was studied in the same phase in winter and in summer. In all cases but one, controls were studied in the same menstrual phase as their respective matches.

Patients were scheduled for winter studies as soon as their scores on the Hamilton Depression Rating Scale–SAD Version were greater than or equal to 18 points.[26] They were restudied in the summer when they were euthymic. All patients discontinued light treatment at least 1 month prior to their summer studies. Winter studies were conducted between late December and early March. Summer studies were conducted between late May and early August. Subjects gave written informed consent before participating in the study, which was approved by the National Institute of Mental Health (Bethesda, Md) institutional review board.

PROCEDURES

Subjects were outpatients except when they were admitted to the National Institutes of Health Clinical Center (Bethesda) for assessments of their melatonin profiles. They maintained their ordinary activity and sleep schedules and recorded times of sleep onset and offset daily. Women recorded days of menstrual periods and documented days of ovulation with a urine test kit.

Subjects were admitted to the research ward and an indwelling intravenous catheter was inserted for plasma sampling. At 4 PM, they entered a dim room (<1 lux overhead, Minolta Chroma Meter II; Minolta Camera Co Ltd, Osaka, Japan) and were seated upright in a lounge chair, where they watched television with a neutral density filter over the screen (<1 lux at eye level) until bedtime. Subjects slept in darkness on schedules derived from their average times of sleep onset and offset for the previous 3 nights. An intravenous line, routed through a port in the door, allowed blood samples to be drawn during the sleep period without disturbing the subjects. Samples were drawn every 30 minutes for 24 hours.

Plasma levels of melatonin were measured in duplicate by radioimmunoassay. The assay had a detection limit of 3 to 4 pg/mL, with intra-assay coefficients of variation of 7.2% (n=10), 5.6% (n=10), 6.2% (n=10), and 4.5% (n=10) at means of 22, 35, 50, and 203 pg/mL, respectively, and interassay coefficients of variation of 11.8% (n=21), 7.6% (n=21), 8.5% (n=15), and 3.8% (n=6) at means of 22, 34, 50, and 205 pg/mL, respectively.[27]

STATISTICAL ANALYSIS

As an indicator of the circadian pacemaker's signal of day length, we measured its reciprocal expression in the duration of the nocturnal period of active melatonin secretion. Three independent raters blind to the diagnoses of subjects and the season of sampling identified the times of onset and offset of active secretion for each 24-hour profile of plasma levels of melatonin. The beginning of active secretion was defined as the time midway between the last nondetectable level and the first detectable level in the evening. The end of active secretion was defined, as described by Lewy et al,[28] as the time of the last local peak that remained within the range of high nocturnal levels and that was immediately followed by a rapid decline toward nondetectable levels in the morning.

It is not precisely known how sites downstream from the pineal gland read the day-length signal that is encoded in the pattern of melatonin levels. They might respond to changes in the duration of the period of active secretion. However, they might respond to an interval whose termination is defined by the rapid fall in levels of melatonin or by the disappearance of melatonin. To explore this last possibility, we also measured the duration of the period when melatonin can be detected in blood. To measure this interval, the blind raters identified the time of disappearance of melatonin from plasma for each profile. The time of disappearance was defined as the time midway between the last detectable level and the first nondetectable level in the morning.

Subjects were included in the analysis if at least 2 of the 3 raters agreed on the timing of each of the 3 events in both winter and summer profiles.

Winter-summer differences in duration of active melatonin secretion and the duration of the interval when melatonin was detected in plasma were calculated for each individual. Differences between patients and healthy volunteers in these measures were assessed with analysis of variance. Sex and diagnosis were used as grouping factors. For each group, post hoc *t* tests were used to determine whether these winter-summer differences were significantly different from zero. Results are reported as mean±SD, α was set at .05, and all tests of statistical significance were 2-tailed.

To investigate the hypothesis that homologous neural circuits mediate the effects of season on behavior in SAD, we asked whether the circadian pacemaker in patients with SAD transmits a signal of change in day length after the transition from winter to summer. To answer this question, we measured the expression of the pacemaker's signal in the nocturnal period of melatonin secretion in constant dim light (<1 lux). In constant dim

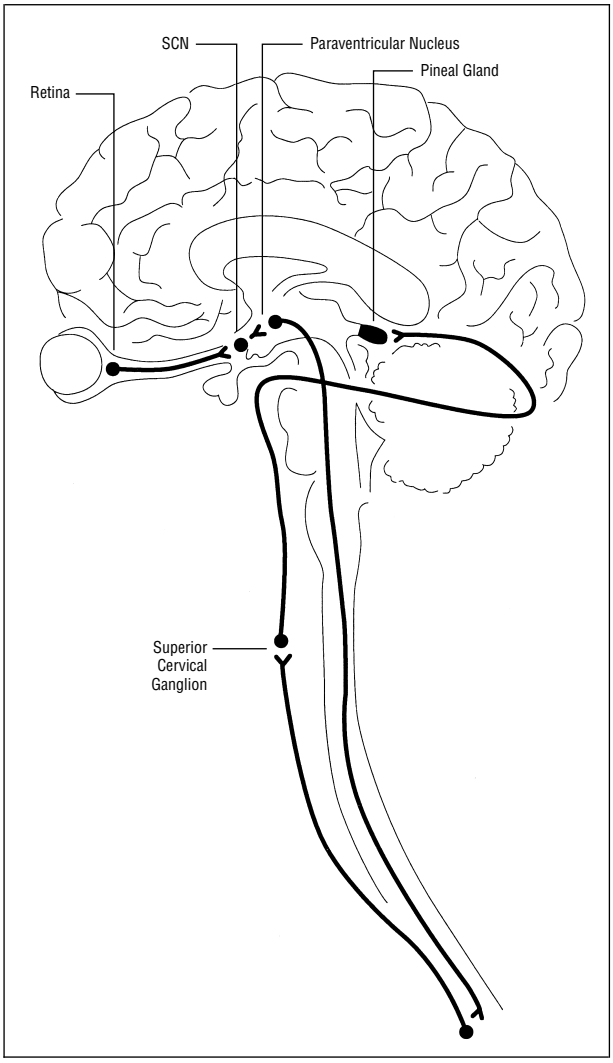

Figure 1. Duration of nocturnal melatonin secretion is programmed by endogenous processes that occur in cells of the circadian pacemaker in the suprachiasmatic nucleus (SCN) of the hypothalamus. The SCN's stimulus for melatonin secretion is transmitted along a multisynaptic pathway that passes through the paraventricular nucleus of the hypothalamus, the sympathetic outflow from the intermediolateral cell column of the spinal cord, the superior cervical ganglion, and the nervi canarii to the pineal gland. As the length of the night changes, the SCN makes proportional adjustments in the duration of melatonin secretion so that it becomes longer in winter and shorter in summer. The SCN receives information about the length of the night through the retinohypothalamic tract. Many mammals use the changes in duration of melatonin secretion to detect change of season and induce seasonal behavior. Melatonin receptors in the posterior hypothalamus and pars tuberalis of the pituitary mediate most of these responses.

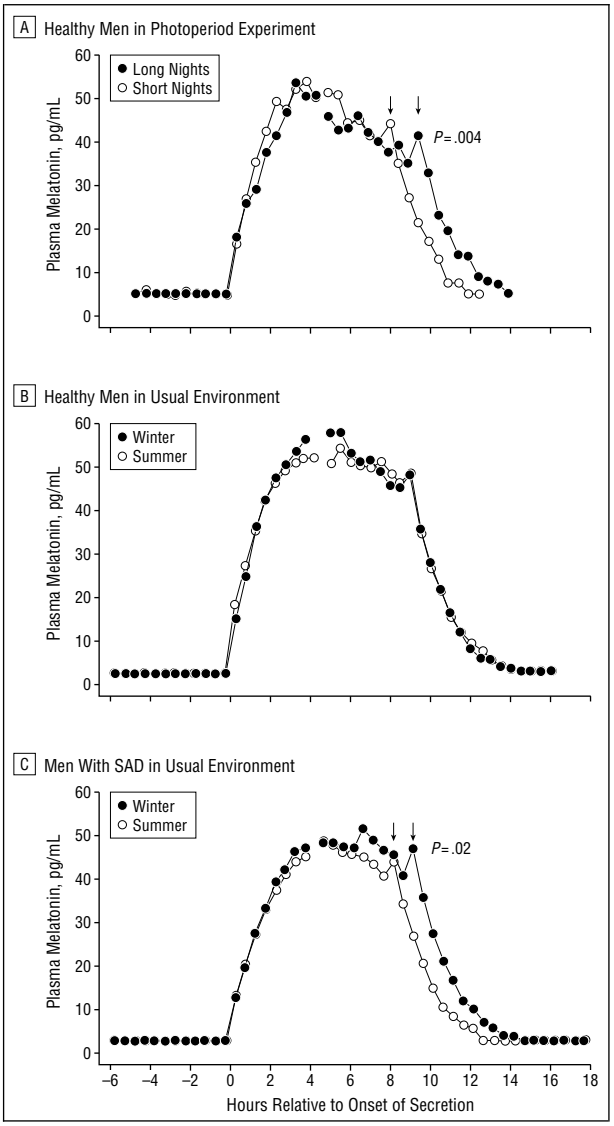

Figure 2. A, Melatonin profiles in constant dim light of healthy men (N=10) who had previously been exposed to long (14-hour) artificial nights on one occasion and to short (8-hour) artificial nights on another in a laboratory environment. The duration of active secretion was longer after exposure to long nights than after exposure to short nights, indicating that the circadian pacemaker in healthy men can detect and respond to changes in night length by making proportional adjustments in the duration of active melatonin secretion. (Data reanalyzed from another study.[16]) B, When healthy men (N=22) had been living in the lighting conditions in their usual environment, however, they failed to exhibit such responses after the change from winter to summer. C, In contrast, the duration of active secretion was longer in winter than in summer in men with seasonal affective disorder (SAD) (N=21) who had been living in the lighting conditions in their usual environment. Levels in the left and right halves of each melatonin profile were averaged with reference to times of onset and offset active secretion, respectively. To facilitate comparisons of duration of secretion, the onset of secretion in each profile is positioned over the x-axis at 0 hours, while the offset is positioned at its average time of occurrence relative to onset. Where differences between conditions were statistically significant, arrows indicate offsets of active secretion.

light, the pacemaker continues to switch on secretion in the evening and switch it off in the morning. The persistence of this cycle in constant dim light reveals an important fact about the pacemaker's signal of day length. It is not simply a passive response to the light-dark cycle but arises from processes that take place within SCN cells. Moreover, these processes possess an inertial property, or memory, such that in constant dim light the pacemaker's signal of day length exhibits aftereffects of photoperiods to which an individual was most recently exposed—longer after exposure to long photoperiods and shorter after exposure to short photoperiods (**Figure 2**A).[13-17]

With the foregoing in mind, we predicted that the circadian pacemaker's signal of night length, as expressed in the duration of melatonin secretion in constant dim light, would be longer in winter than in summer in patients with SAD. One might predict that the same would be true in healthy volunteers but that they differ

Table 1. Duration of Nocturnal Period of Active Secretion of Melatonin*

Group	No.	Season	Onset, Clock Time	Offset, Clock Time	Duration, h	Winter-Summer Difference in Duration, h	*P* Value
Patients with SAD							
Total	**55**	Winter	20:40 ± 1:29	5:41 ± 1:26	9.0 ± 1.3	0.6 ± 1.4	.001
		Summer	20:51 ± 1:18	5:15 ± 1:29	8.4 ± 1.3		
Men	21	Winter	20:53 ± 1:38	6:10 ± 1:25	9.3 ± 1.5	0.8 ± 1.4	.02
		Summer	21:08 ± 1:16	5:36 ± 1:35	8.5 ± 1.4		
Women	34	Winter	20:31 ± 1:23	5:24 ± 1:24	8.9 ± 1.1	0.5 ± 1.4	.03
		Summer	20:40 ± 1:19	5:02 ± 1:22	8.4 ± 1.2		
Healthy volunteers							
Total	**55**	Winter	20:37 ± 1:11	5:37 ± 1:45	9.0 ± 1.6	0.1 ± 1.4	.5
		Summer	20:39 ± 1:05	5:32 ± 1:23	8.9 ± 1.2		
Men	22	Winter	20:40 ± 1:07	5:56 ± 1:27	9.3 ± 1.3	−0.1 ± 1.3	.9
		Summer	20:26 ± 1:03	5:45 ± 1:35	9.3 ± 1.2		
Women	33	Winter	20:35 ± 1:14	5:23 ± 1:54	8.8 ± 1.8	0.3 ± 1.5	.4
		Summer	20:49 ± 1:05	5:23 ± 1:16	8.6 ± 1.2		

*Data are given as mean ± SD unless otherwise indicated. SAD indicates seasonal affective disorder.

from patients in lacking a systemic response to this signal. Alternatively, one might predict that there would be no seasonal change and that this difference would account for the stability of their behavior across the seasons. Since previous work has shown that healthy volunteers exhibit no difference in the duration of melatonin secretion between winter and summer, we predicted that this would be the case in our study too.[18-23]

RESULTS

Fifty-seven patients with SAD (36 women and 21 men) and 62 healthy volunteers (36 women and 26 men) completed the study. Data for 55 of the patients (96%) and 55 of the volunteers (89%) met the criteria for inclusion in the analysis. Ages in these latter 2 groups were similar (40.9±10.3 vs 37.6±9.8 years; t_{109}, P=.2). Minorities constituted 9% of the patient group and 4% of the healthy volunteer group. All patients met *DSM-III-R* and *DSM-IV* criteria for lifetime and current-episode diagnosis of major depressive disorder with a seasonal pattern, none for lifetime diagnosis of mania, and 22% for lifetime diagnosis of hypomania. At the time of the winter study, the patients' depression rating scores on the Hamilton Depression Rating Scale–SAD Version were 15.5±5.0 for typical items, 11.4±3.5 for atypical items, and 26.9±5.2 for total items.

The duration of active melatonin secretion in constant dim light responded differently to change of season in patients and healthy volunteers (analysis of variance, effect of diagnosis on winter-summer differences in duration, $F_{1,106}$=4.3; P=.04). There was no effect of sex or interaction between sex and diagnosis. In patients with SAD, duration of this interval was longer in winter than in summer (9.0±1.3 vs 8.4±1.3 hours; t_{54}=3.4; P=.001) but in healthy volunteers it did not change (9.0±1.6 vs 8.9±1.2 hours; t_{54}=0.7; P=.5 (**Table 1**, Figure 2, and **Figure 3**).

For the duration of the interval in which melatonin was detectable in plasma, there was an interaction between sex and diagnosis ($F_{1,106}$=3.9; P=.05). Duration was longer in winter than in summer in men with SAD (12.6±1.9 vs 11.2±1.7 hours; t_{20}=5.3; P=.001) but not in women with SAD (12.6±1.6 vs 12.3±1.5 hours; t_{33}=1.4; P=.2) (**Table 2**) as previously reported for a subgroup.[29] There was no statistically significant seasonal

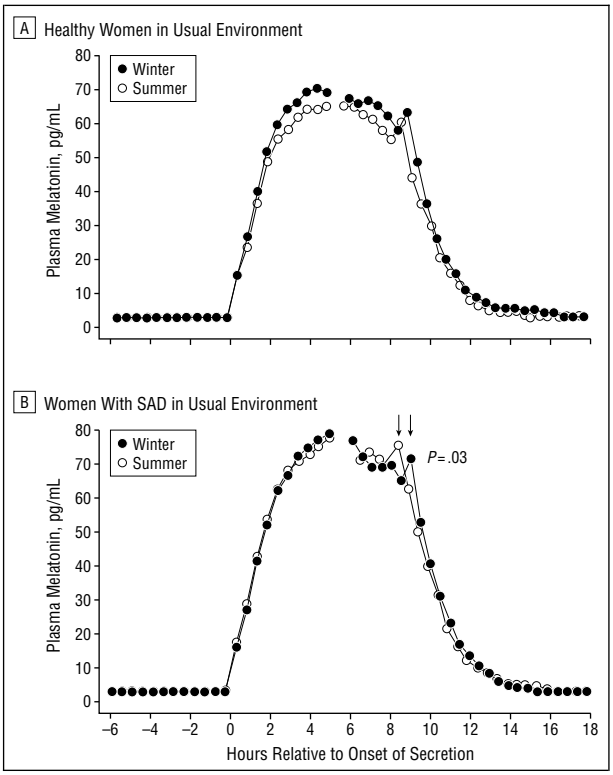

Figure 3. A, Melatonin profiles in constant dim light of healthy women (N=33). B, Women with seasonal affective disorder (SAD) (N=34) who had previously been exposed to lighting conditions in their usual environments in winter and in summer. The duration of active melatonin secretion did not change in healthy women (as in healthy men), but it was longer in winter than summer in women with SAD. Levels in the left and right halves of each melatonin profile were averaged with reference to times of onset and offset active secretion, respectively. To facilitate comparisons of duration of secretion, the onset of secretion in each profile is positioned over the x-axis at 0 hours, while the offset is positioned at its average time of occurrence relative to onset. Where differences between conditions were statistically significant, arrows indicate offsets of active secretion.

Table 2. Duration of Nocturnal Period When Melatonin Is Detectable in Plasma*

Group	No.	Season	Onset, Clock Time	Offset, Clock Time	Duration, h	Winter-Summer Difference in Duration, h	*P* Value
Patients with SAD							
Total	**55**	Winter	20:40 ± 1:29	9:16 ± 1:30	12.6 ± 1.7	0.8 ± 1.3	.001
		Summer	20:51 ± 1:18	8:43 ± 1:36	11.9 ± 1.7		
Men	21	Winter	20:53 ± 1:38	9:21 ± 1:37	12.6 ± 1.9	1.5 ± 1.1	.001
		Summer	21:08 ± 1:16	8:19 ± 1:28	11.2 ± 1.7		
Women	34	Winter	20:31 ± 1:23	9:07 ± 1:25	12.6 ± 1.6	0.3 ± 1.3	.2
		Summer	20:40 ± 1:19	8:58 ± 1:40	12.3 ± 1.5		
Healthy volunteers							
Total	**55**	Winter	20:37 ± 1:11	8:55 ± 1:46	12.3 ± 1.9	0.3 ± 1.4	.1
		Summer	20:39 ± 1:05	8:40 ± 1:31	12.0 ± 1.6		
Men	22	Winter	20:40 ± 1:07	9:07 ± 1:47	12.5 ± 1.8	0.1 ± 1.3	.9
		Summer	20:26 ± 1:03	8:52 ± 1:51	12.4 ± 1.7		
Women	33	Winter	20:35 ± 1:14	8:47 ± 1:46	12.2 ± 2.0	0.5 ± 1.5	.07
		Summer	20:49 ± 1:05	8:22 ± 1:16	11.7 ± 1.4		

*Data are given as mean ± SD unless otherwise indicated. SAD indicates seasonal affective disorder.

Table 3. Duration of Washout Period After End of Active Melatonin Secretion*

Group	No.	Season	Offset of Secretion, Clock Time	Disappearance of Melatonin, Clock Time	Washout Duration, h	Winter-Summer Difference in Washout Duration, h	*P* Value
Patients with SAD							
Total	**55**	Winter	5:41 ± 1:26	9:01 ± 1:30	3.3 ± 1.2	0.1 ± 1.5	.6
		Summer	5:14 ± 1:28	8:28 ± 1:37	3.2 ± 1.7		
Men	21	Winter	6:10 ± 1:25	9:16 ± 1:37	3.1 ± 1.1	0.6 ± 1.1	.01
		Summer	5:36 ± 1:35	8:04 ± 1:28	2.5 ± 1.4		
Women	34	Winter	5:24 ± 1:24	8:52 ± 1:25	3.5 ± 1.3	–0.2 ± 1.6	.4
		Summer	5:02 ± 1:22	8:43 ± 1:39	3.7 ± 1.7		
Healthy volunteers							
Total	**55**	Winter	5:37 ± 1:44	8:40 ± 1:46	3.1 ± 1.4	0.2 ± 1.4	.4
		Summer	5:32 ± 1:23	8:25 ± 1:31	2.9 ± 1.2		
Men	22	Winter	5:56 ± 1:27	8:53 ± 1:47	3.0 ± 1.4	0.1 ± 1.3	.8
		Summer	5:45 ± 1:35	8:37 ± 1:50	2.9 ± 1.3		
Women	33	Winter	5:23 ± 1:54	8:32 ± 1:46	3.1 ± 1.4	0.2 ± 1.5	.4
		Summer	5:23 ± 1:16	8:17 ± 1:16	2.9 ± 1.2		

*Data are given as mean ± SD unless otherwise indicated. SAD indicates seasonal affective disorder.

change in this variable in healthy men (12.5 ± 1.8 vs 12.4 ± 1.7 hours, $t_{21} = .2$; $P = .9$) or healthy women (12.2 ± 2.0 vs 11.7 ± 1.4 hours; $t_{32} = 1.9$, $P = .07$).

Additional post hoc *t* tests were performed. There was a trend for the duration of active melatonin secretion in summer to be shorter in patients compared with healthy volunteers (8.4 ± 1.3 vs 8.9 ± 1.2 hours; $t_{109} = 1.9$; $P = .06$, *t* test). This difference was statistically significant for men (8.5 ± 1.4 vs 9.3 ± 1.2 hours, $t_{41} = 2.2$; $P = .04$). There was no difference in this variable between the groups in winter (Table 1).

Duration of the melatonin washout period, ie, the interval between the end of secretion and the disappearance of melatonin from plasma, was shorter in summer than in winter (3.1 ± 1.1 vs 2.5 ± 1.4 hours; $t_{20} = 2.7$; $P = .01$) in men with SAD but did not differ between seasons in any other group (**Table 3**).

With regard to phase markers in the melatonin circadian rhythm, time of onset of active secretion did not differ between patients and healthy volunteers in winter (20:40 ± 1:29 vs 20:37 ± 1:11 hours) or between winter and summer in patients (20:40 ± 1:29 vs 20:51 ± 1:18 hours) or controls (20:37 ± 1:11 vs 20:39 ± 1:05 hours) (Table 1). Time of offset of active secretion was delayed in winter compared with summer in patients (5:41 ± 1:26 vs 5:15 ± 1:29 hours; $t = 2.5$; $P = .01$) but not in healthy volunteers (5:37 ± 1:45 vs 5:32 ± 1:23 hours).

By definition, seasonal change in the duration of active melatonin secretion is a function of seasonal change in the times of onset and offset of secretion. In patients, stepwise regression revealed that 67% of the variance of seasonal change in the duration of active melatonin secretion was related to the variance of change in the time of offset, while 33% was related to the variance of change in the time of onset. In a separate regression analysis, almost none of the variance of seasonal change in the duration of active melatonin secretion was related to the variance of seasonal change in the duration of sleep (1%) or habitual time of waking (7%).

COMMENT

The results of this study show, for the first time to our knowledge, that patients with SAD generate a biological signal of change in season that is similar to one that other mammals use to regulate seasonal changes in their behavior. From studies in animals we infer that this signal originates in the SCN of the hypothalamus and that the photic input that modifies this signal reaches the SCN through the retinohypothalamic tract (Figure 1). The presence of such a signal in patients with SAD, while not proving causality, is consistent with the hypothesis that these neural circuits and the signals they produce mediate the pathogenesis of winter depression and its response to light treatment.

While a 38-minute change in duration of the circadian pacemaker's day length signal may seem small, a change in the photoperiod of this magnitude is sufficient to elicit behavioral changes in other mammals. For example, mechanisms that regulate reproductive function in hamsters can discriminate between day lengths that differ by no more than 30 minutes and they can respond to simulated annual cycles in which day length varies as little as 34 minutes.[30,31] Such mechanisms can also discriminate between melatonin infusions that differ in duration by no more than 1 hour (the smallest difference tested) in pinealectomized hamsters.[32]

Although laboratory experiments show that the circadian pacemaker in healthy men is capable of transmitting a signal of change in day length when they are transferred from artificial long days (8:00-24:00) to artificial short days (8:00-18:00) (women have not been studied) (Figure 2A), it fails to produce this signal after the transition from winter to summer, when healthy men and women live in their usual environments at temperate latitudes (Figure 2B and Figure 3A).[16,18-23] The latter finding suggests that exposure to domestic artificial light at night and/or shielding from sunlight in the daytime in the modern urban environment masks the contours of the natural photoperiod so that the pacemaker can no longer detect and respond to it.

How can patients with SAD detect and respond to seasonal changes in day length in an urban environment in which healthy volunteers do not (Figure 2B-C and Figure 3)? One possibility is that patients are less exposed to the photoperiod-masking influence of artificial light and/or are more exposed to natural light than healthy volunteers. To date, research on this question is inconclusive.[33,34] Another possibility is that the retina or neural circuits that mediate responses to seasonal changes in day length are less responsive to light in patients with SAD so that they are only slightly affected by artificial light and respond only to the higher luminance of sunlight.[35] Research on this question is mixed.[36]

In mammals, the onset and offset of melatonin secretion seem to be regulated by 2 different circadian processes that are separately entrained to dusk and dawn, respectively.[13,14] Furthermore, changes in timing of the offset of secretion that occur in response to morning light have a greater effect on the duration of secretion than do changes in timing of the onset of secretion that occur in response to evening light.[15,17] These observations seem consistent with our observations. Our findings may indicate that variation in exposure to morning light was more important than variation in exposure to evening light in determining our patients' responses to seasonal changes in day length. This interpretation is consistent with, and might even explain, the well-established finding that morning light treatment of winter depression is superior to evening light treatment.[6-8,37]

So far, we have focused on the way changes in day length can cause the SCN to modify the duration of melatonin secretion that it programs. However, light can also acutely suppress the secretion of melatonin that the SCN programs.[38] Consequently, suppression of secretion by ambient light in the subjects' real-life environment could modify the duration of secretion that we observed in constant dim light. Nevertheless, we think that the findings in constant dim light are likely to be relevant to the individuals' usual environment because (1) the retinohypothalmic tract mediates both responses to light, (2) thresholds for both are similar in humans, and (3) the duration of melatonin secretion in constant dim light reflects the SCN's memory of the day length that it "perceived" in the days that preceded the dim-light measurement period.[15-17,39] In this last regard, measuring the duration of active secretion in dim light may be analogous to developing in a darkroom an image of lighting conditions to which film was exposed on a previous occasion.

Lewy et al[40] advocate the use of the onset of melatonin secretion in dim light as a marker for assessing the phase of the melatonin circadian rhythm, and they have hypothesized that winter depression is caused by a pathogenic phase-delay in this rhythm. However, we found no statistically significant difference in the time of onset of secretion between patients and healthy volunteers in winter or between winter and summer in patients. If one takes the offset or midpoint (Wehr et al, unpublished data, 2001) of secretion as a phase-marker, then our results might be considered to be consistent with their hypothesis.

It may seem paradoxical that there were no differences between patients and healthy volunteers in the duration of active melatonin secretion in winter when patients were symptomatic but that there were differences in summer, at least in men, when patients were asymptomatic. In other mammals, however, the absolute duration of nocturnal melatonin secretion is not usually biologically meaningful. Rather, relative changes are important. This is demonstrated by the fact that an animal can interpret the same duration of melatonin secretion as an indicator of either winter or summer depending on whether the animal was previously exposed to shorter or longer periods of secretion, respectively.[41]

Additional research is needed to determine how patients with SAD detect and respond to seasonal changes in the length of the solar day in an urban environment in which healthy volunteers do not. This work could address the possibilities that there are differences between the groups in the lighting conditions to which they are exposed or in the circadian pacemaker's or circadian photoreceptor's responsiveness to light stimuli. Experiments need to be conducted to test the hypothesis that

the circadian signal of seasonal change in day length that is present in patients with SAD plays a causal role in their illness. For example, one could investigate whether pharmacological manipulations of this signal induce changes in clinical state. Two such experiments were carried out but methodological problems make their results difficult to interpret.[42]

Limitations of our study include lack of information about the lighting conditions to which subjects were exposed in their usual environment and about the effect, if any, of acute suppression of melatonin secretion by light in the subjects' usual environment on the patterns of secretion that we observed in constant dim light.

In conclusion, patients with SAD exhibit seasonal variation in a physiological system that is known to regulate seasonal behavior in other mammals. This finding suggests that neural circuits that have been shown to mediate seasonal behavior in mammals may also mediate the pathogenesis of winter depression in humans.

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Corresponding author and reprints: Thomas A. Wehr, MD, National Institute of Mental Health, 10/3S231, 10 Center Dr MSC1390, Bethesda, MD 20892-1390.

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