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Chronobiological Basis of Female-Specific Mood Disorders

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Women have twice the incidence of major depression compared with men. They are prone to develop episodes of depression during times of reproductive hormonal change at puberty, with use of oral contraceptives, during the premenstrual phase of the menstrual cycle, postpartum and during the perimenopause (see review: Parry 1995a). Wirz-Justice (1995) describes the variety of disturbances in biological rhythms observed in mood disorders. In this report, we describe the chronobiological disturbances observed in female-specific mood disorders, namely, premenstrual dysphoric disorder, pregnancy and postpartum depression and menopause. We hypothesize that changing reproductive hormones, by affecting the synchrony or coherence between components of the circadian system, may alter amplitude or phase (timing) relationships and thereby contribute to the development of mood disorders in predisposed individuals.
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In women, hormonal changes associated with the reproductive cycle may provoke affective changes in predisposed individuals. Examples include depression associated with oral contraceptives (Parry and Rush 1979), the luteal phase of the menstrual cycle (Hamilton et al. 1984; Endo et al. 1978; Halbreich and Endicott 1985), the postpartum period (Parry and Hamilton 1990), and menopause (Winokur 1973). Sex differences in the rates of depression begin to appear after puberty (Weissman et al. 1984; Angold et al. 1998), a time of major change in the neuroendocrine reproductive axis. From this time onward, women have a greater lifetime risk for major depression than men. Women predominate with respect to unipolar depression (Weissman et al. 1984), the depressive subtype of bipolar illness (Angst 1978), and cyclical forms of affective illness such as rapid cycling manic-depressive illness (Wehr 1984) and seasonal affective disorder (Rosenthal et al. 1984). Furthermore, the risk for major depression in both men and women appears to be increasing in recent generations (Weissman et al. 1984; Klerman and Weissman 1989).

The fluctuation of ovarian steroids during specific phases of the reproductive cycle may bear some relationship to the particular vulnerability of women for mood disorders. The ovarian hormones could exert their effects on mood directly or indirectly by their effect on neurotransmitter, neuroendocrine, or circadian systems (McEwen and Parsons 1982; Albers 1981; Albers et al. 1981; Thomas and Armstrong 1989; Parry 1995a,b). Although each of these systems has been implicated in the pathogenesis of depressive illness, the circadian basis of these disorders has received the least attention. We have designed our studies with their particular chronobiological focus because the predisposition of women for major depression has not been investigated systematically with respect to the interaction of

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the unique cyclic reproductive neuroendocrine axis in women and circadian physiology. Although chronobiological disturbances have been described in depression (Kripke et al. 1978; Wehr and Goodwin 1980), the characterization of chronobiological disturbances in reproductive-related mood disorders in women remains to be elucidated.

Below we review the circadian rhythm abnormalities that we have observed in premenstrual dysphoric disorder, pregnancy and postpartum depression and menopause. As reproductive hormones modulate the synchrony or coherence between different components of the circadian system (Thomas and Armstrong 1989), we hypothesize that these changing hormones during the premenstrual, postpartum and menopausal periods may destabilize circadian rhythmicity and thereby contribute to the development of mood disorders at these times in predisposed women.

PREMENSTRUAL DYSPHORIC DISORDER

The mood disturbances associated with the menstrual cycle have been referred to historically as premenstrual syndrome (PMS). They have been defined more rigorously as late luteal phase dysphoric disorder (LLPDD) in the DSM-III-R, and as premenstrual dysphoric disorder (PMDD) in the DSM-IV under the classification of mood disorders, depression, not otherwise specified, although the criteria are listed in the appendix (American Psychiatric Association 1994). One scientific advantage of studying PMDD is that the mood and behavioral disturbances are recurrent and predictable and, thus, can be studied prospectively and longitudinally. In contrast to many other psychiatric disorders in which no confirmed physiologic process precipitates or alleviates the disorder, in PMDD, one physiologic process, the menstrual cycle, is linked to both remission and relapse.

We hypothesize in PMDD that gonadal steroid changes during specific endocrine phases of the menstrual cycle disrupt normal amplitude and phase relationships between circadian rhythms and thereby elicit mood disturbances in vulnerable women. Hormonal alterations may affect circadian regulation by inducing changes in 1) input pathways to the underlying circadian pacemaker, 2) the pacemaker itself or 3) output rhythms from the pacemaker. The output of the circadian pacemaker may be inferred from measuring the onset and offset time, duration and amplitude of melatonin secretion. According to some investigators, melatonin onset and offset time may reflect, respectively, the evening (E) and morning (M) components of a complex (2-oscillator) circadian pacemaker (Pittendrigh and Daan 1976). The coupling or phase-angle (timing relationship) between these E and M components is expressed as $psi_{E\text{-}M}$. To test these hypotheses, we examine influences of depressive diagnosis (PMDD vs. controls), mood state (symptomatic vs. asymptomatic in patient groups) and reproductive hormones (follicular vs. luteal menstrual cycle phase) on the human circadian system including complex pacemaker dynamics (e.g., $psi_{E\text{-}M}$) in relation to other neuroendocrine factors. In our conceptual model, when these neuroendocrine markers become desynchronized with respect to each other and the environment, depression results (Wehr and Wirz-Justice 1981; Wirz-Justice 1995; Parry 1995a).

Our work in this area has focused on the effects of endogenous changes in estradiol and progesterone during the menstrual cycle on measures of circadian rhythmicity (sleep/activity, temperature, melatonin, prolactin, cortisol and TSH) in patients with premenstrual dysphoric disorder (PMDD) vs. normal control (NC) subjects. In summary, we have found changes in sleep EEG during the menstrual cycle (in stage 3 sleep and number of intermittent awakenings) and that PMDD patients have more stage 2 sleep and less REM sleep (Parry et al. 1989b). Temperature minima tend to be earlier and amplitude higher in PMDD vs. NC subjects (Parry et al. 1989b, 1994, 1997b). Compared with NC subjects, PMDD patients have an earlier offset time, a shorter duration and a decreased area under the curve of plasma nocturnal melatonin secretion (Parry et al. 1990). In the luteal compared with the follicular menstrual cycle phase, melatonin onset time is delayed, offset time is advanced, duration is compressed, and amplitude and mean levels are decreased in PMDD patients (Parry et al. 1997a). These findings are consistent with a compressed $psi_{E\text{-}M}$ and increased pacemaker amplitude. They predict our findings of increased resistance to the phase-shifting effects of light (see below).

PMDD patients also have higher prolactin amplitudes and earlier acrophases (Parry et al. 1994, 1996). The peak of the cortisol rhythm is phase-delayed in the luteal compared with the follicular phase in NC, but not in PMDD, subjects (Parry et al. 1994) and cortisol acrophase advances in PMDD, but not in NC, subjects when sleep onset time is advanced (Parry et al. 2000a). Effects on phase or amplitude of multiple output rhythms suggest a pacemaker effect. Light treatment (Parry et al. 1989a, 1993) and sleep deprivation (Parry and Wehr 1987; Parry et al. 1995) improve mood and sleep quality in PMDD patients and, compared with NC subjects, has differential effects on neuroendocrine measures (e.g., evening bright light increases TSH nadir in PMDD subjects; Parry et al. 1994, 1996).

In contrast to the phase-advances seen in NC subjects, PMDD patients display decreased responses and phase-delay shifts to morning bright light (Parry et al. 1997c), suggesting a disturbance in the underlying circadian clock mechanism that regulates normal adaptive synchronization of the circadian clock internally and with the environment. Thus a most important timing

function appears to be seriously impaired in PMDD patients. The finding of altered responses to light is one of the few from challenge studies in PMDD research in which the abnormality is found in the symptomatic luteal, but not the asymptomatic follicular, phase, suggesting a state (vs. trait) marker for the illness. Abnormalities in state variables suggest that the marker is related to the expression of the illness.

We sought to test the hypothesis that the previously observed low melatonin rhythms in PMDD (Parry et al. 1990, 1997a) were a function of 1) altered input pathways to the circadian clock or 2) a disturbance in the underlying circadian pacemaker. To test hypothesis 1 (H1), we measured the suppressive effects of light on melatonin secretion. To test hypothesis 2 (H2), we measured the magnitude and direction of light-induced phase-shift responses, a critical test of pacemaker function.

Preliminary findings suggest that there is a statistically significant suppression of melatonin to 200 lux of light in PMDD, but not NC, groups (ANOVA, group effect, $p = .04$; group by lux interaction, $p = .012$ for relative decline). If replicated in larger sample sizes, the data would suggest that PMDD patients may be more sensitive than NC subjects to the acute suppressive effects of light on melatonin secretion as were the depressed vs. control subjects reported in initial studies by Lewy et al. (1981) and Nurnberger et al. (1988).

Phase and Amplitude Shifting Effects of Bright Light on Melatonin (H2)

In the follicular phase (when PMDD subjects are asymptomatic), we found that after the light pulse, the melatonin offset time advanced significantly to a similar degree for both NC and PMDD subjects. In the luteal phase (when PMDD subjects are symptomatic), NC subjects display an advance in the offset time of melatonin secretion indistinguishable from that of the follicular phase. In contrast, in the luteal phase, PMDD patients show either no change in offset time (five of nine subjects) or they show phase-delay shifts up to 1.5 h (four of nine subjects), rather than the expected phase-advance response (group effect, $p = .012$; post-hoc testing, $p = .01$ for NC vs. PMDD).

The primary finding of either a lack of response or an abnormal direction of change in melatonin offset time to a bright morning light stimulus supports our hypothesis that PMDD subjects have an increased resistance to light-induced phase-shift responses. It may be that sufficient critically timed bright light, melatonin (reflective of the strength of the underlying circadian pacemaker), serotonin (as a substrate) and reproductive hormonal change appropriate to the luteal phase are required for a functional phase-shift response. The fact that offset, but not onset, time changed in response to a light pulse also supports a 2-oscillator model of melatonin regulation in humans in which onset and offset time of melatonin secretion are differentially regulated. These preliminary findings suggest differential responses to morning light between NC and PMDD groups in the timing (offset) of melatonin secretion in the luteal phase.

Summary

The findings described above suggest that disturbances in the timing and secretion patterns of circadian rhythms and their response to critically timed light administration characterize PMDD patients. Interventions with bright light, which alter, among other things, the relationship between different biological rhythms, improve mood in these depressed patients.

PREGNANCY AND POSTPARTUM DEPRESSION

The clinical phenomenology of postpartum major mood disturbances parallels that of a mood disorder, the DSM-IV category under which a postpartum episode is classified as an onset specifier (American Psychiatric Association 1994). Given the relationship of postpartum psychiatric illness to major mood disorders and to other reproductive-related mood disorders (Wisner et al. 1993, 1995; Cox et al. 1993), and the efficacy of sleep deprivation in major mood disorders and PMDD (Gillin 1983; Parry and Wehr 1987; Parry et al. 1995), we reasoned that sleep deprivation might serve as a useful clinical strategy to improve mood in patients with a MDE occurring during pregnancy or the postpartum period (Parry et al. 2000b). Also, given that many women would prefer to remain drug-free during pregnancy or lactation, a treatment such as sleep deprivation, which potentially can exert its therapeutic benefit in one to two days, could serve to mitigate the devastating effects of these mood disorders in women.

Methods

Twelve women who met DSM-IV criteria for a major mood disorder with onset during pregnancy or within one year postpartum underwent a trial of either early-night sleep deprivation (ESD), in which they were sleep deprived in the early part of one night and slept from 3 to 7 A.M., or late-night sleep deprivation (LSD), in which they were deprived of sleep in the latter part of one night and slept from 9 P.M. to 1 A.M.. Mood and sleep EEG were assessed before, during and after the night of sleep deprivation.

Results

An analysis of covariance was calculated using only patients with a baseline Hamilton score $\geqq 14$. The baseline

value was used at a covariate. Adjusted post-treatment Hamilton means were 5.5 for LSD and 18.9 for ESD (p = .135, two-tailed). Although the sample size was small and these results are not statistically significant, it would appear from these data that severely depressed patients obtained relatively little benefit from ESD and much more benefit from LSD. In this trial we used modified Terman criteria (Terman 1998) to define responders as those patients, who after a night of sleep deprivation or recovery sleep, had Hamilton or Beck scores in which there was either a) a 50% decrease in scores compared with baseline 2 ratings, or b) a score of $\leqslant 8$. Of 17 trials of LSD (11) or ESD (6) , there were nine responders to LSD (82%) and two responders to ESD (33%). Of the LSD responders, 6 (55%) met criteria for response after the night of sleep deprivation, and 9 (82%) after the night of recovery sleep. During ESD, one patient (17%) responded after the night of sleep deprivation, and two (33%) after the night of recovery sleep. The only patient (1) who did not respond to LSD was pregnant; the only responders (2) to ESD also were pregnant. Four postpartum patients (66%) were non-responders to ESD. The quality of sleep as assessed by total sleep time, sleep efficiency, sleep latency and delta sleep improved during recovery sleep more after LSD than ESD.

Conclusions

Although the findings are preliminary, the results suggest that with further study, critically timed sleep deprivation interventions may benefit women with pregnancy or postpartum major mood disorders and potentially provide a viable alternative treatment modality for those women who are not candidates for pharmacological or psychotherapeutic interventions. Such interventions are needed to help prevent the devastating effects of depression during pregnancy and the postpartum period on the mother, infant, her family and society. The mechanisms are unknown but may be related to improving the quality of sleep on recovery nights.

MENOPAUSE

Currently 35 million American women are postmenopausal and over a million enter menopause each year (U.S. Congress of Technology Assessment). A majority remain physically and mentally healthy. A small, but significant, minority may develop clinical depression. The role of changing reproductive hormones during menopause in the development of depressive vulnerabilities has clinical and theoretical importance: Its investigation potentially may shed light on the role of changing reproductive hormones in precipitating or alleviating depressive mood changes at other times of reproductive hormonal change at puberty, during the menstrual cycle, with the use of oral contraceptives or during pregnancy and the postpartum period. It also may clarify the role of reproductive hormones in maintaining health and well-being during the aging process. Estrogen and progesterone have important roles in regulating and stabilizing the circadian system in animals. Aging is associated with loss of this regularity and stability (Wise et al. 1996, 1997). In fact, Youngstedt et al. (1997), Smith et al. (1997) and Kripke et al. (1997) have reported a greater range of circadian rhythm phases and amplitudes in elderly women. Thus, estrogen and progesterone may be important modulators that help maintain the health of the circadian system. When reproductive hormones diminish in aging menopausal women, the deleterious effect of both age and the loss of hormonal input to the circadian system may result in impaired mental or physical health in vulnerable individuals.

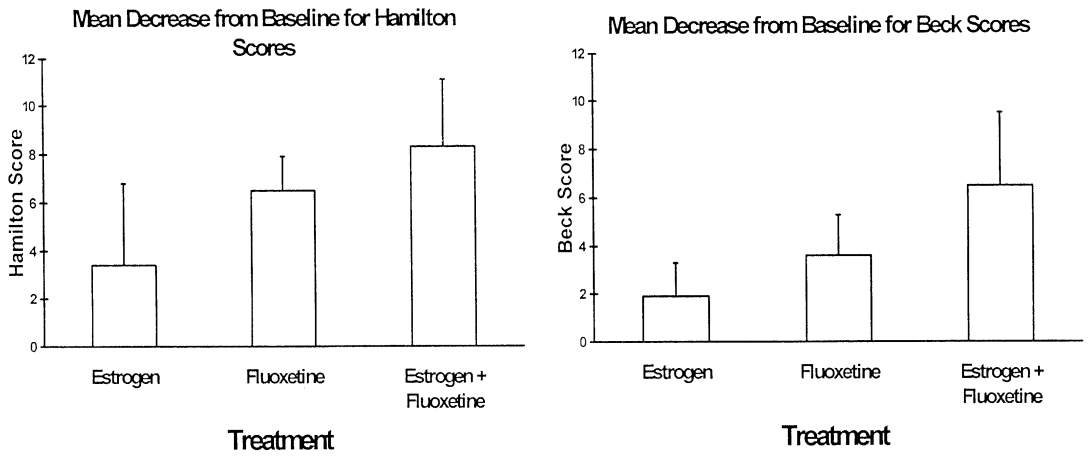

Figure 1. Mean (+ SE) decrease from baseline for Hamilton and Beck depression ratings after treatment with estrogen, fluoxetine or estrogen plus fluoxetine.

Methods

In a pilot study of 11 subjects, five normal control (NC) women and six depressed patients, NC women were randomized to a cross-over trial of estrogen (Estraderm patch 0.1–0.2 mg or Estrace 1–2 mg) or estrogen plus progesterone (2.5–5.0 mg medroxprogesterone acetate). Depressed women were randomized to a cross-over trial of estrogen, antidepressant (fluoxetine 10–40 mg) or estrogen plus antidepressant treatment.

Results

Mood ratings (Hamilton, Beck, Atypical and Mania) of NC subjects did not vary to a clinically significant degree documenting normal control status (all mean scores < 3). Mood ratings in depressed patients are shown in Figure 1 to illustrate the change in scores from baseline to after treatment (eight weeks in most cases) with either estrogen alone, antidepressant (fluoxetine) alone or estrogen plus antidepressant. The bar graphs represent the magnitude of improvement with each treatment regimen:

Plasma Melatonin Data

Plasma melatonin was measured every 30 min from 6 P.M. to 10 A.M. at baseline and at the end of each treatment condition: estradiol (E_2) or estradiol and progesterone (E_2 + P_4). Figure 2 illustrates the mean melatonin profiles from normal control (NC) subjects (top panel) and depressed patients (bottom panel). The findings are consistent with the hypothesis that estrogen treatment alone increases the amplitude of melatonin circadian rhythms and that progesterone antagonizes these effects:

Summary

The results from these preliminary findings suggest that similar to the effects documented in rodents, estradiol and progesterone, by altering the phase and amplitude of biological rhythms in humans, may serve to maintain rhythm stability. In depressed menopausal women, estrogen replacement therapy may enhance the effect of antidepressant medication.

SUMMARY

Thus in PMDD, pregnancy, and postpartum depression and menopause, reproductive hormones may alter circadian rhythmicity and thereby contribute to the predilection for mood disturbances at these times. Interventions designed to re-establish normal phase relationships between these component rhythms may improve mood in these depressed women.

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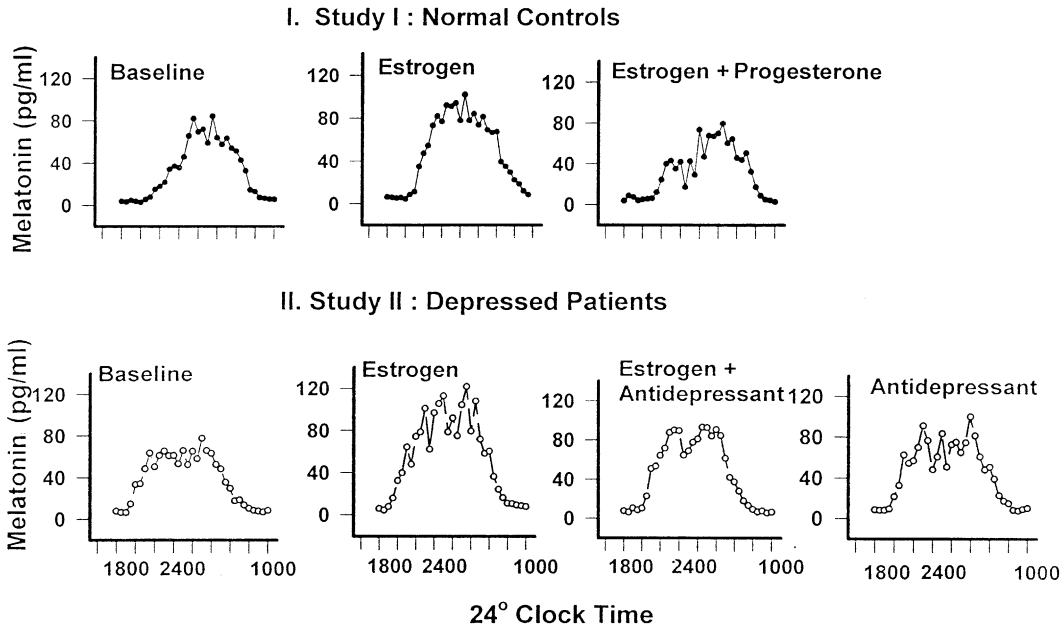

Figure 2. Mean melatonin levels (pg/ml) obtained every 30 min from 18:00- 10:00 h in dim/dark light in normal control menopausal women at baseline and after treatment with estrogen or estrogen plus progesterone; and in depressed menopausal women at baseline and after treatment with estrogen, estrogen plus antidepressant (fluoxetine) or antidepressant alone.

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