S.15 Pharmacotherapy of affective disorders in women

S.15.01 Stress, depression and hormones

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Depression is twice as common in women and a number of theories have been proposed to explain this increased vulnerability. Our own studies have focused upon HPA axis regulation in depression and differences in stress responsiveness and glucocorticoid negative feedback between men and women. Sex differences in stress response have been shown for a number of species including rats and human. Basic science studies examining the direct effects of gonadal steroids on HPA axis function have suggested that progesterone can function as a glucocorticoid antagonist and that estrogen may affect both stress responsiveness and glucocorticoid negative feedback. Our own studies in rats suggest that gonadally intact female rats are very resistant to the inhibitory effects of glucocorticoids. In normal women, we also noted resistance to the suppressive effects of infused cortisol, when cortisol was administered during the luteal phase, but normal suppression to cortisol during the follicular phase. We hypothesized that the resistance to glucocorticoids would also protect premenopausal depressed women from the negative sequelae of hypercortisolism that occurs during a depressive episode. Indeed we found higher average baseline glucocorticoid levels in premenopausal than post-menopausal women who were dexamethasone non-suppressors. Finally, our data and those of others suggest a complex interaction between the hypothalamic-pituitary-adrenal and gonadal axes that affects overall stress responsiveness in women and while protecting pre-menopausal women from hypercortisolism also results in failure to terminate the response to stress which may contribute to increased vulnerability to depression.

S.15.02 Gonadal steroids, brain, and behavior

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The role of gonadal steroids in the regulation of mood state has been inferred for centuries, but it is only in recent years that the powerful neuroregulatory effects of gonadal steroids have been detailed. Indeed, gonadal steroids have been shown to play a role in all stages of neural development, including neurogenesis, synaptogenesis, and neural migration, growth, differentiation, survival, and death (Pilgrim and Hutchinson, 1994). Two elements of the neural effects of gonadal steroids are particularly noteworthy: 1) the effects are time and development stage-dependent, with early exposure responsible for organizing or permanently altering brain structure and function; 2) the organizational and functional effects of gonadal steroids create gender-related differences or sexual dimorphisms in brain structure and physiology as well as in behavior. Apart from the myriad effects of gonadal steroids on brain and behavior in animals, much indirect evidence suggests their role in the regulation of mood and cognition in humans. Premenstrual syndrome (PMS) is a mood disorder that occurs in concert with the luteal phase of the menstrual cycle. Nonetheless, the role of gonadal steroids in this syndrome is unclear, as their levels do not appear to differ in patients and controls, and PMS can occur in the absence of the mid-luteal phase (Schmidt et al, 1991). Our recent data suggests that medical oophorectomy will eliminate the symptoms of PMS, while their return is precipitated by hormone replacement. Similar manipulations of ovarian function in control subjects produce no perturbations of mood. Women with PMS, therefore, appear to display differential susceptibility to mood disturbances associated with normal changes in gonadal steroid levels. The substrate for this increased vulnerability remains to be determined.

References


S.15.03 Serotonin reuptake inhibitors in the treatment of premenstrual dysphoria

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Selective serotonin reuptake inhibitors (SSRIs), as well as clomipramine (a tricyclic antidepressant with a major SRI component) have demonstrated excellent efficacy and minimal side effects in both open and clinical trials for women with premenstrual dysphoric disorder (PMDD). A recent large multi-centre, double-blind, randomized controlled trial (RCT) has shown that fluoxetine 20 mg/d or 60 mg/d was significantly superior to placebo in relieving the psychological symptoms of PMDD, and that fluoxetine at 20 mg/d was just as efficacious as 60 mg/d while reported side effects were greatly reduced. This study confirmed the results of several smaller RCTs and open label studies. Most other SSRIs are proving to be as efficacious. In an open study, paroxetine was effective in women diagnosed with PMDD who received placebo for one cycle followed by paroxetine 10 to 30 mg/d for 3 cycles. Paroxetine was also compared with maprotiline in a double-blind, RCT and was found to be significantly superior to maprotiline as well as placebo. Preliminary results from a multi-centre RCT of sertraline have also demonstrated that sertraline was significantly more effective than placebo in the treatment of these women. An open study of sertraline versus desipramine for 2 cycles has also identified improvement in the sertraline group. Citalopram, the most selective of the SSRIs has recently been shown to be effective in PMDD, both in continuous and intermittent dosing. Only one RCT of fluvoxamine has been reported in the literature. Women with premenstrual complaints were randomised to receive either placebo or fluvoxamine (50–150 mg/dag) for two consecutive cycles. A beneficial effect was reported in both groups, but the effect of fluvoxamine was not statistically different from placebo. A more recent open-label study of fluvoxamine in women with PMDD showed significant improvement from baseline, with a starting dose of 50 mg/d increased to 100 mg/d. In reviewing all these studies, there were no differences in the type of side effects between SSRIs, the most frequently reported side effects attributed were mild and transient and included: disturbed sleep, nausea, headache, fatigue, sexual disturbance, sweating, dry mouth, and sedation. The etiology of PMDD is still unclear, however, changes along the central serotonergic cascade continue to be identified as relevant to mood and behavioral disturbances prior to menstruation. Recent RCTs have shown that most of the SSRIs, as well as clomipramine, are efficacious in helping women with premenstrual dysphoria. Further studies are required to address the issues of SSRi non-responders, as well as continuous versus intermittent treatment and long-term maintenance.

References


S.15.04 Identification and treatment of postpartum depression

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Psychiatric illness following childbirth has been described since the time of Hippocrates. In a widely cited study, the profound increase in psychiatric hospitalizations for women during the first three months postpartum was clearly documented (Kendall 1987). It is estimated that up to 12.5% of psychiatric hospitalizations for women occur during