13. GONADAL STEROIDS, BRAIN, AND BEHAVIOR

P.J. Schmidt (1), K.F. Berman (1), M.A. Danaeau (1), P. Keenan (2), L.K. Nieman (3), and D.R. Rubinow (1)

(1) Behavioral Endocrinology Branch, NIMH; (3) Developmental Endocrinology Branch, NICHD, Bethesda, MD 20892; (2) Harper Hospital, Detroit, MI 48201

We evaluated the effects of hypogonadism and gonadal steroid replacement on measures of CNS physiology and behavior in women with perimenopause-related depression and in three groups of subjects with GnRH agonist (GnRH-A)-induced hypogonadism. Women with perimenopause-related depression participated in a double-blind, placebo-controlled trial of the antidepressant efficacy of estradiol (E2). GnRH-A induced hypogonadism was compared with testosterone (T) replacement in asymptomatic men and progesterone (P4) and E2 replacement in both asymptomatic (AS) women and those with menstrual-related mood disorder (MRMD). Compared to hypogonadism, gonadal steroid replacement was associated with the following: 1) Re-emergence of symptoms in MRMD but not AS controls (E2 or P4, but not placebo); 2) Remission of depressive symptoms in depressed perimenopausal women (E2); 3) Restoration of normal sexual function in men (T) but not women (E2, P4); 4) No effects on neuropsychological test scores in younger women (E2, P4), but decreased visual spatial performance in men (T) and improvement in verbal memory in depressed perimenopausal women (E2); 5) Normalization of cognition activated regional cerebral blood flow in the dorsolateral prefrontal cortex in younger women (E2, P4) and men (T); and 7) Increased m-CPP stimulated prolactin secretion and basal core temperature (P4 only). Our observations demonstrate that sex steroids regulate several measures of CNS function. However, the direction and patterns of effects vary with context including age and gender.

14. EFFECTS OF GONADAL STEROIDS ON THE HPA AXIS RESPONSE TO STRESS

C.A. Roca (1), P.J. Schmidt (1), M.A. Altemus (2), G. Cizza (3), P. Deuster (4), P.W. Gold (3), G.P. Chrousos (5), and D.R. Rubinow (1)


The ability of gonadal steroids to modulate hypothalamic-pituitary-adrenal (HPA) axis function is not well established in humans, but may be of importance in understanding sexual dimorphisms in the stress response. To investigate these effects, we studied normal women (n = 8) and men (n = 5) during pharmacologically-induced hypogonadism and during gonadal steroid replacement. We measured the HPA axis response to three different stimuli: 1) treadmill exercise stress, 2) low-dose dexamethasone suppression test (DST), and 3) ovine corticotropin (oCRH) stimulation. Data were analyzed by analysis of variance with repeated measures (ANOVA-R) and post hoc Bonferroni t tests. Women exhibited a blunted cortisol response to exercise stress (p = 0.05) and increased dexamethasone suppression (p < 0.01) in the hypogonadal compared with the progesterone replaced condition. In men, however, there was no effect of hormonal condition on either the exercise stress or DST results. Exercise stimulated cortisol (p < 0.05) and ACTH (p < 0.01) were significantly increased in men compared with women during the hypogonadal condition. Finally, a significant (p < 0.05) increase in o-CRH stimulated ACTH was seen in men during testosterone replacement. Gonadal steroids appear to more actively regulate HPA axis function in women than men, and the appearance of dimorphic response to exercise under hypogonadal conditions may imply an organizational origin to these gender-related differences.

15. NEUROSTEROIDS IN REPRODUCTIVE ENDOCRINE-RELATED MOOD DISORDERS

R.C. Daly (1), M.Y. Kim (2), M. Bloch (3), P.J. Schmidt (1), R.M. Purdy (4), D.R. Rubinow (1)


Abnormal levels of neurosteroids may play a role in the symptoms of reproductive endocrine-related mood disorders. We attempted to test this hypothesis by examining plasma levels of four neurosteroids (iso-tetrahydropregesterone, pregnenolone, pregnanolone, and allopregnanolone) in two study groups: 1) women with premenstrual syndrome (PMS) (n = 15) and matched controls (n = 12) during the luteal phase of the menstrual cycle; and 2) women with (n = 7) and without (n = 7) a past history of PPD (in whom a hypogonadal baseline was established with the GnRH agonist Lupron) during two study phases: high dose administration of estrogen and progesterone (simulating pregnancy), and two weeks after abrupt withdrawal of steroids (simulating the early postpartum period). Women with PMS did not differ significantly from controls in luteal phase levels of any of the neurosteroids measured. Similarly, despite the appearance of mood symptoms in the women with a history of PPD (but not controls), no differences were observed either in plasma levels of neurosteroids during the two study phases or in the magnitude of the decline of neurosteroids during the withdrawal phase. Despite the conceptual appeal of disturbances in neurosteroids as precipitants of reproductive endocrine-related mood disorders, our data support neither a deficiency of neurosteroid levels in PMS nor abnormal fluctuations in neurosteroid levels as mediators of the differential sensitivity to the mood destabilizing effects of ovarian steroids seen in women with PPD.

Imaging Serotonin in the Psychiatric Disorders
Thursday, May 11, 2:30 PM–5:00 PM
Location: Comiskey
Chair: Larry J. Siever
Co-Chair: Walter H. Kaye

20. PET IMAGING OF SEROTONIN RESPONSIVITY: RELATIONSHIP TO MOOD AND IMPULSIVITY


Department of Neuroscience, New York State Psychiatric Institute; Dept. of Psychiatry, Columbia University, New York, NY 10032

Postmortem studies by our group and others have shown that a ventral prefrontal cortical abnormality in serotonin indices is associated with