13. GONADAL STEROIDS, BRAIN, AND BEHAVIOR

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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

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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 p-oCRH 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

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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-tetrahydrodroprogesterone, 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


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Postmortem studies by our group and others have shown that a ventral prefrontal cortical abnormality in serotonin indices is associated with
suicidal behavior in contrast to major depression, where a diffuse abnormality in serotonergic function is found throughout the prefrontal cortex. Differences also exist in other brain regions between the findings in depression vs. suicidal behavior. Given that suicidal behavior is also associated with increased lifetime aggression and impulsivity, we have postulated that there is a fundamental deficiency in the restraint mechanisms located in the prefrontal cortex and the amygdala, in terms of aggression. We have evaluated serotonergic responses to fenfluramine using positron emission tomography (PET) with \(^{18}F\)-fluorodeoxyglucose (\(^{18}FDG\)) and found that there are abnormalities associated with depression and a specific abnormality in the prefrontal cortex associated with highly lethal suicidal behavior. The degree of this abnormality in depression is reduced by serotonin release with fenfluramine. The difference between individuals who have made low lethality suicide attempts and those who have made high lethality suicide attempts is also sensitive to the effects of serotonin release. These studies add to the body of literature implicating serotonergic function in suicidality, an abnormality that is independent of that associated with mood disorders.

21. BULIMIA NERVOSA: A DISTURBANCE OF SEROTONIN/ORBITAL FRONTAL CORTEX MODULATION?

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Bulimia nervosa (BN), which tends to occur in adolescent women, is characterized by extremes of eating, mood, an impulse control. Recent studies suggest that BN is highly heritable and may involve a trait related disturbance of serotonin activity. For example, recovered BN women have increased levels of CSF 5-HIAA compared to control women (CW), but normal CSF HVA and MHPG concentrations. Positron emission tomography (PET) with serotonin radioligands, such as \(^{18}F\)altanserin, a 5-HT2A receptor antagonist, offers the potential for new understanding of previously inaccessible brain 5-HT function and its dynamic relationship with human behaviors. To avoid the confounding effects of pathologic eating behavior, we studied women after long-term recovery (>1 y no bingeing or purging, normal weight, and regular menstrual cycles) from BN. Nine BN subjects were compared to 12 healthy CW of similar ages and weight. \(^{18}F\)altanserin binding was significantly reduced (p < 0.05) in both medial orbital frontal cortex regions of recovered BN women compared to CW but not in other cortical regions. Persistent serotonergic and behavioral abnormalities after recovery raise the possibility that these psychobiological alterations may be trait-related and contribute to the pathogenesis of BN. In human and non-human primates, disturbances of both the orbital frontal cortex and serotonin neuronal activity has been implicated in disorders characterized by either behaviorally overcontrol or dyscontrol. These findings raise the possibility that extremes of control and dyscontrol in BN may be related to 5-HT alterations in the medial orbital frontal cortex.

Age was significantly inversely correlated with 5-HT2A binding in CW for almost all cortical regions. In contrast, there was no relation between receptor binding and age in any cortical region in recovered BN women. It is well known that age-related changes occur in 5-HT neuronal activity. BN invariably begins within a narrow post-pubertal age range. While speculative, these data suggest the possibility that the age specific onset of eating disorders may reflect the failure to engage some developmental mechanism related to 5-HT neuronal activity.

22. SEROTONERGIC RESPONSIVENESS IN IMPULSIVE/AGGRESSIVE PERSONALITY DISORDERS


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Reduced serotonergic activity has been implicated in the impulsive/aggressive personality disorders for over two decades in studies of CSF serotonin metabolites, neuroendocrine responses to serotonergic probes, postmortem studies, and peripheral measures of serotonergic activity. It is now possible to image serotonergic responsiveness in relevant brain systems in response to serotonergic probes to evaluate serotonergic responsiveness in critical regions that modulate aggression. These include prefrontal cortex, particularly orbital frontal cortex, cingulate and related limbic structures. In the first study, 6 impulsive aggressive patients and 5 normal controls were administered 30 mg of the 1-Fenfluramine or placebo. The impulsive aggressive patients demonstrated reduced activation in regions of orbital frontal cortex, medial frontal cortex, and cingulate cortex. In a second study 14 impulsive-aggressive personality disorder patients, 2 patients with other personality disorders, and 6 normal controls were administered 0.08 mg/kg of m-chlorophenylpiperazine (m-CPP) and/or placebo to determine whether this more selective 5HT2 probe also results in blunted prolactin responses. Results of the m-CPP study in relation to the fenfluramine study and pilot studies of serotonergic ligands will be presented.

23. IMAGING THE SEROTONIN SYSTEM IN AGING AND LATE-LIFE NEUROPSYCHIATRIC DISORDERS

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Serotonin (5-HT) plays a modulatory role in the central control of mood, cognitive function and a variety of human behaviors. Age effects on serotonergic function may be responsible for the normal spectrum of behavioral alterations observed in the elderly, and may contribute to the vulnerability of the elderly to depression. Further, pathologic changes in serotonergic function could be linked to mood and behavioral changes frequently accompanying Alzheimer’s disease (AD).

The recent development of selective markers for the 5-HT system, in conjunction with methodological advances in image processing, including partial volume correction, have made it now possible to quantitatively image important 5-HT markers in aging and late-life neuropsychiatric disorders. These include ligands for the 5-HT transporter, and the 5-HT1A and 5-HT2A receptors. The in vivo measurement of 5-HT markers provides a means to evaluate serotonergic function in early disease states and serially pre- and post-intervention, features that represent substantial advantages over postmortem assays. PET imaging has verified a striking reduction in 5-HT2A receptor binding with age, and preliminary evidence suggests an interaction between gender and aging effects on the 5-HT1A receptor. These findings are in accord with the hypothesis that aging changes in serotonergic function may predispose the elderly to depression and behavioral alterations. Preliminary data on 5-HT PET imaging in depressed patients and in AD will also be reviewed. The long-term goals of this work are to further characterize the serotonergic profile of normal aging and to guide therapeutic approaches to late-life neuropsychiatric disorders.