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 med orbitofrontal 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 behavioral 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 support 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-HT1A 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.