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?

W.H. Kaye, G.K.W. Frank, C. Meltzer, J. Price, W.C. McConaha

Western Psychiatric Institute and Clinic, Pittsburgh, PA 15213

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 $^{18}$Faltanserin, 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. $^{18}$Faltanserin 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 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


Department of Psychiatry, Mount Sinai School of Medicine, New York, NY 10029

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 $\beta$-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 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

C.C. Meltzer

Departments of Radiology and Psychiatry, University of Pittsburgh School of Medicine, Pittsburgh, PA 15213

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-HT2A receptor, and the 5-HT1A and 5-HT3A 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.
Frontotemporal Dementias: Clinical Correlates to Cellular Substrates
Thursday, May 11, 2:30 PM–5:00 PM
Location: Toronto
Chair: Anand Kumar
Co-Chair: Ralph Nixon

24. CLINICAL, NEUROPATHOLOGICAL AND NEUROIMAGING CORRELATES OF FRONTOTEMPORAL DEMENTIA (FTD)

A. Kumar
U.C.L.A. School of Medicine, Neuropsychiatric Institute, Los Angeles, CA 90024-1759

Frontotemporal dementias (FTD) comprise a heterogeneous group of neurobehavioral disorders characterized by behavioral aberrations and progressive cognitive decline. The behavioral features typically include disinhibition, verbal outbursts, and apathy. The cognitive abnormalities comprise of decline in memory, language and executive functions. Visual-spatial functions are noticeably spared. The pathologic correlates of FTD include neuronal atrophy, gliosis and spongiosis in the frontal and temporal lobes with sparing of the more posterior regions. Neuritic plaques and neurofibrillary tangles are characteristically absent in FTD. Neuroimaging studies with single photon emission computed tomography and Xenon inhalation techniques demonstrate deficits in perfusion largely restricted to the frontal and anterior temporal regions. Both sporadic and familial forms of the disorder have been described and extrapyramidal features occur in certain, though not all, subgroups. FTD is a compelling model of behavioral disorders with clear-cut neurologic and neurobiological underpinnings. They comprise approximately 15 percent of early onset degenerative disorders and their clinical impact in getting increasing recognition. This presentation will focus on new developments within the clinical and neuropathological realm, and emphasize the neurobiological implications of the clinical and genetic heterogeneity frequently encountered in FTD. It will also serve as a broad based introduction to the other components of this panel—which will underscore the genetic, cellular and gene therapeutic aspects of FTD and closely related neurodegenerative disorders.

25. NEUROGENETICS OF FTD—RECENT DEVELOPMENTS

D. Geschwind
U.C.L.A. School of Medicine, Department of Neurology, Los Angeles, CA 90024-1759

There is a striking genetic predisposition to FTD, as from 40 to 50% of patients have a family history of an FTD spectrum disorder, and most are consistent with dominant transmission. Genetic analysis has determined that a series of disorders related clinically and pathologically to frontotemporal dementia (FTD), collectively labeled FTDP-17 disorders, are etiologically related. The relationship between these disorders although initially based on linkage analysis, has been confirmed by the discovery of causal mutations in the tau gene in some families with FTDP-17 disorders. Mutations affecting the expression or structure of the microtubule binding domain of the tau gene have been found about 25% of large families with chromosome 17q21-22-linked disease, but rarely in sporadic cases. Functional studies implicate alterations in the microtubule binding domain in various splice isoforms of tau, but other genes are likely to be involved. Remarkable heterogeneity in clinical and pathological presentations can be seen, even among those with the same mutation. The basis for this variability is unknown. The functional implications of known mutations will be emphasized and the phenotype-genotype correlations will be discussed.

26. THE PATHOBIOLOGY OF TAU PROTEIN IN NEURODEGENERATIVE DISEASES

R.A. Nixon, K. Duff, Y. Matsuoka
Nathan Kline Institute and New York University School of Medicine, Orangeburg, NY 10962

Aggregates of the tau protein in the form of paired-helical filaments are one of the hallmark lesions of Alzheimer’s Disease. The significance of tau to mechanisms of neurodegeneration is now underscored by the identification of mutations of tau causing frontotemporal dementia (FTD). As one of a diverse group of microtubule-associated proteins (MAPs), tau binds and stabilizes microtubules (MT), which serve as structural elements and as tracks for the axonal transport of vesicular organelles, thereby supporting axon function and synaptic transmission. The six isoforms of tau generated by alternative splicing of a single gene vary in their affinity for MT and efficiency in inducing the polymerization of tubulin to form MT. FTD-causing mutations alter the proportions of tau isoforms and result in tau proteins with reduced ability to promote MT assembly although this effect alone is unlikely to account for the autosomal dominant nature of FTD. When the tau gene is deleted in mice, only subtle phenotypic changes are seen suggesting that other MAPs can substitute for tau function. These and other findings support a toxic gain of function, rather than loss of tau function, as the underlying effect of FTD-related mutations. In this regard, recent studies suggest that FTD-mutant tau may bind abnormally and disassemble MT, which might then lead to axonal transport failure. Another property of tau is its proclivity for aggregating into inclusions with distinctive morphologies (eg. NFT in AD, ribbon-like filaments in FTD). As in other human neuronal inclusion diseases, the role of aggregation in the degenerative mechanism (eg. protection vs toxicity) is unclear. Tau undergoes complex phosphorylation during development. In human tauopathies, tau is hyperphosphorylated, which decreases its association with MT and promotes its aggregation. Recently, tau has been found to interact with the non-receptor tyrosine kinase fyn and other src family tyrosine kinases and is tyrosine phosphorylated suggesting a role for tau in signal transduction. A host of tau transgenic mouse models are being developed to investigate tau pathobiology and new findings on these models and their relationship to FTD in humans will be discussed.

27. REVERSAL OF SPONTANEOUS ATROPHY OF CHOLINERGIC BASAL FOREBRAIN NEURONS IN THE AGED PRIMATE BY EX VIVO GENE THERAPY

D.E. Smith (1), J. Roberts (2), F. Gage (3), M.H. Tuszyński (4)

(1) Department of Neurosciences, University of California at San Diego, La Jolla, CA; (2) California Regional Primate Research Center, University of California at Davis, Davis, CA; (3) Salk Institute for Biological Studies, La Jolla, CA; (4) Veterans Affairs Medical Center, San Diego, CA

Recent pre-clinical developments in gene therapy in primates could have practical implications for degenerative disorders such as frontotemporal dementias (FTD) in humans. Ex vivo gene therapy is a...