strategies for providing therapeutic substances to brain parenchyma in a regionally-restricted and sustained manner. A potentially therapeutic substance is nerve growth factor (NGF), a target-derived neurotrophic factor known to influence phenotypic expression in neurons of the basal forebrain cholinergic (BFC) system. Neurons in this region provide essentially all cholinergic innervation to the cortex, have been shown to regulate cortical activity, and are involved in modulation of attention and some aspects of memory. Further, these neurons are known to degenerate as a prominent component of Alzheimer’s disease. Delivery of NGF to the cholinergic basal forebrain has been shown to prevent injury-induced degeneration in both rats and primates. However, delivery of NGF to extensive areas of the brain can induce hyperalgesia, hypophagia, weight loss, and sprouting of sensory and sympathetic neurons into the central nervous system. NGF, delivered to the BFC neurons by intraparenchymal ex vivo gene therapy, was previously demonstrated to reverse naturally-occurring age-related memory loss in aged rats, without inducing any of the aforementioned adverse reactions. In this study (D.E. Smith et al, PNAS 1999, Vol. 96:10893–10898), we investigated the effects of NGF on the BFC neurons in the aged primate. Basal forebrain cholinergic neurons in the aged primate were found to have reduced expression of phenotype-specific markers and to have undergone cellular atrophy, when compared with younger primates. Primary autologous fibroblasts were transduced to express and secrete NGF and then transplanted into the aged primate cholinergic basal forebrain. NGF restored expression of cholinergic-specific proteins and reversed cellular atrophy in the aged primate brain. The implications of these findings to degenerative disorders in general, and FTD in particular, will be discussed.

From Molecular Genetics to Gene Expression Profile Analysis in Mental Retardation—Making Sense Out of Sequence
Thursday, May 11, 2:30 PM–5:00 PM
Location: Acapulco
Chair: Giulio Maria Pasinetti
Co-Chair: Eric London


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Rett syndrome (RTT) is a progressive neurodevelopmental disorder with an incidence of 1 in 15,000. Girls with classic RTT appear to develop normally until 6–18 months of age, then gradually lose speech and purposeful hand use and develop microcephaly, growth retardation, seizures, ataxia, intermittent hyperventilation and stereotypical hand movements. RTT occurs sporadically in 99.5% of cases. Exclusion mapping studies of a few familial RTT cases, assuming X-linked inheritance, mapped the locus to Xq28. By positional candidate gene testing, we identified mutations in the gene encoding the X-linked methyl-CpG-binding protein 2 (MeCP2) as the cause of Rett syndrome. MeCP2 selectively binds to 5-methylcytosines in CpG dinucleotides and mediates transcriptional repression through interaction with the histone deacetylase/Sin3A silencing complex. All missense mutations are de novo and affect evolutionarily conserved amino acids in the region encoding the methyl-binding domain (MBD) and/or the transcriptional repression domain (TRD). Mutations causing premature termination of translation include nonsense and frameshift mutations that predict the synthesis of truncated proteins. Both nonsense (R168X, R255X) and missense (R106W, R306C) mutations have been found with multiple recurrences. The R168X mutation was identified in six unrelated sporadic cases as well as in two affected sisters and their normal mother. All nucleotide substitutions involved C to T transitions at CpG hotspots. This mechanism would account for preferential paternal origins of de novo MeCP2 mutations. A 806delG deletion causing a V288X stop in the TRD was identified in; a woman with motor coordination problems, mild leaning disability and skewed X inactivation; in her sister and daughter affected with classic RTT; and in hemizygous son who died from congenital encephalopathy. Thus, some males with RTT-causing MeCP2 mutations may survive to birth and female heterozygotes with favorably skewed X inactivation patterns may have little or no involvement. Therefore, MeCP2 mutations are not limited to clinically defined RTT and may be implicated in a much broader phenotypic spectrum. Current work aims to identified the target genes of MeCP2-dependent silencing that may be abnormally expressed as a result of MeCP2 mutations.

29. DIFFERENTIAL GENE EXPRESSION IN HUMAN POSTMORTEM RETT SYNDROME BRAIN REVEALED BY cDNA MICROARRAY

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Rett Syndrome (RS) is a developmental neurological disorder which has been described virtually exclusively in females. Previous studies have described gross anatomical and neurochemical pathology in RS, while genetic linkage analysis has identified Xq28 as the chromosomal region harboring the primary genetic defect in RS. Recently, it has been discovered that mutations in the MeCP2 gene cause RS. Despite this intense investigation, the molecular basis of RS neuropathology remains unclear, and there exists no effective therapy for RS. In order to gain
30. GENETICS OF AUTISM


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Concordance rates for monozygotic and dizygotic co-twins of autistic probands indicate that there is a profound genetic component to autism and that inheritance is likely to be non-Mendelian. We have ascertained families with two or more individuals with autism or the related disorders of pervasive developmental disorder (PDD) and Asperger’s syndrome. Blood samples were collected from affected, parents, and unaffected siblings and used for a genome-wide linkage study. A two-stage design was adopted in which genotyping is first carried out with markers at an average density of 10 cM in one set of families and markers demonstrating evidence for linkage passing threshold (HLOD or NPL > 1) are then genotyped in an additional sample. In our initial sample of ~60 families, over 30 markers surpassed the threshold. Second stage screening for an additional ~60 families is underway and will be followed by analyses of flanking markers in the entire sample for markers passing threshold in both samples. Attempts to replicate other studies indicating linkage to chromosomes 6, 7, 13 and 15, or allelic disequilibrium to chromosome 15 are being carried out in the combined sample. In our initial sample of 60 families is underway and will be followed by analyses of flanking markers in the entire sample for markers passing threshold in both samples. Attempts to replicate other studies indicating linkage to chromosomes 6, 7, 13 and 15, or allelic disequilibrium to chromosome 15 are being carried out in the combined sample. In the first sample, no evidence of linkage to chromosome 6, 13, or 15 were observed. In contrast, allelic disequilibrium with GABAR markers was observed in the larger sample.

31. MOLECULAR CHARACTERIZATION OF THE AUTISTIC BRAIN USING THE HIGH-DENSITY MICROARRAY TECHNIQUE

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Autism is a severe, lifelong behavioral disorder characterized by deficits in reciprocal social interactions and communication in conjunction with restricted and stereotypic behaviors and interest. Presently the neurobiological basis of autism is not well established. The most consistent observations are those based primarily on postmortem neuropathological studies, which associated autism with a reduction in the number of Purkinje cells in the cerebellum. Accumulating evidence suggests the cerebellum may have a significant role in a variety of nonmotor functions including sensory and motor integration, learning and modulation of affect, motivation and social behavior. Thus cerebellar neuropathology likely contributes to autistic behavioral dysfunction. There is little information at the molecular level on how the structure and function of the cerebellum is affected in autism. To extend our understanding of how cerebellar changes may contribute to autistic dysfunction, we have initiated a program to identify and characterize genes with abnormal patterns of expression in the cerebellum of autistic patients. Our strategy is to compare the gene expression profile of postmortem cerebellar specimens from autistic patients against normal age-matched, non-demented control subjects using the microarray hybridization technology. Using this process, we are analyzing 5,700 genes of known function and will be able to identify autism-related genes. We will categorize these genes into functional clusters defined by their cellular and biochemical functions. Results from our studies are expected to provide insight into the cellular and biochemical pathways underlying the relationship between autistic neuropathology and symptomatology.

Serotonin Transporter Genotype Effects on the Development of CNS Serotonin Function, Behavior, and Psychopathology

Thursday, May 11, 2:30 PM–5:00 PM
Location: Gold Coast
Chair: J. Dee Higley
Co-Chair: Klaus-Peter Lesch

32. BEHAVIOR GENETICS OF THE SEROTONIN TRANSPORTER: SEARCHING FOR EPISTATIC INTERACTIONS

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The serotonin transporter (5HTT) is critical to the subsistence of brain serotonin (5HT) homeostasis. It is the initial target for both antidepressant compounds and drugs of abuse. A polymorphism in the 5-flanking regulatory region of the 5HTT gene that results in allelic variation in 5HTT expression and function is associated with anxiety-, depression-, and aggression-related personality traits and is likely to influence syndromal dimensions of various psychiatric disorders associated with these traits. The relative influence of genetic and environmental factors on human temperamental and behavioral differences is among the most prolonged and contentious controversies in the intellectual history of man. Although current views emphasize the joint influence of genes and environmental sources, the complexities of gene-gene and gene-environment interaction represents a research area which has barely been touched empirically. Investigation of epistatic interactions in rhesus monkeys and humans as well as gene inactivation studies in mice support the view that adaptive 5HT uptake function is essential for brain development, neuroplasticity, and complex behavior. Despite evidence for a substantial contribution of the 5HTT to the formation of synaptic connections in the mammalian brain during development, adult life, and old age, detailed knowledge of the molecular mechanisms involved in these fine-tuning processes are