functioning, serotonin-related behaviors, and psychopathological disorders. A similar polymorphism, believed to be homologous, also exists in nonhuman primates. We have recently analyzed the relationship between the rhesus macaque serotonin transporter (rh5-HTTLPR) genotypes, CSF 5-HIAA concentrations, and aggression. Our results show that rhesus macaques with the short rh5-HTTLPR allele have low CSF 5-HIAA concentrations, and are highly aggressive. However, the phenotypic expression of this short allele is environmentally-dependent, with the short allele associated with low CSF 5-HIAA concentrations only in subjects reared in age-matched peer groups that lack adult influence. Aggression was shown to be higher in subjects with the short allele than in subjects with the long allele regardless of early rearing experiences. In humans, the 5-HTTLPR is associated with early infant temperament. Similar data for neonatal rhesus monkeys were collected during assessments on days of life 7, 14, 21 and 30. Subjects with the short rh5-HTTLPR variant exhibit diminished orientation, attention, and increased emotional responses. Consistent with our earlier findings, these differences were generally exaggerated by paternal deprivation. These findings illustrate the interacting influence of genotype and early rearing experiences on the developing phenotype.

37. REDUCED EXPRESSION OF PKC ISOZYMES IN THE BRAINS OF TEENAGE SUICIDE VICTIMS

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We have recently reported that the binding of [3H]phorbol dibutyrate to protein kinase C (PKC), which is an important component of the phosphoinositide (PI) signaling system, is significantly reduced in Broadmann’s Areas (BA) 8/9 of suicide victims. We have now determined PKC activity; and protein and mRNA expression of PKC isozymes by immunolabeling and quantitative RT-PCR, respectively, in BA 8/9 and hippocampus of suicide victims and matched control subjects. Postmortem brain samples were obtained from the brain collection program of the Maryland Psychiatric Research Center and the diagnosis was made by DSM-IV and diagnostic evaluation after death (DEAD) instruments. We found that PKC activity was significantly lower in BA 8/9 and hippocampus in suicide victims as compared with the control subjects. We also observed that the immunolabeling of PKCα, β, and γ isozymes was significantly decreased in both the brain areas of the suicide victims. To examine if the decrease in protein expression of PKC isozymes is associated with decreased mRNA level, we are currently determining mRNA levels of PKC isozymes using RT-PCR method and so far have observed that the PKCα mRNA expression is significantly decreased in BA 8/9 of suicide victims. Further results are awaited. Our results suggest that the reduction in PKC recognition sites in BA 8/9 of teenage suicide victims is associated with decreased PKC activity as well as the immunolabeling of PKCα, β, and γ isozymes, and further suggests that teenage suicide may be associated with an impaired PI signaling system.

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38. MOTOR PROGRAMMING DEFICITS IN DEPRESSION: SUPPORT FOR A DOPAMINERGIC MECHANISM

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Several investigators have reported parallels between motor and cognitive slowing in patients with major depression (MD). Such a relationship between depression and motor function suggests the possibility of a shared neuropathologic mechanism. This mechanism has remained elusive largely because depression may involve any of several neurotransmitters. While others have shown that MD and parkinsonism share a number of features, especially in the motor domain, previous technologies have not delineated the cognitive from neuromotor aspects of the motor impairment in MD. The aim of the present study was to examine motor programming in MD patients...
using a measure adopted from studies of parkinsonian bradykinesia. There is a general consensus that parkinsonian bradykinesia stems from an inability to modify, or scale, velocity during movement. In the present study, we hypothesized that a substantial proportion of MD patients would exhibit deficits in velocity scaling. Our measure of velocity scaling quantifies the extent to which a subject programs or scales movement velocity in anticipation of increasing target distance. We studied 54 patients who met DSM-IV criteria for major depression and 26 age and gender comparable healthy comparison subjects. All MD patients were unmedicated at the time of testing. An instrumental measure of wrist movement was developed to quantify several aspects of movement including reaction time (RT), peak velocity (PV), and velocity scaling (VS). Subjects were instructed to flex their wrist when a target box appeared on the computer screen and to reach the target as quickly and as accurately as possible. Results indicated that MD patients exhibited significantly (p < 0.001) longer mean RT (477 ms) than comparison subjects (391 ms). There was a trend (p = 0.07) for MD patients to have lower scores on the VS measure (2.68 deg/sec/deg) compared with comparison subjects (3.33 deg/deg). 53.7% of the MD patients had VS scores lower than the 95th percentile of the comparison subjects. These findings suggest that MD patients as a group exhibit delayed reaction times. Nevertheless, a significant proportion of MD patients also exhibit disturbances in the programming of movement velocity reflective of a putative dopaminergic disturbance, similar to that seen in parkinsonism.

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39. INHIBITORY EFFECTS OF OMEGA-3 FATTY ACIDS ON PROTEIN KINASE C ACTIVITY IN VITRO

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Preliminary data indicate that omega-3 fatty acids may be effective mood stabilizers for patients with bipolar disorder. Both lithium and valproic acid are known to inhibit protein kinase C (PKC) activity after subchronic administration in cell culture and in vivo. The current study was undertaken to determine the effects of the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) on protein kinase C phosphotransferase activity in vitro. Various concentrations of DHA, EPA, arachidonic acid, lithium and valproic acid were incubated with the catalytic domain of protein kinase C beta from rat brain, as well as the alpha and epsilon isoforms of protein kinase C. Protein kinase C activity was measured by quantifying incorporation of [32P]PO4 into a synthetic peptide substrate. Both DHA and EPA, as well as the combination of DHA and EPA, inhibited activity of the catalytic subunit of PKC beta at concentrations as low as 10 micromoles/L. In contrast, lithium, valproic acid and arachidonic acid had no effect on PKC activity. Results of the effects of omega-3 fatty acids, lithium, and depakote on the alpha and epsilon isoforms of PKC will also be reported. DHA and EPA significantly inhibit the activity of the catalytic domain of PKC beta in a manner distinct from lithium and valproic acid. Hence, PKC represents a potential site of action of omega-3 fatty acids in their effects on treatment of bipolar disorder.

40. SMOKING AND PANIC DISORDER: AN EPIDEMIOLOGIC INVESTIGATION

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Epidemiologic studies have reported a lifetime association between smoking and panic disorder. In this study we examine potential explanations for this association. Analysis was conducted on data from two epidemiologic studies, the Epidemiologic Study of Young Adults in southeast Michigan (N = 1,007) and the National Comorbidity Survey, Tobacco Supplement (public use data) (n = 4,411). Cox proportional hazards models with time-dependent covariates were used to estimate the risk for onset of panic disorder associated with prior daily smoking and vice versa, controlling for history of major depression. The role of lung disease in the smoking—panic association was explored. Parallel analyses of the two epidemiologic data sets revealed that daily smoking signaled an increased risk for first occurrence of panic attack and disorder; the risk was higher in active smokers than in past smokers. These relationships held in both males and females with no evidence of sex interactions. No significant risk was detected for onset of daily smoking in persons with prior panic attack or disorder. Exploratory analyses suggest that lung disease might be one of the mechanisms linking smoking to panic attacks. The evidence that the association between smoking and panic disorder might result primarily from an influence in one direction, i.e., from prior smoking to first panic attack, and the possibility of a higher risk in active than in past smokers suggest a causal hypothesis for the smoking—panic relationship.

41. FAMILIAL SCHIZOPHRENIA SPECTRUM DISORDERS IN CHILDHOOD- AND ADULT-ONSET SCHIZOPHRENIA


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Preliminary evidence suggests an increased rate of schizophrenia spectrum disorders in the relatives of patients with childhood-onset schizophrenia when compared with relatives of control children. In this study, the rates of schizophrenia spectrum disorders were compared in parents of childhood-onset and adult-onset schizophrenics. Eighty-nine parents of 49 childhood-onset schizophrenia patients and 53 parents of 32 adult-onset schizophrenics were interviewed using structured instruments to determine the presence of schizophrenia spectrum disorders. Information on a further six parents of adult-onset patients was obtained through structured interviews of family members. Parents of the adult-onset patients were significantly older than parents of the childhood-onset patients. Despite this, and without correction for age differences, the interviewed parents of the childhood-onset patients had significantly more schizophrenia spectrum disorders (20: 1 schizophrenia, 10 schizotypal personality disorder, 9 paranoid personality disorder), whether when compared with only those parents of adult-onset patients who had been interviewed in person (3: 1 schizotypal personality disorder, 2 paranoid personality disorder) (χ² = 7.1, df = 1, p = 0.008) or if the relatives about whom information was obtained from family members were included (6: 1 schizotypal personality disorder, 5 paranoid personality disorder) (χ² = 3.8, df = 1, p = 0.05). Among interviewed reatives, the risk