out = −0.90, early in vs. late out = −0.061, early out vs. late in = 0.195. The early gating in measure positively correlated with the amplitude of the P300 (r = 0.806, p (two tailed) <.02). These data suggest that the four components of sensory gating may be reflecting different neural sensory processes and also suggest a possible influence of the early capacity to identify deviant input on amplitude of the P300.

65. 31P NMR OF PHOSPHOLIPIDS IN POSTMORTEM SCHIZOPHRENIC BRAINS

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It has been hypothesized that schizophrenia arises from cell membrane abnormalities due to changes in phospholipid (PL) composition. Studies on erythrocytes and platelets suggest that alterations in membrane PL composition play a role in schizophrenia. It is essential to measure PL composition in the brain itself, which typically is only possible postmortem. In vivo 31P NMR of PL precursors and degradation products suggested changes in PL metabolism in the brain in schizophrenia, but solid-like PLs are not visible in typical in vivo NMR studies. Tissue PLs can be characterized according to headgroup and acyl-side-chain unsaturation using in vivo 31P NMR. Postmortem brain tissue (gray matter) was obtained from left frontal cortex of 5 schizophrenics and 5 controls. High resolution 31P NMR spectra were obtained at 121.65 MHz. Phosphatidylinositol (PI) was significantly higher in the schizophrenic group relative to controls (p < 0.045). There were no differences between the two groups for other PL headgroups. The intensity of the PC peak representing molecular species with one saturated and one unsaturated acyl chain was higher in the schizophrenic group (p < 0.043). These results support the notion that PL abnormalities occur in the brain in schizophrenia, and that fatty acid metabolism may be abnormal. These observations have the advantage that they pertain to brain tissue, and not peripheral tissue. However, the possible confounding effects of antipsychotic medication and perinortem factors must be considered.

66. NEUROPSYCHOLOGICAL FUNCTION DURING SMOKING CESSATION IN SCHIZOPHRENIA


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Schizophrenic patients have high co-morbid rates of nicotine dependence (58–88%) and well-characterized deficits in neuropsychological function. In particular, there is evidence that schizophrenic patients have abnormalities in executive function, response inhibition, visuospatial working memory, and attention and concentration. Cigarette smoking by schizophrenics may reduce negative symptoms and cognitive deficits through amelioration of prefrontal cortical dopaminergic (DA) hypofunction. There is evidence from our group and others that atypical antipsycho-otic agents, which augment cortical DA function, may ameliorate negative symptoms and neurocognitive deficits and reduce cigarette smoking in schizophrenics. Thus, evaluation of neuropsychological function in smoking maxerics during a smoking cessation trial may yield important information on the effects of cigarette smoking and tobacco withdrawal on neuropsychological function in these patients.

Given the role of catecholamine mechanisms in nicotine dependence, the present study evaluated the effects of two catecholaminergic agents, Buproprion SR [a DA and norepinephrine (NE) reuptake inhibitor] and Selegiline [a monoamine oxidase B inhibitor which preferentially augments DA and NE function], on neuropsychological function in schizophasenic (Buproprion SR) and control smokers (Selegiline) participating in placebo-controlled smoking cessation pharmacotherapy studies. We have developed a computerized neuropsychological battery which includes the Wisconsin Card Sorting Test (executive function), Stroop Test (response inhibition), Continuous Performance Test (attention and concentration), visuospatial working memory and Serial Reaction Time (procedural memory). Schizophrenic subjects are known to have performance deficits on these tasks. Preliminary results indicate discrete baseline deficits in neuropsychological function (i.e. VSTM, Stroop Test) in schizophrenic vs. control smokers, and these changes in neuropsychological function are dependent on smoking status during the trial (i.e. abstinence vs. continued smoking) and study medication. Results from the complete sample of n = 30 schizophrenic and n = 30 healthy control smokers will be presented at the meeting.

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67. NEUROPROTECTIVE ACTIONS OF OLANZAPINE IN RAT: CHOLINERGIC FUNCTION

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Olanzapine (OLZ) treatment does not seem to induce extrapyramidal side-effects (EPS, i.e., drug-induced parkinsonism) similar to the haloperidol (HAL) treatment of psychotic patients. These EPS are indicative of the later development of serious abnormal involuntary movements, Tardive Dyskinesias (TD). In addition, olanzapine treatment seems to very significantly improve cognitive performance and decrease negative symptoms, particularly in patients previously treated with haloperidol. Haloperidol treatment in rats has been found to affect the brain, particularly the cholinergic system, and behavior. Therefore, the possible neuroprotective actions of OLZ against the haloperidol effects were studied in rats.

Three groups of rats (CON, HAL, OLZ) were treated for 45 days and 90 days. After 45 days of treatment, one third (N = 15) of the rats in each of the HAL and OLZ groups were switched to OLZ and HAL, respectively, in order to determine the protective/restorative actions of OLZ against HAL effects. Cognitive performance was determined using Morris Water Maze, and then the alterations in CNS cholinergic system were determined by immunohistochemical method using antibody to choline acetyl transferase (anti-ChAT). The forty five days of treatment with either HAL or OLZ did not affect the cognitive performance. However, 90 days of HAL but not OLZ treatment significantly impaired cognitive performance and also reduced the swim speed. Furthermore, both 45 as well as 90 days of HAL treatment altered the cholinergic system: reduced number of ChAT reactive neurons, processes, varicosities and synapses indicating that the structural changes precede the behavioral effects. However, both 45 or 90 days of OLZ treatment did not
affect the cholinergic system. Moreover, both pre- as well as post-treatment with OLZ prevented the haloperidol effects on the cholinergic system cognitive performance, indicating that OLZ may have neuroprotective effects.

68. NEUROPROTECTIVE ACTIONS OF OLanzapINE IN RAT: MECHANISM

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Psychotic patients treated with olanzapine (OLZ) do not exhibit extrapyramidal side-effects (EPS) similar to patients treated with haloperidol (HAL). Also, OLZ treated patients show significantly improved cognitive performance and negative symptoms, including patients previously treated with HAL. Haloperidol has been suggested to cause/exacerbate the neuropathological changes that are relevant to some of the side-effects associated with its treatment. In animals, chronic HAL treatment has been found to cause neuropathology that is relevant to the behavioral effects, and this neuropathology is suggested to be a result of HAL associated free radical-mediated cellular damage. A possible mechanism of neuroprotection by OLZ against HAL induced neuropathology were studied in rats.

Three groups of rats (CON, HAL, OLZ) were treated for 45 days and 90 days. After 45 days of treatment, one third (N = 15) of the rats in each of the HAL and OLZ groups were switched to OLZ and HAL, respectively, in order to determine the protective/restorative actions of OLZ against HAL effects. The cellular effects were investigated by staining for DNA breaks that are often caused by free radical action and/or during replication/translation. The cells were also stained with neuronal and glial markers to identify the cell types. After 45 days of treatment, a higher number of cells were labeled in cerebral cortex in OLZ group than HAL group, but fewer number of cells were labeled in caudate/putamen. The labeled cells were of both neuronal and glial types. There were no labeled cells in control group. The number of cells labeled decreased after 90 days of treatment proportionately in both drug groups but did not reach to the levels in controls. Pre-treatment with OLZ reduced the number of cells labeled compared to HAL treatment alone. The level of brain lipid peroxides, index of free radical damage, was higher in HAL group than OLZ group and was reduced by pre or post OLZ treatment, indicating that OLZ prevents the cellular neuropathology.

69. THOUGHT DISORDER AND LANGUAGE IN SCHIZOTYPAL PERSONALITY DISORDER


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Preliminary data from our laboratory have suggested that the amount and quality of thought disorder (as measured by the Thought Disorder Index [TDI]) in Schizotypal Personality Disorder (SPD) is similar to that found in schizophrenic (SZ) subjects and their relatives. The TDI score is based on a verbatim sample of language. Because verbal skills can be reduced in SPD, it is unclear how TDI scores might be related to general deficits in language skills. The purpose of the current study was to examine the relationship between TDI scores and performance on verbal neuropsychological measures in SPD. In addition to the TDI, 20 right-handed male SPD subjects were administered a battery of language-based neuropsychological tests, including vocabulary, reading, spelling, naming, repetition, comprehension, verbal fluency, and verbal learning. The group was divided into low (n = 10) and high (n = 10) TDI scorers; performance on verbal neuropsychological tests and demographic variables in these groups were compared. The groups did not differ in general verbal ability or language skills, nor were differences apparent in demographic variables, depression, or positive/negative symptom profile. In contrast, SPDs with higher TDI scores learned fewer words and used fewer semantic clusters on the California Verbal Learning Test (CVLT; p < .05), a measure which may be selectively impaired in SPD. The results suggest that thought disorder may be related to impaired verbal learning in SPD, and support hypotheses of disinhibition of the semantic language network in schizophrenia spectrum disorders.

70. ABNORMAL CORTICO-THALAMIC- CEREBELLAR CIRCUITRY IN SCHIZOPHRENIA

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Recent studies suggest that the dorsolateral prefrontal cortex (DLPFC), thalamus, and cerebellum may be important brain regions implicated in the neural circuitry of schizophrenia. Theoretical and empirical arguments have been presented for the importance of a cortico-thalamic cerebellar circuit (CTCC) both as a neural substrate for complex mental activities (such as language and memory), and to facilitate the smooth planning and execution of motor and cognitive activities. Substantial PET and fMRI data also appear to support the role of the CTCC in normal cognition. Furthermore, it has been suggested that disturbances in the CTCC could result in a number of the observed clinical symptoms in schizophrenia. In this study, proton magnetic resonance spectroscopic imaging ($^1$H MRSI) was performed to determine whether there was evidence for disturbances in neuronal/axonal integrity in the CTCC of male patients with schizophrenia by examining N-acetylaspartate (NAA; a selective neuronal/axonal marker). Seventeen medicated male schizophrenic patients (diagnosed by DSM-IV criteria) and eleven normal male controls underwent MRSI using a Siemens VISION MRI/MRS system. MRI included axial DSE and coronal MP-RAGE images. Multislice $^1$H MRSI (TR/TE = 1960/135 ms; $280 \times 280$ mm$^2$ FOV providing $8 \times 8$ mm$^2$ in plane resolution) was acquired using 3 parallel slices along the same orientation as the axial DSE. $^1$H spectra were obtained from individual voxels (1.5 ml) bilaterally in the DLPFC, prefrontal white matter, thalamus, and cerebellar vermis to obtain concentration estimates of NAA. SICORE software developed in our laboratory was used to determine the tissue contributions (gray matter, white matter, hyperintense white matter, CSF) to each MRSI voxel. Repeated measures ANOVA showed bilateral NAA reductions in the DLPFC (p = 0.0029), prefrontal white matter (p = 0.0072), and the thalamus (p = 0.0477) in the schizophrenic group compared to controls. ANOVA also revealed a significant NAA decrease in the cerebellar vermis of schizophrenics (p = 0.0019) compared to controls. There were no significant group or lateralized differences in voxels tissue composition for any of the brain regions studied. The NAA reductions in this neuronal circuit implies that there is neuronal and axonal dysfunction or loss in multiple neuroanatomically linked brain regions, and provides additional evidence that the CTCC is abnormal in schizophrenia.