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- or the post-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 (1H 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 MRA/MRSI using a Siemens VISION MRI/MRS system. MRI included axial DSE and coronal MP-RAGE images. Multislice 1H MRSI (TR/TE = 1960/135 ms; 280 x 280 mm2 FOV providing 8 x 8 mm2 in plane resolution) was acquired using 3 parallel slices along the same orientation as the axial DSE. 1H 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, hypointense 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 thalami (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 voxel 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.