45. CORTISOL LEVELS ARE CORRELATED WITH HIPPOCAMPAL N-ACETYLASPARTATE

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Background: We have recently reported that N-acetyl aspartate (NAA, a neuron marker) and creatine concentrations are significantly reduced in the hippocampus of PTSD patients when compared to control subjects in the absence of volume loss. This study focuses on the relationship of clinical symptoms and measures of HPA function in explaining the variance seen in hippocampal NAA in PTSD and control subjects.

Methods: Eighteen male patients with combat-related PTSD (mean age $51.2 + 2.5$ years) and 19 male control subjects (mean age $51.8 + 3.2$) were studied using MRI and 1H MRSI. Both groups had no alcohol and drug abuse during the past 5 years. HPA function was measured by sampling morning salivary cortisol pre and post low dose dexamethasone (0.5mg). PTSD symptoms were assessed with the Clinician Administered PTSD scale (CAPS).

Results: There were no significant differences between PTSD and control subjects in volumes of the hippocampus ($F=1.87$, $df=2$, 34, $p>0.1$) and the entorhinal cortex ($F=0.36$, $df=2$, 34, $p>0.5$). NAA concentrations were significantly lower by about 23% ($F=5.69$, $df=2$, 34, $p=0.008$) in both left and right hippocampus of PTSD when compared with controls. NAA was correlated to both pre-dex cortisol levels ($N= 22$, $r= .53$, $p= 0.013$) and post dex cortisol ($N=22$, $r= .65$, $p=.002$). A hierarchical linear regression model was developed to explain both left and right hippocampal NAA in the combined sample. In step 1 of this model, the CAPS score accounted for 13.2% of the variance in left hippocampal NAA ($F =4.2$, $p= .054$). In step 2, the addition of left hippocampal volume and entorhinal cortex volume added 15.7% of incremental variance ($F = 3.8$, $p= .027$). In step 3, entering pre- and post dexamethasone cortisol levels accounted for an additional 22.1% of the variance ($F = 5.4$, $p = .004$). For right NAA, in step 1 of this model, the CAPS score accounted for 13.6% of the variance ($F =4.3$, $p= .051$). In step 2, the addition of left hippocampal volume and entorhinal cortex volume added 6.5 % of incremental variance ($F = 2.7$, $p= .074$). In step 3, entering pre- and post dexamethasone cortisol levels accounted for an additional 11.8% of the variance ($F = 2.9$, $p = .045$).

Conclusions: The direct relationship between cortisol and NAA is consistent with the literature showing both low cortisol levels and hippocampal damage in PTSD. There are at least three possible interpretations of this: 1) at the level of cortisol values seen in our subjects, cortisol has a trophic effect on the hippocampus; 2) reduced hippocampal NAA is associated with altered hypothalamic input resulting in reduced CRF and ACTH production; and 3) the relationship is driven by chance alone.

46. IMPACT OF HALOPERIDOL ON MEASURES OF ATTENTION AND LEARNING IN HEALTHY NORMALS

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Background: Studying monkeys, Suri and Shultz conceptualized the patterns of discharge of dopamine neurons in the ventral tegmental area as an error signal assisting the animal to learn a delayed motor response task. In humans, haloperidol, a dopamine blocker decreases procedural learning when compared to placebo or amphetamine. The purpose of this study is to investigate the impact of haloperidol and diphenhydramine, a sedative devoid of dopamine blocking properties, on measures of attention and learning. Although we also measured treatment effects on error related negativities (ERNs) in the electroencephalogram (EEG), we report here only the behavioral findings.

Methods: 58 subjects were randomly assigned to one of three double-blinded conditions: haloperidol 3mg (N=18), diphenhydramine 25mg (N=20) and placebo (N=20) taken PO. After three hours, they completed the Eriksen Flanker task (EFT), part of the Miltner et al time estimation task and a time estimation learning task. The EEG was co-registered.

Results: The haloperidol group committed significantly more errors on the EFT when age was used as a covariate, but there was no statistical difference between diphenhydramine and placebo. Learning rates on the time estimation task showed the haloperidol group performed significantly worse than placebo, when age was used as a covariate.

Conclusions: These results suggest dopamine blockers such as haloperidol, even at low doses, selectively increase performance errors and impair learning. This appears to be attributable to dopamine blockade, and not to sedation, muscarinic or antihistamine properties, supporting the role of dopaminergic neurons in learning in humans.

47. COGNITIVE ENHANCEMENT IN SCHIZOTYPAL PERSONALITY DISORDER: A STUDY OF ADRENERGIC AND DOPAMINERGIC APPROACHES

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Background: Cognitive deficits are present in schizotypal personality disorder. Although these deficits are milder than those seen in schizophrenia, they are qualitatively similar. Modification of these cognitive deficits with pharmacological agents may provide insights into the basic biological processes underlying these impairments. Thus, in this study, treatment agents that specifically stimulate the adrenergic (guanfacine) and dopaminergic (pergolide) systems were administered to patients with SPD, with a focus on tests that had been shown in animal models to be related to these two transmitters.

Methods: Patients with schizotypal personality disorder (SPD) were treated with either guanfacine (2.0 mg./day) or pergolide (0.1 mg./day) or placebo. These patients were examined with traditional neuropsycholgical tests and cognitive measures of the maintenance and processing of contextual information. These tests include the modifixed A-X CPT, the n-back working memory test, and the Eriksen Flanker test as well as a number of comparison tests that meaure more general aspects of cognitive function.

Results: After four weeks of treatment, guanfacine-treated patients manifested several improvements in performance, relative to placebo: reductions in errors of commission due to responding to the X stimulus when it was not preceded by an A (B-X Errors) and increases in errors of commission due to responding to a non-X stimulus when preceded by the A (A-Y) errors on the CPT (both reflecting improved context processing), as well as improvement in n-back working memory performance. Further, verbal learning improved, while there were no changes in visuo-spatial processing compared to placebo. For pergolide, n-back performance also improved, as did performance on the PASAT, an additional working memory test. More modest improvements in accuracy on the Eriksen test and word-list learning were detected, while motor speed and spatial measures did not change with treatment.

Conclusions: These data provide preliminary evidence from an ongoing clinical trial, indicating that adrenergic and dopaminergic agents improve cognitive functions in SPD. The improvement effects appear relatively specific, in that tasks previously found to be sensitive to dopaminergic manipulations in primates were most responsive to these two pharmacological manipulations. These data provide some evidence for the promise of these two compounds to treat cognitive impairments in SPD and also may provide additional insights into the translation of animal pharmacological models into human use. Finally, these data suggest that treatment of cognitive deficits in SPD may be feasible with existing compounds, readily available to practicing psychiatrists.

48. ERK1/2 NUCLEAR TRANSLOCATION AND APD-INDUCED PLASTICITY

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Background: Dopamine D2 receptors are typical Gi/o-coupled receptors that represent key targets for antipsychotic drugs (APD). The therapeutic effects of these drugs are delayed, suggesting long-term adaptations mediated by changes in gene expression possibly involving activation of the mitogen-activated protein kinase ERK1/2 cascade.

Methods: Using western blot analysis, we investigated the regulation of ERK1/2 in both total and nuclear fractions from two cell lines, HEK293 and COS-7 cells, transiently expressing D2L or D2S receptors, following stimulation by the D2-specific agonist quinpirole (QUIN).

Results: Immunoblots with antibodies to the basal and phosphorylated forms of ERK1/2 in whole cell extracts from D2L-COS7 cells, showed that QUIN stimulates a marked increase in the levels of p42 and p44 kDa phosphorylation whereas the total ERK1/2 is unaffected. QUIN-induced phosphorylation of ERK1/2 is concentration-dependent, transient, and prevented by prior treatment with APDs. The same overall pattern is observed with D2L-HEK293 cells, or using D2S. Pharmacological analysis of ERK1/2 phosphorylation following D2L activation revealed that the signal transduction pathways involved are regulated by BgG-protein subunits, PI3K, and tyrosine kinase and tyrosine phosphatase activities. All these pathways seem to lead to activation of Ras and the Raf1/MEK/ERK cascade. The downstream transcription factor Elk-1 is one of the main nuclear targets of activated ERK1/2. After addition of QUIN to D2L-COS7 cells, Elk-1 is phosphorylated following a similar time course to that of ERK1/2 phosphorylation, and this is likewise almost totally abrogated by prior administration of PD98059 or APDs.

Regulation of the nuclear import of activated ERK1/2 by D2 receptors was studied in digitonin permeablised cells through Western blot analysis after subcellular fractionation. Under basal conditions, ERK1/2 was mainly localized in the cytosol. Upon activation by QUIN, a strong staining appeared in the nuclear fraction, suggesting nuclear translocation of activated ERK1/2 proteins. WGA (wheat germ agglutinin) pre-treatment inhibited QUIN-induced phospho-ERK1/2 staining at the level of the nucleus but not in the total extract. Similar results were obtained following incubation with a dominant negative importin-beta. Thus, despite the lack of an obvious nuclear localization sequence, ERK1/2 appears to be transported into the nucleus through a Ran-regulated importin-beta-dependent pathway. Furthermore, a marked increase in phospho-Elk-1 immunolabeling was observed in the nuclear fraction immediatly following QUIN, and this effect was not completely abolished by WGA.

Conclusions: Overall, these results provide evidence that ERK1/2 activation and nuclear translocation are regulated by dopamine D2 receptors, suggesting these events play a role in APD-induced gene expression via phosphorylation of Elk-1.

49. PET STUDIES OF ARIPIPRAZOLE SHOW HIGH D_2/D_3 RECEPTOR OCCUPANCY WITHOUT EPS

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Background: Aripiprazole is a dopamine-serotonin system stabilizer. Aripiprazole is a partial agonist at the D_2 and $5-HT_{1A}$ receptors and an antagonist at the $5-HT_{2A}$ receptor. Previous studies have shown a correlation between D_2 binding of neuroleptics and their antipsychotic effect. A study was done to determine whether a dose response with aripiprazole could be correlated with its occupancy of human D_2 and D_3 dopamine receptors.

Methods: Dopamine D_2 and D_3 receptor occupancy in the corpus striatum of fifteen normal male human brains was measured using positron emission tomography (PET) with [^{11}C] raclopride (RAC). PET studies were performed before and after two weeks of aripiprazole 0.5, 1, 2, 10, and 30 mg per day.

Results: Increasing doses of aripiprazole correlated with proportional increases in plasma concentration and dose-dependent decreases in the binding potential of [^{11}C] RAC. Treatment with 0.5 mg aripiprazole resulted in 40% receptor occupancy while 30 mg resulted in approximately 90%. EPS was not detected in this sample of normal volunteers, even at 30 mg, despite current literature showing acute EPS occurring with higher DA receptor occupancies of approximately 80% in other antipsychotics. However, the partial agonism of dopamine receptors by aripiprazole may underlie this apparent discrepancy that occupancy does not always equal inhibition.

Conclusions: High receptor occupancy without EPS most likely reflects partial agonist activity by aripiprazole and is undoubtedly associated with its clinical benefits, including improvement of positive and negative symptoms, and its excellent safety and tolerability profile.

50. NEURONAL CORRELATES OF PREPULSE INHIBITION IN NORMALS AND SCHIZOPHRENIA: A [H2150] PET STUDY

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Background: Schizophrenia patients show dramatic deficits in sensori-motor gating as indexed by prepulse inhibition (PPI) of the startle reflex. In animals, PPI deficits have been associated with functional abnormalities within cortico-striato-thalamic circuitry. The neuronal basis of PPI has not yet been studied in humans.

Methods: The present study aimed to identify the neuronal basis of PPI in healthy human subjects (n=15) and first break schizophrenia patients (n=8) using [H215O]PET. Each subject received in a pseudo-random order 9 one-minute trial blocks consisting of 3 'no stimulus (back ground noise),' 3 'pulse-alone', and 3 'prepulse-pulse' trial blocks. The