COCAINE ADMINISTRATION DOES NOT INDUCE ACUTE EXPRESSION OF STRESS PROTEIN GENES.

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Stress proteins coordinate cellular responses to potentially damaging environmental changes, and are expressed abnormally in various disease states including fever, tissue trauma, oxidant injury, experimental models for aging, heavy metals, and neuronal damage. To determine if cocaine induces stress protein gene expression, we administered cocaine hydrochlorlde (30 mg/kg or 60 mg/kg) to male Sprague-Dawley rats per intraperitoneal injection. Animals were sacrificed 0, 2, 4 and 8 hours after injection, their brains removed and rapidly dissected, and total RNA isolated from frontal cortex, subcortical brain, and cerebellum. RNA was separated by denaturing gel electrophoresis, transferred to nitrocellulose membranes, and probed using (32-P)-labelled riboprobes for stress protein mRNAs. There was no change in Hsp60, Hsp70, or ubiquitin message after either dose of cocaine in any of the brain regions that we sampled. We conclude that either acute cocaine exposure does not induce a stress response, or such a response is confined to discrete brain regions too small to be detected in these experiments. Follow up studies of stress protein gene expression in ventral tegmental area, substantia nigra, nucleus accumbens, and caudate nucleus are under way.

PRECLINICAL ANTIPSYCHOTIC ACTIVITY OF THE SELECTIVE 5-HT2 ANTAGONIST, MDL100,907.

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The predictive value of currently available preclinical models for the selection of non-dopaminergic antipsychotic agents is unknown. Although devoid of direct antidopaminergic activity, MDL 100,907 has demonstrated activity in a wide-range of paradigms believed to indicate antipsychotic efficacy. In electrophysiological tests, acute administration of MDL 100,907 reverses amphetamine-induced slowing of A10 dopaminergic neurons and blocks MK-801-induced increases in firing without altering basal firing rates. Chronic administration of MDL 100,907 decreases A10 activity without affecting A9 cell firing. Neurochemically, MDL 100,907 antagonizes the MDMA-induced synthesis and release of striatal dopamine without affecting basal dopamine turnover in either the striatum or nucleus accumbens. In contrast, an increase in dopamine release in the medial prefrontal cortex is observed following administration of MDL 100,907. Although inactive in behavioral tests of extrapyramidal side-effect liability, MDL 100,907 dose-dependently reverses amphetamine-stimulated locomotor activity in mice or rats. Deficits in sound-induced prepulse inhibition produced by excessive serotonergic activity are normalized by MDL 100,907 as are amphetamine-induced deficits in latent inhibition. Based on this profile, clinical evaluation of MDL 100,907 as an antipsychotic agent will not only provide insight into the role of the serotonergic system in schizophrenia but also into the predictive validity of our preclinical models of the disorder.

THE PAIRED FDG PET SCAN METHOD : VALIDATION USING PLACEBO INFUSIONS

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Introduction : We have been using a method of paired FDG PET scans immediately prior to and following infusion with psychoactive compounds as a means of assessing regional effects of these drugs on brain metabolism. We wished to test the validity of this method by use of placebo (PBO) infusions. Results from this study can help us estimate the likelihood of observed differences between the scans occurring from chance or the imaging method. **Methods:** Five healthy males (mean age 26.2 yrs) underwent 18 fluoro-2-deoxy glucose PET scans immediately before (3 mCi) and after (5 mCi) a 30 minute infusion with PBO. Five templates (A-E) comprised of 62 regions of interest (ROIs) were applied to five matched transaxial planes from each pair of scans. Differences in the mean global, absolute and normalized regional metabolic rates between the pre- and post- scans (within subjects) were evaluated using paired t-tests, uncorrected for multiple comparisons. **Results:** Absolute Metabolic Rate: No difference was detected in the global metabolic rate between the two scans; of the 62 regions tested, only one, the Anterior Medial Frontal ROI in the D plane, showed a significant difference (increase). Normalized Metabolic Rate: Of the 62 regions tested, three were significantly different: right parietal occipital in the C plane (decrease), Anterior Medial Frontal in the D plane (increase), and the Right Primary Visual Cortex (increase). **Discussion:** The absence of any significant global difference between test and retest scans suggests that the method of correcting for residual activity is valid. The occurrence of significant differences in normalized metabolism in three ROIs indicates the possibility of systematic changes in regional brain activity during the procedure. However, in applying paired t-tests to sixty-two ROIs with a significance level of .05, it is expected that three regions would appear to be significantly different on the basis of chance alone.

ROLE OF GONADAL STEROIDS IN MRMD

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We evaluated the efficacy of ovarian suppression with a GnRH agonist in the treatment of women with prospectively confirmed menstrual-related mood disorders (MRMD) during a double-blind, placebo-controlled, parallel design trial. All women (patients and controls) received either GnRH agonist (depot leuprolide acetate) or placebo (N saline) IM every four weeks for 24 weeks and received in random sequence estradiol and progesterone as "add back" hormones during the latter 12 weeks. ANOVA-R was employed to examine the effects of depot lupron in women with MRMD compared with placebo and compared to controls.

ANOVA-R demonstrated significant improvements in MRMD symptoms after two months in the women receiving active depot lupron compared with symptoms at baseline and during placebo treatment. A reappearance of significant mood and behavioral symptoms was experienced by several women with MRMD, but none of the control women, during both estradiol and progesterone "add back" phases. We are presently attempting to determine whether the clinically significant mood and behavioral symptoms in women with MRMD during "add back" represents a re-emergence of typical symptom cyclicity or gonadal steroid-induced affective state changes.