PRETREATMENT WITH THE SPECIFIC NEUROTOXIN PARACHLOROAMPHETAMINE REDUCES THE CEREBRAL METABOLIC RESPONSES TO THE TRYCICLIC ANTIDEPRESSANT CLOMIPRAMINE.

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The aim of this study was to determine if the reported reductions of regional cerebral metabolic rates for glucose (rCMRglc) induced by the tryciclic antidepressant clomipramine (CMI) are due to the inhibition of serotonin (5-HT) reuptake or to interactions with other receptors systems (e.g. dopamine D_2, histamine H_1, adrenergic α_1). Three mo old, male, Fischer-344 rats were given parachloroamphetamine (PCA), a 5-HT neurotoxin, and rCMRglc was measured 3 weeks later with the quantitative autoradiographic [^{14}C]2-deoxyglucose technique in 55 brain regions 120 in after administering saline or CMI 10 mg/kg i.p. PCA alone increased rCMRglc in the visual cortex. CMI alone reduced rCMRglc in 18 regions (33%) including areas of the visual and limbic systems and the raphe nuclei. In PCA-lesioned rats, metabolic responses to CMI 10 mg/kg were greatly reduced and rCMRglc was significantly decreased only in 3 regions (e.g. hippocampus and raphe nuclei). These findings demonstrate that CMI, at the dose studied, reduces rCMRglc in the forebrain via a presynaptic mechanism that is relatively spared by PCA in the raphe-hippocampal system.

INDIVIDUAL DIFFERENCES IN THE REINFORCING EFFECTS OF *d*-AMPHETAMINE.

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This study was designed to replicate the finding that individuals who choose to self-administer a drug in a laboratory-based drug choice procedure tend to experience stimulant-like subjective drug effects. We wished also to identify groups of subjects, differing on this variable, who would be studied further to define neurobiological correlates of drug choice. Of 29 subjects tested in a 9-session choice procedure (10 mg *d*-amphetamine vs. placebo), 11 chose the drug consistently, 11 chose placebo consistently, and 7 did not show any clear preference. ANOVA revealed significant Choice Group x Drug x Time interactions for the Addiction Research Center Inventory subscale PCAG (a measure of sedation), the Profile of Mood State (POMS) subscale Fatigued, and the Visual Analog Scale subscales Sedated and Stimulated. There was a trend toward a significant 3-way interaction for the POMS subscales Vigor and Arousal. These results are consistent with those of previous studies in that individuals who chose to self-administer *d*-amphetamine experienced stimulant-like drug effects, peaking at 3 hours, whereas individuals who chose to self-administer placebo experienced sedative rather than stimulant *d*-amphetamine effects. We are now testing the hypothesis that groups defined by their drug choice can be differentiated on the basis of their electrophysiological response to *d*-amphetamine.

NEUROLOGICAL CHANGES WITH CLOZAPINE TREATMENT

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It has been established that clozapine is more effective in decreasing both the negative and positive symptoms of schizophrenia than standard antipsychotics. In addition to having positive and negative symptoms, however, persons with schizophrenia have multiple deficits on neuropsychological exams. Some of these deficits have been shown to be mediated by functioning in the dorsolateral prefrontal cortex, and have been found to be correlated with prominent symptoms of schizophrenia such as conceptual disorganization and the deficit syndrome. These prefrontal deficits seriously impair the learning of new material, ability to problem-solve, and attentional functioning. Whether clozapine ameliorates these underlying deficits is not known as the literature in this area presents a mixed picture. The current study tested the hypothesis that some neuropsychological measures known to be impaired in schizophrenic patients both on and off standard medication would improve with clozapine treatment. The Neurological Exam Scale (NES) is a 26-item test covering three functional areas: integrative sensory dysfunction, motor incoordination, and impaired sequencing of complex motor acts. The NES was administered to 8 patients with chronic schizophrenia when they were on stable doses of standard antipsychotics (Time I) and after they were stabilized on clozapine (Time II). A paired t-test was utilized to examine change in the NES factor measuring prefrontal functioning (three items testing complex motor sequencing plus memory) from Time I to Time II. There was a statistically significant improvement in scores on this factor ($t(7)=4.25$ $p<.005$) even though changes across time on the Brief Psychiatric Rating Scale and the Negative Symptom Assessment did not reach significance in this small sample. Analysis of each individual item showed that no item by itself improved significantly. This finding indicates a generalized improvement in cognitive function in patients on clozapine. Results suggest that either standard medications impair performance on these tests or that clozapine actually improves some areas of cognitive functioning. Either explanation holds hope for improved outcomes for patients on newer antipsychotics.

BRAINSTEM CORRELATION OF THE METABOLITES OF EXOGENOUS D AND L-TRYPTOPHAN IN BLOOD PRESSURE CHANGES IN WISTAR-KYOTO AND SPONTANEOUSLY HYPERTENSIVE RATS.

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The normotensive Wistar-Kyoto rats (WKYs) serve as controls in the "genetic model" of hypertension as represented by the spontaneously hypertensive rats (SHRs). L-Tryptophan does lower blood pressure in SHRs [cf. D. Ghosh et al., In: "Advances in Experimental Biology and Medicine (Kynurenine and Serotonin Pathways)," 294: 615 (1991)/Plenum, New York]. Administered D-tryptophan is rapidly converted into L-tryptophan in the periphery, and the D isomer is equally effective as L-tryptophan in elevating brain serotonin [5-hydroxy tryptamine (5-HT) and 5-hydroxy indole-3-acetic acid (5-HIAA)[vide: W. A. Wolf & D.M. Kuhn, Brain Research, 295: 356 (1984)]. Our results show that both D and L-tryptophan (administered intraperitoneally; 100 mg/kg; 2 hrs) lowered blood pressure in WKYs and SHRs, as measured by the tail-cuff method of Udenfriend. Thus, unlike the results of Wolf and Kuhn, D-tryptophan - in our experiments - lowered blood pressure in SHRs almost to the same extent (by 22 mmHg) as in the L-tryptophan-treated rats; such reductions with the D isomer was twice as much in WKYs as compared to L-tryptophan. Brainstem concentrations of 5-HT and 5-HIAA were analyzed by high pressure liquid chromatography/electro chemical detection (HPLC/EC). Our data indicate a highly significant ($P<.01$) relation between elevated levels of brainstem 5-HT and 5-HIAA (caused by D and L-tryptophan) and the reduction in blood pressure in WKYs and SHRs. (This work was supported in part by NIH grant (RR 03045.)