FUNCTIONAL CORRELATES OF 5-HT_{1A} RECEPTOR ACTIVATION AFTER EXPOSURE TO REPEATED COCAINE ADMINISTRATION IN RATS. Michael H. Baumann and Richard B. Rothman, Clinical Psychopharmacology Section, NIDA/NIH, Addiction Research Center, Baltimore, MD, 21224, USA.

It is well known that acute cocaine treatment has profound effects on serotonin (5-HT) neurons, but the consequences of chronic cocaine administration on 5-HT neurotransmission are not well studied. We used the 5-HT agonist 8OH-DPAT as a probe to assess 5-HT_{1A} receptor function in vivo in rats previously exposed to cocaine. Rats were treated with cocaine (15 mg/kg, ip) twice daily for one week. After 42 hr and 8 days of withdrawal, rats were challenged with 8OH-DPAT (10-300 µg/kg, sc) or vehicle, and various endpoints were evaluated including: 5-HT synthesis in discrete brain regions, feeding, plasma prolactin, and the 5-HT behavioral syndrome. Prior cocaine exposure did not alter the 8OH-DPAT-induced inhibition of 5-HT synthesis in any brain region examined. Although cocaine-treated rats exhibited higher basal rates of feeding, the hyperphagia produced by 8OH-DPAT was comparable in cocaine- and saline-treated groups. The plasma prolactin response to 8OH-DPAT was significantly blunted in cocaine-treated animals at 42 hr of withdrawal, and this effect was maintained at 8 days. Cocaine exposure did not affect the 5-HT behavioral syndrome elicited by 8OH-DPAT. These data indicate that prior cocaine administration does not change 5-HT_{1A} autoreceptor sensitivity (as measured by inhibition of 5-HT synthesis and hyperphagia). However, the attenuated prolactin response to 8OH-DPAT suggests that cocaine renders postsynaptic 5-HT_{1A} receptor mechanisms subsensitive in some brain regions. Deficits in 5-HT_{1A} receptor function may underlie feelings of anxiety experienced by cocaine addicts during periods of drug withdrawal.

AGE AT ONSET AND TREATMENT OF GERIATRIC DEPRESSION

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In geriatric patients, clinical predictors of response to antidepressant pharmacotherapy have not been well delineated. Age at onset of illness can be an useful differentiating feature in geriatric major depression [ALEXOPOULOS et al 1993]. In a recent double blind randomized trial of moclobemide and flovoxamine for geriatric major depression, better response to moclobemide (n=20) vs flovoxamine (n=20) was noted [BOCKSBERGER et al 1993]. The patient sample was heterogeneous as regards illness course. In a repeated measures ANCOVA model accounting for age, drug, and number of previous episodes, later age at onset was associated with better response ($F=3.59$, $p<0.03$). Interpretation of these findings is limited by small sample size and short (4 weeks) duration of treatment. In a study of moclobemide in young adult depressives a better response was noted in patients with first episode compared to those with recurrent illness [ANGST et al 1994]. More investigation of relationships between antecedent illness course and response to pharmacotherapy is needed in geriatric depression.

UTILIZATION OF BAYES' THEOREM TO ESTIMATE THE PREDICTIVE VALUE OF THE A1 ALLELE OF THE D2 DOPAMINE RECEPTOR GENE IN COMPULSIVE DISEASE.

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Since the initial findings by our laboratories showing a strong association of the A1 allele of the D2 dopamine receptor gene and alcoholism, a number of reports have either failed to support the association, while a Meta Analysis confirms the association of this allelic variant in alcoholism ($p<10^{-7}$). Moreover, the overwhelming evidence supports an association of variants of the DRD2 gene with risk in developing compulsive disease (CD). Specifically, variants of the DRD2 gene (A1, B1, Int[6]-Ex[7], D1) have been correlated with increased risk of severe alcoholism, crack/cocaine dependence, polysubstance abuse, carbohydrate bingeing, obesity, ADHD, Tourette's and severe gambling. We utilized Bayes' Theorem as a mathematical method to assist in evaluating the predictive value of the A1 allele of the DRD2 gene in compulsive disease. According to Bayes' rule, the *predictive value positive* (PV^+) of a screening test is the probability that a person has the disease given that the test is positive. Whereas, the *predictive value negative* (PV^-) of a screening test is the probability that a person does not have the disease given that the test is negative. We found that when we combined data including severe alcoholism, severe cocaine dependence, polysubstance abuse, severe overeating, ADHD and restricted our control data to only well characterized accessed controls screened for alcohol, drug and in some cases tobacco abuse, the PV^+ was 45.5% risk for compulsive disease. Moreover, interpretation of a negative result from the A1 allelic genotype is very predictive, since we found that $PV^- = 81\%$. Finally, an analysis of pooled data related to CD resulted in an odds ratio of 3.62 (95% confidence limits [2.59-5.07]) with a P value of 0.00001 indicating a similarly strong positive correlation of the DRD2 gene variant and this disease (Yates $^2 = 64.9$, df = 1, $p< 1X10^{-5}$).

RECEPTOR BINDING AUTORADIOGRAPHY WITH PRAMIPEXOLE, A CLINICALLY USEFUL D3-PREFERRING DOPAMINE AGONIST.

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Because it most potently stimulates dopamine (DA) autoreceptors, pramipexole (PPX) (EJPharmacol 215:161, 1992) can depress DA tone. PPX is currently being evaluated as a novel autoreceptor agonist antipsychotic. At higher doses, PPX also stimulates DA postsynaptic receptors belonging to the D2 receptor subfamily. It is also useful for treating Parkinson's disease (Neurol 43:879P, 1993). The D2 receptor subfamily is composed of the broadly-distributed D_2, the mesolimbic-preferring D_3, and the mesocortical-preferring D_4 receptor subtypes. We report that, in studies with cloned subtypes of the D2 receptor subfamily, PPX has higher affinity for the D_3 as compared to the D_2 and D_4 subtypes. Receptor binding autoradiography with ^{3}H-PPX (5 nM, 62 Ci/mmole) was used to evaluate the distribution of PPX binding sites within the rat brain. Talipexole, 10 µM, was used to evaluate nonspecific binding. Consistent with its preference for D_3 binding sites, the highest concentrations of ^{3}H-PPX binding sites were found in the islets of Calleja, previously reported to contain D_3 but not D_2 or D_4 receptors (PNAS 89:8155, 1992). ^{3}H-PPX binding was also high in other mesolimbic areas such as the nucleus accumbens, olfactory tubercle and amygdala. However, ^{3}H-PPX binding was also high in caudate, a DA postsynaptic area thought to be high in D_2 receptors, but in which some D_3 pharmacological effects have also been described (Neurosci Abs 19:80, 1993). Fewer ^{3}H-PPX binding sites were found in VTA and substantia nigra, areas rich in cell bodies for DA neurons. Although PPX most potently stimulates DA autoreceptors, PPX binding sites have their highest concentrations in projection areas containing both DA terminal and postsynaptic receptors. PPX's preferential affinity for the D_3 receptor subtype could render it less likely to produce adverse affects than D2 subfamily agonists non-selectively interacting with D_2, D_3 and D_4 receptor subtypes.