

PLASTICITY OF DELTA-9-TETRAHYDROCANNABINOL RECEPTOR GENE EXPRESSION IN THE STRIATUM.

P. Mailleux*, X. Preud'homme** and J.-J. Vanderhaeghen*, *Unité de Recherche sur le Cerveau, **Service de Psychiatrie, Hôpital Académique Erasme, Faculté de Médecine, Université Libre de Bruxelles, Belgique.

First, by receptor autoradiography and in situ hybridization (ISH) we have determined the neuronal localization of 8-9-tetrahydrocannabinol (THC) receptor and its mRNA in the adult brain of the rat and human as well as during development and aging. High concentrations were observed in the cerebral cortex, basal ganglia, hippocampus, hypothalamus and cerebellum in accordance with the clinical effects of cannabis use. In the basal ganglia, THC receptor mRNA were exclusively found in the striato-nigral and -pallidal neurons. Secondly, in the rat caudate-putamen (C-P), by ISH, those mRNA levels were increased after adrenalectomy, and were recovered following the addition of dexamethasone. They were also increased after 6-hydroxydopamine lesion and pharmacological blockade of dopamine receptors by antagonists SCH-23,390 (D1), haloperidol (D1&2) and sulpiride (D2), while they were decreased after aspiration cortectomy and MK801 treatment (glutamate antagonist of the NMDA type). Thus, in the C-P, there is a plasticity of THC receptor synthesis: down-regulation by glucocorticoids and dopamine and up-regulation by glutamate. Thirdly, in the rat C-P, by ISH, THC increased mRNA levels of the neuropeptides substance P and enkephalin. Thus, THC is a novel modulator of gene expression in the striatum. Together, these data suggest that THC and its endogenous cannabinoid play key functions in cognitive and motor regions of the brain.

P. Mailleux is Senior Research Assistant of FNRS. Supported by Belgian Grants from the FRSM (3.4574.90), FMRE (1992-95) and Ministère de la Politique Scientifique (PAI 1990-95) and Loterie Nationale (1991, 1993).

PHARMACOKINETICS AND PHARMACODYNAMICS OF NEFAZODONE AND PROPRANOLOL CO-ADMINISTRATION.

Punit Marathe¹, Howard Uderman², Ralph Raymond³, Neville Ford³ and Daniel Salazar³

Bristol-Myers Squibb, ¹Syracuse NY & ²Princeton NJ and ³The Clinical Pharmacology Unit, Princeton Medical Center.

Eighteen healthy male subjects received the following treatments (Q12h for 6.5 days) in randomized order with 14 day washout between periods: nefazodone 200 mg (NEF), propranolol 40 mg (PRO), and co-administration of NEF and PRO (NEF/PRO). Measurements of heart rate (HR) and systolic blood pressure for calculation of double product (DP=HRxSBP), an index of cardiac oxygen demand, were obtained prior to, during and after exercise on a treadmill using a multistage graded exercise protocol on Days 1 (pretreatment) and 6 (2 hr post dose) of each leg. Pharmacokinetics (PK) were evaluated on Day 7.

There was no significant effect of NEF treatment on HR or DP compared to pretreatment. PRO and NEF/PRO produced similar decreases in HR at rest and during the exercise protocol. NEF/PRO reduced pre-exercise DP by 21% which was not different than PRO. However, post-exercise DP with NEF/PRO was decreased 40%, compared with the 23% decrease produced by PRO ($p < 0.05$). This difference is not considered clinically significant. There was no effect of co-administration on PK of nefazodone and two metabolites, hydroxynefazodone and triazole dione. However, the AUC_{0-12} and C_{max} of mCPP were increased by 28% and 22% with co-administration. Furthermore, the C_{max} and AUC_{0-12} of propranolol were 30% and 14% lower with NEF/PRO than with PRO, however, there was no change in $T_{1/2}$. Similar changes in the PK of 4-OH propranolol were observed.

In conclusion, co-administration of NEF and PRO caused modest changes in the PK of mCPP, propranolol and 4-hydroxypropranolol. However, the suppression of exercise-induced tachycardia and DP produced by PRO were not significantly affected by NEF. Thus, the PK inequivalencies are not clinically significant. Therefore, no change in initial dose of either drug is necessary and dose adjustments should be made on the basis of clinical response.

(S,S)-[I-125]QNB SPECIFIC BINDING TO RAT BRAIN MUSCARINIC RECEPTORS IN VIVO. R.C.

McRee, S.F. Boulay, V.I. Cohen, V.K. Sood, B.R. Zeeberg, and R.C. Reba. Geo Wash Univ Med Cent, Wash, D.C.

Using the inactive isomer of a receptor ligand to define nonspecific binding in vivo may not be an accurate method. Diastereomers of the muscarinic acetylcholine receptor (mAChR) ligand IQNB (3-quinuclidinyl-4-iodobenzilate) were used in vivo to ascertain the conditions necessary for determining nonspecific binding with an inactive ligand. A 1 μ M blocking dose of QNB was administered 1 h prior to the (S,S)-[I-125]IQNB. The rats were sacrificed 1 or 3 h after the (S,S)-[I-125]IQNB injection. The brains were dissected into 9 regions containing mAChRs in a range from 21-251 nM and the data were converted to % dose/g tissue. Rats sacrificed one hour after the (S,S)-[I-125]IQNB injection had a difference in binding between the QNB-blocked and control groups with the largest differences found in the regions with the highest mAChRs. In rats sacrificed three hours after the (S,S)-[I-125]IQNB injection no regions had any differences in the binding of (S,S)-[I-125]IQNB. The difference in the amount of (S,S)-[I-125]IQNB bound under control conditions and with the QNB block is the amount of specific binding. We conclude that three hours after (S,S)-[I-125]IQNB injection its binding can be considered nonspecific.

DIFFERENTIAL INDUCTION OF c-fos mRNA IN RAT PREFRONTAL CORTEX BY TYPICAL VERSUS ATYPICAL ANTIPSYCHOTICS.

Kalpna Merchant, Dawna Evans, Lana Figur. CNS Disease Research, The Upjohn Company, Kalamazoo, MI 49001.

Atypical antipsychotic drugs (APDs) typified by clozapine differ from the typical agents (e.g., haloperidol) by displaying superior efficacy in the treatment of negative symptoms and reduced liability of motor side effects (EPS). The clinical efficacy of APDs is thought to involve participation of the prefrontal cortex (for negative symptoms) and nucleus accumbens (for positive symptoms) whereas the caudate-putamen may be the site underlying EPS. In agreement, our previous studies have demonstrated: a) induction of the neurotensin and c-fos gene in rat caudate by only typical APDs; but b) induction of the neurotensin gene in the nucleus accumbens-shell by all clinically efficacious APDs. In the present study, we investigated alterations in c-fos mRNA expression in rat prefrontal cortex following haloperidol, clozapine, and a new putative atypical APD, remoxipride. Acute administration of clozapine (20 mg/kg, i.p.) markedly increased c-fos mRNA expression in deep layers of the infralimbic and ventral prelimbic cortex (IL/vPL); however, a single dose of haloperidol (1 mg/kg, i.p.) was significantly less effective. Like clozapine, remoxipride (0.3 mg/kg, i.p.) robustly increased c-fos mRNA expression in IL/vPL. Interestingly, 0.6 and 1.25 mg/kg of remoxipride were less effective than 0.3 mg/kg. These data suggest that prefrontal cortical neurons may contribute to the atypical pharmacologic profile of APDs.