In: 12th Congress of the Collegium Internationale Neuro-Psychopharmacologicum
268 [CINP], Göteborg (S), 22-26 June, 1980. Pergamon Press, Oxford, New York et. 1980, p. 268, Abstr. No. 496 Progress in Neuro Psychopharmacol. 1980, Suppl. 1

3402

Serum AT III in both groups showed slight decrease, but no significant difference was observed between the two groups. Serum sex hormone levels of group 2 were similar to those of pill takers, but other coagulation factors were all in normal range. The data were analyzed and it was concluded that thrombogenic mechanisms of neuroleptics were different from those of oral contraceptives.

495. BIOCHEMICAL AND PHARMACOLOGICAL PROPERTIES OF A NEW SELECTIVE AND REVERSIBLE MONOAMINE OXIDASE INHIBITOR, FLA 336 (+). Sven-Ove Ögren, Anna-Lena Ask, Lennart Florvall, Lars-Olov Lindbom, Jan Lundström and Svante B. Ross, Research and Development Laboratories, Astra Läkemedel AB, S-151 85 Södertälje, Sweden.

In the search for a new and clinically useful monoamine oxidase (MAO) inhibitor the following criteria were set up: 1) selective inhibition of the A-form of MAO, 2) reversible action in order to avoid diminished selectivity on prolonged treatment, 3) weak interaction with tyramine. Among the compounds tested FLA 336 (+) (the (+)-enantiomer of 4-dimethylamino-2-methyl-α-methyl phenethylamine hydrogen(+)-tartrate) fulfills these objectives. It inhibited the deamination of ^{14}C-5-HT in brain, liver and duodenal slices after oral administration (ED_{50}=4-7 umol/kg p.o.), increased the 5-HT concentration in whole rat brain with 50% at 3 µmol/kg p.o. and potentiated the 5-HTP syndrome in the rat (ED_{50}= 5 µmol/kg p.o.). FLA 336 (+) weakly blocked the deamination of phenethylamine in the rat (ED_{50} >100 µmol/kg p.o.). Maximal inhibition of brain MAO was found 2 hours after administration, was still pronounced at 8 hours, but had terminated 24 hours after administration. Repeated administration of FLA 336 (+), 2.5-10 µmol/kg p.o. twice daily for 2 weeks did not change the inhibitory potency or the selectivity. Similar results were obtained in the dog after 3 weeks treatment with 2.5 and 10 umol/kg p.o. of FLA 336 (+) twice daily. FLA 336 (+) was in acute experiments equipotent with the irrversible MAO-A inhibitor clorgyline in inhibiting the deamination of 5-HT in rat brain after oral administration but was much less active (1000 times) than clorgyline in the duodenum. The deamination of tyramine, a mixed substrate for MAO, was less inhibited by FLA 336 (+) in the rat brain than was that of 5-HT. In duodenum, however, which seems to contain mainly the MAO-A form, deamination of the two substrates were equally inhibited. Clorgyline was about 800 times more potent to inhibit the deamination of tyramine in duodenum than in brain, most likely due to the high local concentration of clorgyline in duodenum producing an effective irreversible inhibition of MAO-A. The increase in blood pressure produced by tyramine in the rat was only weakly potentiated by FLA 336 (+) at 58 µmol/kg p.o.. Other MAO inhibitors tested including clorgyline, α-ethyltryptamine, tranylcypromine and pheniprazine produced quantitatively greater potentiation of tyramine.

X 496. THE EFFECTS OF CHRONIC TREATMENT WITH NOMIFENSINE AND ZIMELIDINE ON ^{3}H-5-HT AND ^{3}H-d-LSD BINDING IN THE RAT CEREBRAL CORTEX. S-O Ögren, Astra Läkemedel AB, Södertälje, Sweden K. Fuxe, Department of Histology, Karolinska Institutet, Stockholm and L.F. Agnati, Department of Human Psysiology, University of Bologna, Bologna, Italy.

Groups of male rats (each n = 8) were administered orally with saline, the NA and DA uptake inhibitor nomifensine and the 5-HT uptake inhibitor zimelidine twice daily (10 umol/kg per dose) for a period of 14 days. The rats were decapitated 24 hours after the last administration. The effect of this treatment on specific ^{3}H-5-HT and ^{3}H-d-LSD binding in the dorsal cerebral cortex was examined according to the procedure of Bennett & Snyder (Molec. Pharmac. 12, 373-389, 1976) and modified by Nelson et al (Molec. Pharmac. 14, 983-995, 1978). In the saline group evidence was obtained for only one type of binding site for ^{3}H-5-HT (K_D = 1.2 nM, B_{max} = 7.8 pmol/g) and for ^{3}H-d-LSD (K_D = 3.8 nM, B_{max} = 38.5 pmol/g). Long term treatment with nomifensine induced a low affinity site for both ^{3}H-5-HT and ^{3}H-d-LSD. The K_D values and B_{max} of the low affinity site for ^{3}H-5-HT were: K_D = 7.7 nM, B_{max} = 5.6 pmol/g. Corresponding values for the high affinity site: K_D = 2.4 nM, B_{max} = 2.5 pmol/g. The K_D values of the low affinity site for ^{3}H-LSD binding were: K_D = 12.6 nM, B_{max} = 33.5 pmol/g and for the high affinity site: K_D = 2.3 nM, B_{max} = 13.7 nmol/g. Long term treatment with zimelidine produced in accordance with previous results (Fuxe et al, Neurosc.Lett. 13, 307-312, 1979) a low affinity site for ^{3}H-5-HT. This treatment induced also a low affinity site for ^{3}H-d-LSD binding. The values for the low-affinity site were: K_D = 23.5 nM, B_{max} = 70.5 pmol/g and for the high affinity site: K_D = 3.0 nM, B_{max} = 15.0 pmol/g. These results suggest that chronic treatment with antidepressant drugs may produce adaptive changes at postsynaptic 5-HT receptor sites.