Eur Psychiatry (1994) 9, Suppl 1, 54s–55s

S25. New discoveries in dopamine
(supported by an educational grant from Astra S)

DUAL EFFECTS OF ANTIPSYCHOTICS THROUGH DOPAMINE D_2 AND D_3 RECEPTORS

P Sokoloff, D Levesque, M-P Martres, N Griffon, C Pilon, F Sautel and J-C Schwartz *Unité de Neurobiologie et de Pharmacologie de l'INSERM, Paris, France*, J Diaz and V Dimitriadou, *Laboratoire de Physiologie, Université René Descartes, Paris, France*, P Simon and J Costentin, *Laboratoire de Pharmacodynamie, UER de Médecine et de Pharmacie, Rouen, France*, A Mann and CG Wermuth, *Laboratoire de Pharmacochimie Moléculaire, Centre de Neurochimie, Strasbourg, France*.

Dopamine D_2 and D_3 receptors (D_2R and D_3R) are both blocked by antipsychotics. In a transfected neuroblastoma cell line, D_3R increases mitogenesis through a mechanism independant of adenylyl cyclase inhibition and of stimulation of phospholipase C. D_3R activation also induces Fos immunoreactivity, suggesting that D_3R may activate genes that contain an AP-1 domain, such as neurotensin (NT) gene. The distributions of D_2R, D_3R and NT mRNAs assessed in *in situ* hybridization studies were compared in nucleus accumbens, which has been subdivided into a 'core' part, structurally and functionally related to striatum and into a 'shell' part, possibly involved in many aspects of emotion, cognition and motivated behaviour through a control feedback loop with the prefrontal cortex.. D_2R mRNA is expressed mostly in the core and marginally in the shell, whereas the D_3R mRNA is mostly present in the shell, where its distribution overlaps that of NT mRNA. Co-hybridization studies showed that the D_3R mRNA is expressed by NT neurons. Treatment by haloperidol and other D_2R/D_3R antagonists increase NT mRNA in the D_2R mRNA expressing areas, but decreased NT mRNA in the D_3R mRNA expressing areas, suggesting opposite effects of these two receptors on NT expression. In addition, D_3R mRNA is not modified by chronic haloperidol treatment, in accordance with its participation in the antipsychotic drug treatment, for which there is no tolerance. D0 779, a partially selective D_3R antagonist produces paradoxical behavioral activations in rodents, suggesting that DA exerts tonic inhibition on locomotor behaviours via D_3R, an effect opposite to that DA exert via D_2R. Hence, by blocking two opposing receptors, antipsychotics may have both inhibitory and stimulating effects. The greater efficiency of these drugs against positive symptoms of schizophrenia than negative symptoms might be related to the D_2R-preferring properties of the available antipsychotics. This hypothesis will be evaluated in clinical assessment of D_3R-preferring antagonists.

Supported by the Biomedical and Health Research Programme EEC CT92-1086

POSSIBLE MECHANISMS UNDERLYING THE ATYPICAL ANTIPSYCHOTIC PROFILE OF CLOZAPINE AND REMOXIPRIDE

Sven Ove Ögren
Division of Histology, Dept. of Neuroscience,
The Karolinska Institute, S-171 77 Stockholm, Sweden.

The atypical antipsychotic drug clozapine produces significantly less extrapyramidal side-effects (EPS) than typical neuroleptic drugs (haloperidol). Several hypotheses have been proposed to explain the atypical action of clozapine including a combined blocking action at DA and muscarinic cholinergic receptors or a combined blocking effect at DA and serotonin (5-HT-2) receptors. Recent in vitro receptor binding data have led to the suggestion that the unique action of clozapine is due to a preferential action on a subtype of the DA D-2 receptor, i.e. the D-4 receptor. The development of the selective DA D-2 antagonist remoxipride as an efficacious antipsychotic agent with a low EPS potential challenges current concepts on mechanisms underlying atypical antipsychotic activity. Both clozapine and remoxipride display an atypical antipsychotic profile in the rat, since they preferentially block behaviours associated with the mesolimbic compared to those associated with the nigroneostriatal DA system. However, unlike clozapine, remoxipride lacks affinity for muscarinic, 5-HT-2, DA D-1 and DA D-4 receptors and, unlike most other antipsychotic drugs, remoxipride has negligible affinity for the DA D-3 receptor (Malmberg et al. 1993) (Ögren et al. 1994). Moreover, recent studies based on studies of DA D-2 receptor inactivation using N-ethoxy-carbonyl-2-ethoxy-1,2-dihydroxyquinoline indicate that remoxipride in vivo may act on a subpopulation of DA D-2 receptors. Different mechanisms were found to underlie the atypical antipsychotic profile of clozapine and remoxipride.

References

Malmberg et al. (1993) Mol. Pharmacol. 43:749-754.
Ögren et al. (1994) Neuroscience (in press)

AUTORADIOGRAPHIC STUDIES OF EXTRA-STRIATAL DOPAMINE RECEPTORS USING [^{125}I]EPIDEPRIDE AND ANALOGUES

Håkan Hall, Lars Farde, Christer Halldin, Göran Sedvall
Department of Clinical Neuroscience, Psychiatry and Psychology Section, Karolinska Hospital, S-17176 STOCKHOLM, SWEDEN

The highest densities of dopamine-D_2 receptors in the mammalian brain are found in the striatum (N. caudatus and putamen). There is growing evidence that the extra-striatal dopamine-D_2 receptors, in spite of the low density, play important roles in dopaminergic neurotransmission. Previously used radioligands have too low affinity for visualizing these receptors. Recently developed high potency benzamide ligands, such as [^{125}I]epidepride and [^{125}I]NCQ 298, give the potential to quantitatively study the extra-striatal dopamine-D_2 receptors with radioligand binding and autoradiography.

Both epidepride and NCQ 298 have been used in animal *in vivo* and *in vitro* studies, as well as in SPECT in monkeys. NCQ 298 labels predominantly striatal areas, although receptors in cortex and hippocampus also have been visualized, whereas epidepride in addition to the striatal labelling also labels extra-striatal receptors.

In recent PET examinations, Farde et al. have shown using PET-techniques, that the benzamide [^{11}C]FLB 457, which is the bromine analogue to epidepride, labels dopamine-D_2 receptors not only in the nucleus caudatus and putamen but also in extra-striatal areas of the human brain, such as in the thalamus and amygdala.

In this presentation we report on the distribution and pharmacology of dopamine-D_2 receptors using human whole hemisphere autoradiography with [^{125}I]epidepride. The results indicate that [^{125}I]epidepride labels receptors in nucleus caudatus, putamen and pallidum and also in extra-striatal areas such as thalamus and the substantia nigra. The intensity of the labelling is different in the various nuclei of the thalamus. The highest densities are seen in the nucleus parataenialis and nucleus anteroprincipalis, with lower binding in nucleus pulvinaris and nucleus centralis. Moreover, [^{125}I]epidepride also accumulates in cortical layers. The binding in striatal as well as in extra-striatal areas is blocked by dopamine-D_2 receptor antagonists.

PET-STUDIES ON EXTRASTRIATAL DOPAMINE RECEPTORS USING [^{11}C]FLB457

Lars Farde, Christer Halldin, Svante Nyberg, Håkan Hall, Stefan Pauli, Göran Sedvall, *Nina Mohell and *David Jackson
Dept of Clinical Neuroscience, Karolinska Hospital, S-171 76 Stockholm, Sweden, and *Astra Arcus AB, Sweden.

Studies on brain biochemistry, morphology and physiology indicate that the function of extrastriatal brain regions may be disturbed in patients with schizophrenia. Positron Emission Tomography (PET) has hitherto been used for quantitative determination of dopamine receptors in the major basal ganglia, which are large brain structures with a high dopamine receptor density. In extrastriatal regions the potential for PET-examination is limited by the low receptor densities, which are 10 -100 times lower than in the basal ganglia.

[^{11}C]FLB 457 is a substituted benzamide which has the extremely high affinity (Kd) of 20 pM for D2-dopamine receptors in vitro. FLB 457 has virtually no affinity for any other transmitter receptor besides D3.

[^{11}C]FLB 457 was prepared by O-alkylation from [^{11}C]methyl iodide. In initial experiments [^{11}C]FLB 457 was injected into cynomolgus monkeys. There was a high uptake of radioactivity in the striatum. Striatal but not cerebellar radioactivity was displaced after i.v. injection of raclopride (2 mg/kg). In PET-studies on 5 healthy human subjects [^{11}C]FLB457 accumulated not only in the basal ganglia but also in several extra-striatal regions. Uptake in the thalamus, amygdala, substantia nigra, colliculus and neocortex was 2-5 times higher than in the cerebellum.

In extrastriatal brain regions radioactivity reached a plateau at about 50 minutes after injection. Assuming that radioactivity in the cerebellum reflects the level of free and non-specific binding, the specific binding in extrastriatal regions was on a maximal level within 60 minutes. Specific [^{11}C]FLB 457 binding should thus be suitable for a quantitative equilibrium analysis of extrastriatal dopamine receptor densities.

[^{11}C]FLB 457 binding was examined in 2 patients treated with conventional doses of haloperidol. Specific [^{11}C]FLB457 binding in extrastriatal regions was 70 % lower than in the control subjects. This is the first demonstration that antipsychotic drug treatment has effect on dopamine receptors in extra-striatal regions.

FAILURE TO DEMONSTRATE ANTIPSYCHOTIC EFFECT OF THE DOPAMINE D_1-RECEPTOR ANTAGONIST SCH 39166 IN SCHIZOPHRENIC PATIENTS

P Karlsson[1], L Smith[2], L Farde[1], C Härnryd[1], GC Sedvall[1] and FA Wiesel[2]
[1]Department of Clinical Neuroscience, Psychiatry and Psychology Section, Karolinska Hospital, S-171 76 Stockholm, Sweden, [2]Department of Psychiatry, Akademiska Hospital, S-751 85 Uppsala, Sweden

SCH 39166 is the first selective D_1-receptor antagonist developed for clinical trials. Behavioural, biochemical and electrophysiological effects in animal models indicate that dopamine D_1-receptor antagonists may be effective to treat schizophrenia. PET-experiments with ^{11}C labelled SCH 39166 indicate stereoselective binding to D_1-dopamine receptors in the human brain. More than 70 % of specific [^{11}C]SCH 39166 binding in the basal ganglia was blocked after treatement of healthy men with single oral doses of 100 mg SCH 39166.

To examine safety, tolerability and potential antipsychotic effect we gave SCH 39166 to 17 acutely ill drug free schizophrenic patients (DSMIIIR) in an open 4 week study. Doses were escalated according to fixed schedule from 10 to 100 mg b.i.d. during 17 days. In eight patients the drug was withdrawn due to deterioration or failure to comply. In the nine patients participating for more than 2 weeks, none had an apparent reduction of BPRS or CGI scores. Side effects were emesis and akathisia in single patients. After withdrawal of SCH 39166 most of the patients improved when treated with conventional neuroleptics.

The result of the study does not support the prediction that selective D_1-dopamine receptor antagonism will produce antipsychotic effects in schizophrenia. Since most of the patients responded to conventional neuroleptics the results further emphasise the critical role of D_2-antagonism as principle for antipsychotic action. The results do not preclude that a combined D_1- and D_2- receptor antagonism may have synergistic ameliorative effects in schizophrenia.

Supported by NIMH, Swedish Medical Research Council and Schering-Plough