DRAY, A., OAKLEY, N.R. & SIMMONDS, M.A. (1975). Rotational behaviour following inhibition of GABA metabolism unilaterally in the rat substantia nigra. *J. Pharm. Pharmac.*, **27**, 627–629.

FOWLER, L.J. (1973). Analysis of the major amino acids of rat brain after inhibiton of rat brain 4-aminobutyrate aminotransferase by ethanolamine-*O*-sulphate *in vitro* and *in vivo*. *Biochem. J.*, **130**, 569–573.

JATON, A.L., LOEW, D.M. & VIGOURET, J.M. (1976). CF 25-397 (9,10-Didehydro-6-methyl-8β-[2-pyridilthiomethyl]ergoline), a new central dopamine agonist. *Br. J. Pharmac.*, **56**, 371P.

KIM, J.S., BAK, I.J., HASSLER, R. & OKADA, Y. (1971). Role of γ-aminobutyric acid (GABA) in the extrapyramidal motor system. 2. Some evidence for the existence of a type of GABA-rich strio-nigral neurons. *Exp. Brain Res.*, **14**, 95–104.

McGEER, P.L., McGEER, E.G., WADA, J.A. & JUNG, E. (1971). Effect of globus pallidus lesions and Parkinson's disease on brain glutamic acid decarboxylase. *Brain Research*, **32**, 425–431.

Specificity of monoamine neurotoxins: rotational responses to dopaminergic agonists after unilateral 6-OHDA and 5,6-DHT lesions of the median forebrain bundle

J.L. WADDINGTON
(introduced by T.J. CROW)

Division of Psychiatry, Clinical Research Centre, Harrow, Middlesex HA1 3UJ

The relative specificity of the catecholamine neurotoxin 6-hydroxydopamine (6-OHDA) contrasts with the non-specific degeneration of both 5-hydroxytryptamine (5-HT) and dopamine (DA) neurones induced by the indolamine neurotoxin 5,6-dihydroxytryptamine (5,6-DHT) following intracerebral injection (Saner, Pieri, Moran, Da Prada & Pletscher, 1974). Recent studies suggest that ascending 5-HT neurones may modulate the output of nigrostriatal DA mechanisms. When these effects are investigated using the rotating rat model (Ungerstedt & Arbuthnott, 1970), circling responses to both direct and indirect DA agonists are potentiated by drugs attenuating whole brain 5-HT transmission while treatments enhancing 5-HT transmission decrease such rotation (Milson & Pycock, 1976). To investigate this interaction further, circling responses have been investigated following unilateral depletion of DA and unilateral rather than whole brain depletion of 5-HT induced by injection of neurotoxins into the median forebrain bundle (MFB) (Costall, Naylor & Pycock, 1975).

Male Sprague-Dawley rats, 150 ± 20 g, were given unilateral stereotaxic injections of 6-OHDA) 8 μg/4 μl saline), or 5,6-DHT (5 μg/4 μl saline) into the MFB. Groups of rats from each lesion procedure received i.p. injections of either apomorphine (1 mg/kg) or (+)-amphetamine (5-mg/kg) 8 days after surgery; they were then placed in automated rotometer bowls for continuous recording of all rotations. Rats were sacrificed and striata assayed spectrophotofluorimetrically for DA and 5-HT content 14 days after lesion. Rotations were assessed conventionally and after orthogonal polynomial transformation.

6-OHDA lesions produced an 85.5% depletion of striatal DA ($P < 0.0005$) together with a 28.0% depletion of striatal 5-HT ($P < 0.05$); 5,6-DHT lesions produced a 53.8% depletion of 5-HT ($P < 0.01$) together with a 84.9% depletion ($P < 0.001$) of DA. 6-OHDA lesioned animals showed the expected contralateral and ipsilateral rotation to apomorphine and amphetamine respectively. 5,6-DHT lesioned animals showed more rapid onset of contralateral rotation to apomorphine compared with 6-OHDA lesioned animals ($P < 0.02$), indicating that unilateral depletion of striatal 5-HT produces the same facilitation of apomorphine-induced rotation in unilaterally DA lesioned animals as bilateral depletion of 5-HT; rotational responses to amphetamine after 5,6-DHT lesions, however, were attenuated when compared with 6-OHDA lesions ($P < 0.05$), contrary to the enhancement seen after bilateral 5-HT reduction (Milson & Pycock, 1976). This suggests a 5-HT inhibition of nigrostriatal output which, when reduced by unilateral 5-HT lesion enhances apomorphine effects on the ipsilateral side; this procedure attenuates the effects of amphetamine, which acts on the contralateral side, by enhancing the opponent ipsilateral output.

These results suggest that the influence of 5-HT on DA-dependent rotation is exerted at sites within the striatum rather than on the cell bodies or terminals of the nigrostriatal DA pathway. In addition, they emphasize the non-specificity of the degenerative effects of 6-OHDA and 5,6-DHT on catecholamine and indolamine neurones, especially when applied to densely packed monoamine pathways in the MFB.

J.L.W. is an MRC scholar. The transformation analysis was performed by Dr C.D. Frith.

References

COSTALL, B., NAYLOR, R.J. & PYCOCK, C. (1975). The 6-hydroxydopamine rotational model for the detection of dopamine agonist activity; reliability of effect from different locations of 6-hydroxydopamine. *J. Pharm. Pharmac.*, **27**, 943–946.

MILSON, J.A. & PYCOCK, C.J. (1976). Effects of drugs acting on cerebral 5-hydroxytryptamine mechanisms on dopamine-dependent turning behaviour in mice. *Br. J. Pharmac.*, **56**, 77–85.

SANER, A., PIERI, L., MORAN, J., DA PRADA, M. & PLETSCHER, A. (1974). Decrease of dopamine and 5-hydroxytryptamine after intracerebral application of 5,6-dihydroxytryptamine. *Brain Res.*, **76**, 109–117.

UNGERSTEDT, U. & ARBUTHNOTT, G.W. (1970). Quantitative recording of rotational behaviour in rats after 6-hydroxydopamine lesions of the nigrostriatal dopamine system. *Brain Res.*, **24**, 485–493.

Stereochemical specificity in the antipsychotic effects of flupenthixol in man

T.J. CROW & EVE C. JOHNSTONE

Division of Psychiatry, Clinical Research Centre, Harrow, Middlesex HA1 3UJ

Deniker (1960) suggested that ability to induce extrapyramidal side-effects was related to the therapeutic action of chlorpromazine in schizophrenia. Drugs with antipsychotic effects exert actions on central dopaminergic mechanisms (Carlsson & Lundqvist, 1963; O'Keefe, Sharman & Vogt, 1970) and studies of the sensitive adenylate cyclase in the corpus striatum suggest that ability to block the dopamine receptor correlates well with the therapeutic effects of these drugs (Miller, Horn & Iversen, 1974). It has been demonstrated that the two isomers of the thiaxanthene flupenthixol differ widely in their ability to block the dopamine receptor (Miller *et al.*, 1974) although they resemble each other in several other pharmacological properties (Enna, Bennett, Burt, Creese & Snyder, 1976). We have investigated whether these two isomers differ in their therapeutic effects.

Forty-five patients with acute schizophrenic illnesses diagnosed according to Present State Examination criteria were randomly allocated to α-flupenthixol, β-flupenthixol and placebo in a dose of 6 mg for 6 days followed by 9 mg for 22 days. All patients received orphenadrine HCl (50 mg) three times a day, and where additional medication was urgently required chlorpromazine (100 mg). Mental state ratings were made before and at weekly intervals during the trial. All patients showed a decrease in total symptoms over the trial period. This decrease was significantly greater in the group of patients treated with α-flupenthixol, than in the groups treated with β-flupenthixol and placebo. The overall improvement on placebo was slightly greater than on β-flupenthixol.

These findings demonstrate that the therapeutic potency of flupenthixol is confined to the α-isomer and therefore on the basis of *in vitro* receptor studies (Miller *et al.*, 1974; Enna *et al.*, 1976) eliminate the possibilities that the antipsychotic effects are related to blockade of acetylcholine, noradrenaline, GABA, glycine or opiate receptors.

We are grateful to Lundbeck Ltd. for making available preparations of the isomers of flupenthixol.

References

CARLSON, A. & LINDQVIST, M. (1963). Effect of chlorpromazine or haloperidol on the formation of 3-methoxy tyramine and normetanephrine in mouse brain. *Acta pharmacol. Toxicol.*, **20**, 140–144.

DENIKER, P. (1960). Experimental neurological syndromes and new drug therapies in psychiatry. *Comprehensive Psychiatry*, **1**, 92–102.

ENNA, S.J., BENNETT, J.P., BURT, D.R., CREESE, I. & SNYDER, S.H. (1976). Stereospecificity of interaction of neuroleptic drugs with neurotransmitters and correlation with clinical potency. *Nature, Lond.*, **263**, 338–341.

MILLER, R.J., HORN, A.S. & IVERSEN, L.L. (1974). The action of neurolpetic drugs on dopamine stimulated adenosine cyclic 3',5'-monophosphate production in rat neostriatal and limbic forebrain. *Mol. Pharmac.*, **10**, 759–766.

O'KEEFE, R., SHARMAN, D.F. & VOGT, M. (1970). Effect of drugs used in psychoses on cerebral dopamine metabolism. *Br. J. Pharmac.*, **38**, 287–304.