Dexamphetamine-induced EEG arousal in rats: a possible new test model for potential anti-schizophrenic agents

M.G. BAXTER, A.A. MILLER & P.L. WHEATLEY

Pharmacology Laboratory, The Wellcome Research Laboratories, Langley Court, Beckenham, Kent BR3 3BS

Potential anti-schizophrenic drugs are commonly assessed on their ability to antagonise the behavioural effects (stereotypy, hyperactivity) induced in laboratory animals by apomorphine or dexamphetamine. We had previously suggested that antagonism of dexamphetamine-induced EEG arousal in rats may provide a more useful test in predicting the clinical usefulness of neuroleptics in that three clinically used drugs, chlorpromazine, pimozide and haloperidol were effective whereas metoclopramide, an anti-emetic with a characteristic neuroleptic profile in laboratory animals but which apparently possessed little anti-schizophrenic action in man was ineffective (Baxter, Miller & Wheatley, 1976). We have now extended our studies to include further examples of known anti-schizophrenic drugs, two of their inactive isomers and one central depressant (diazepam).

EEG studies were undertaken in conscious rats (Wistar, male, 250–350 g) chronically implanted with skull electrodes (Goff, Miller, Smith, Smith & Wheatley, 1975). Parietal EEG, recorded on magnetic tape, was analysed by passing it through four broad waveband filters (Baxter *et al.*, 1976). Hourly mean integrated voltage was calculated for each frequency and for total voltage (2.3–26.0 Hz). Test drugs or control vehicle were injected subcutaneously (s.c.) at the end of a 2 h control period and 1 h before dexamphetamine sulphate (0.3 mg/kg s.c.). EEG was recorded continuously for up to 2 h after dexamphetamine administration.

In control rats ($n = 9$) dexamphetamine produced no overt behavioural stimulation but EEG total voltage was significantly reduced for the first hour ($P < 0.05$). This response was blocked by pretreatment with d-butaclamol ($n = 5$) and α-flupenthixol ($n = 5$), the active isomers of the anti-schizophrenic drugs, tested at their ED_{95} values against apomorphine-induced stereotypy i.e. 0.25 and 0.20 mg kg^{-1}, and also by clozapine ($n = 3$) and thioridazine ($n = 6$), tested at 20 mg/kg as they were both inactive in the stereotypy test. Two isomers, 1-butaclamol ($n = 3$) and β-flupenthixol ($n = 3$) which are inactive or only weakly active in pharmacological and biochemical tests for neuroleptics were inactive at 20 mg/kg: β-flupenthixol has been reported inactive as an anti-schizophrenic by Johnstone, Crow, Frith, Carney & Price (1978). Diazepam ($n = 3$) was also ineffective at 7.7 mg/kg (anticonvulsant ED_{95} against leptazol-induced limb extension).

The possible value of the dexamphetamine-induced arousal test has been further demonstrated: all seven clinically useful drugs so far tested have been found active whereas the test failed to reveal the two clinically ineffective drugs, metoclopramide and β-flupenthixol and the pharmacologically inactive isomer, 1-butaclamol. The blockade of arousal is apparently not attributable to a general non-specific depressant effect as diazepam was ineffective as was ethanolamine o-sulphate, an inhibitor of GABA-transaminase, when given at a behaviourally depressant dose (Baxter, Leach, Miller, Sethna & Wheatley, 1976).

Of possible relevance to our model are the suggestions that schizophrenics may be in a state of chronic hyperarousal (Kornetsky & Mirsky, 1966) and that the underlying biochemical disorders in schizophrenia may be attributable to a combination of changes in the reticular formation noradrenergic systems and the forebrain dopamine systems (Hornykiewicz, 1977).

References

BAXTER, M.G., LEACH, M.J., MILLER, A.A., SETHNA, D.M. & WHEATLEY, P.L. (1976). Some behavioural and EEG studies on the behavioural depression induced in the rat by ethanolamine o-sulphate, an inhibitor of GABA-transaminase. *Br. J. Pharmac.*, **57**, 431–432P.

BAXTER, M.G., MILLER, A.A. & WHEATLEY, P.L. (1976). Comparative studies on the effects of metoclopramide and some known neuroleptics on the EEG of the conscious rat. *Br. J. Pharmac.*, **58**, 269P.

GOFF, D., MILLER, A.A., SMITH, R.E., SMITH, S.J. & WHEATLEY, P.L. (1975). Combined EEG recording and intraventricular administration of drugs in the conscious rat. *Br. J. Pharmac.*, **55**, 312–P313P.

HORNYKIEWICZ, O. (1977). Psychopharmacological implications of dopamine and dopamine antagonists: a critical evaluation of current evidence. *Ann. Rev. Pharmacol. Toxicol.*, **17**, 545–549.

JOHNSTONE, EVE C., CROW, T.J., FRITH, C.D., CARNEY, M.W.P. & PRICE, J.S. (1978). Mechanism of the anti-psychotic effect in the treatment of acute schizophrenia. *Lancet* **1**, 848–851.

KORNETSKY, C. & MIRSKY, A.F. (1966). On certain psychopharmacological and physiological differences between schizophrenic and normal persons. *Psychopharmacologia*, **8**, 309–318.