SO rats were chronically treated (i.p.) with either saline, AMI (3 or 10 mg kg^{-1} day^{-1}), Org GB 94 (5 or 15 mg kg^{-1} day^{-1}), chlorpromazine (1 or 3 mg kg^{-1} day^{-1}), chlordiazepoxide (10 or 20 mg kg^{-1} day^{-1}), (+)-amphetamine (1 or 3 mg kg^{-1} day^{-1}) and lithium sulphate (1 or 3 mEq kg^{-1} day^{-1}). After 7 days of pretreatment motor activity was recorded in the open field test for a 2.5 min period. From day 8 onwards the rats were food deprived. Acquisition of appetite motivated behaviour was studied during 20 daily trials on days 11 and 12. A two compartment box was used. The rats were placed in one compartment and the time taken by the animals to reach a food cup on the back wall of the other compartment was recorded. Acquisition of passive avoidance behaviour was tested on day 13 by electrifying the floor of the 'food' compartment. Rats were considered as exhibiting passive avoidance when they remained in the safe compartment for 20 seconds.

Amphetamine increased, whereas chlorpromazine and chlordiazepoxide decreased open field activity in SO as well as in OB rats. The antidepressants, and to a lesser extent lithium, reduced activity in OB rats but had little effect on SO rats. AMI and ORG GB 94 also had distinct effects on acquisition. Bulbectomy produced deficient acquisition of appetite motivated and avoidance behaviour and the antidepressants reversed this deficit. However, they worsened the performance of the SO rats. A similar result was obtained with rats treated with amphetamine but not with those receiving chlorpromazine, chlordiaze poxide and lithium.

It is concluded that the OB rat is a possible model for the detection of antidepressant drugs. Using more than one behavioural test, the effects of antidepressants can easily be differentiated from those of other psychotropic compounds.

Miss Wren is in receipt of a grant from the SRC.

References

CAIRNCROSS, K.D. & KING, M.G. (1971). Facilitation of avoidance learning in anosmic rats by amitriptyline. *Proc. Aust. physiol. pharmacol. Soc.*, **2**, 25.

ITIL, T.M., POVLAN, N. & HSU, W. (1972). Clinical and E.E.G. effects of GB 94, a 'tetracyclic' antidepressant. *Curr. Ther. Res.*, **14**, 395–413.

MARKS, H.E., REMLEY, N.R., SEAGO, J.D. & HASTINGS, D.W. (1971) Effects of bilateral lesions of the olfactory bulbs of rats on measures of learning and motivation. *Physiol. Behav.*, **7**, 1–6.

VAN RIEZEN, H. (1972). Different central effects of 5-HT antagonists mianserin and cyproheptadine. *Arch. int. Pharmacodyn. Ther.*, **198**, 256–269.

UEKI, S., NURIMOTO, S. & OGAWA, N. (1972). Effects of psychotropic drugs on emotional behaviour in rats with limbic lesions, with special reference to olfactory bulb ablations. *Folia Psychiat. Neurol. Jap.*, **26**, 229–239.

Plasma concentrations in the monkey *(Macaca mulatta)* of six related benzodiazepines after intraperitoneal injection

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Recent studies in the monkey (*Macaca mulatta*) on the behavioural activity of benzodiazepines have been concerned with effects on delayed differentiation and spatial delayed alternation (Nicholson & Wright, 1974, 1976). We have determined the concentrations of six related benzodiazepines in monkeys from the same population. The compounds studied were: medazepam, diazepam, *N*-desmethyldiazepam (nordiazepam) and oxazepam, which are metabolized one to another in that order, plus clorazepate (a precursor of nordiazepam) and temazepam, an intermediate in metabolism of diazepam to oxazepam (Robin, Curry & Whelpton, 1974). Concentrations were determined by solvent extraction and gas-chromatography (de Silva & Puglisi, 1970). Eight monkeys were used, in groups of six for each drug, so that each monkey took part in not less than two, and up to six, trials with at least one month between trials.

Five of the six compounds have similar molecular weights (range 271–291) and their doses were 3.0 mg/kg. In contrast, clorazepate, with its molecular weight 1.4–1.5 times that of the others (409) was given at 4.5 mg/kg. Doses were in 5 ml polyethylene glycol. Samples were taken from the saphenous vein into heparin anticoagulant tubes.

Highest mean concentrations of unchanged drug were mostly at the initial time point ($\frac{1}{2}$ h). The exception was nordiazepam (1 h), (Table 1). The only compound quantitatively assessable when occurring as a metabolite was nordiazepam (after medazepam, diazepam and chlorazepate) though traces (< 0.05 µg/ml) of diazepam following medazepam, of temazepam following diazepam and oxazepam, and of oxazepam following medazepam, diazepam and chlorazepate, were detected.

Table 1 Mean plasma concentrations (μg/ml) in the monkey (*Macaca mulatta*) after intraperitoneal injection

Compound		Time (h) ½	1	2	4	8	24
(i) *Unmetabolized drugs*							
Medazepam	Mean	2.41	2.27	1.60	1.06	2.04	2.05
	s.e. mean	0.40	0.35	0.27	0.18	0.48	0.37
Clorazepate	Mean	1.81	1.10	0.80	0.30	0.045	0.015
	s.e. mean	0.70	0.31	0.20	0.11	0.019	0.009
Diazepam	Mean	0.55	0.33	0.11	0.043	0.033	0
	s.e. mean	0.13	0.07	0.02	0.011	0.013	—
Nordiazepam	Mean	2.61	2.72	2.11	1.84	1.40	0.35
	s.e. mean	0.67	0.38	0.29	0.24	0.21	0.07
Temazepam	Mean	0.71	0.46	0.17	0.042	0.023	0.002
	s.e. mean	0.23	0.13	0.05	0.008	0.002	0.001
Oxazepam	Mean	1.38	0.87	0.39	0.22	0.053	0.013
	s.e. mean	0.42	0.19	0.13	0.06	0.021	0.006
(i) *Nordiazepam as a metabolite of other drugs*							
Following medazepam	Mean	0.40	1.07	1.29	1.07	1.09	0.39
	s.e. mean	0.06	0.29	0.15	0.10	0.09	0.10
Following clorazepate	Mean	0.99	1.16	1.08	0.57	0.51	0.09
	s.e. mean	0.19	0.37	0.27	0.09	0.11	0.01
Following diazepam	Mean	1.77	2.05	1.57	1.27	1.06	0.25
	s.e. mean	0.39	0.38	0.20	0.21	0.13	0.05

The decline of medazepam concentrations was erratic, relatively fast at first, but with unexplained fluctuations which prevented mathematical interpretation. Diazepam, clorazepate, temazepam and oxazepam concentrations declined according to a bi-exponential model. These graphs were assessed by a method of residuals (Riggs, 1970; Curry, 1974). Mean half-times of decline for the two phases in each case were as follows: diazepam 0.50 and 9.69 h; clorazepate 0.6 and 11.0 h; temazepam 0.60 and 4.56 h; oxazepam 0.57 and 4.88 hours. Nordiazepam concentrations, which were at an overall higher level, declined following their highest levels in accordance with a single exponential model, the half-time being 8.15 hours.

We are grateful to Mr J.H. Cookson for administration of drugs and collection of samples, and to Mrs Susan Evans for analytical assistance.

References

CURRY, S.H. (1974). In: *Drug Disposition and Pharmacokinetics*, Oxford: Blackwell.

NICHOLSON, A.N. & WRIGHT, C.M. (1974). Inhibitory and disinhibitory effects of nitrazepam, diazepam and flurazepam hydrochloride on delayed matching behaviour in monkeys (*Macaca mulatta*). *Neuropharmacology*, **13**, 919–926.

NICHOLSON, A.N. & WRIGHT, C.M. (1976). Behavioural activity in the monkey (*Macaca mulatta*) of the metabolites of diazepam in man. *Br. J. Pharmac.*, **57**, 429P.

RIGGS, D.S. (1970). *The Mathematical Approach to Physiological Problems*, Cambridge (Massachusetts): M.I.T. Press.

ROBIN, A.A., CURRY, S.H. & WHELPTON, R. (1974). Clinical and biochemical comparison of clorazepate and diazepam. *Psychol. Med.*, **4**, 388–392.

de SILVA, J.A.F. & PUGLISI, C.V. (1970). Determination of medazepam (Nobrium), diazepam (Valium) and their major biotransformation products in blood and urine by electron-capture gas-liquid chromatography. *Anal. Chem.*, **42**, 1725–1736.