LAVERTY, R. & SHARMAN, D. F. (1965). *Br. J. Pharmac. Chemother.*, **24**, 333–335.

LLOYD, K. G., STADLER, H. & BARTHOLINI, G. (1973). *Frontiers in Catecholamine Research*, pp. 777–779. Editors: Usdin, E. & Snyder, S. H. Oxford: Pergamon.

MURPHY, G. F., ROBINSON, D. & SHARMAN, D. F. (1969). *Br. J. Pharmac.* **36**, 107–115.

O'KEEFFE, R., SHARMAN, D. F. & VOGT, M. (1970). *Ibid.*, **38**, 287–304.

PEREZ-CRUET, J., GESSA, G. L., TAGLIAMONTE, A. & TAGLIAMONTE, P. (1971). *Fedn Proc. Fedn Am. Socs exp. Biol.*, **30**, 216.

PLETSCHER, A. (1975). *Antipsychotic Drugs, Pharmacodynamics and Pharmacokinetics.* Editors: Sedvall, G. & Uvnäs, B. Oxford: Pergamon, in the press.

Effect of metoclopramide on turnover of brain dopamine noradrenaline and 5-hydroxytryptamine*

Metoclopramide (4-amino-5-chloro-*N*-[2-(diethylamino) ethyl]-*O*-anisamide) a powerful anti-emetic agent, has been used in various clinical conditions, including Parkinson's disease. However, in a small percentage of patients it causes acute dystonic reactions similar to those produced by neuroleptic drugs such as phenothiazines and butyrophenones (Borenstein & Bles, 1965; Casteels-Van Daele, Jaeken & others, 1970; Robinson, 1973). The most characteristic biochemical effect of neuroleptics is their capacity to increase central dopamine turnover (Carlsson & Lindqvist, 1963; Andén, Butcher & others, 1970; Nybäck & Sedvall, 1969) due, it is believed, to blockade of dopamine receptors causing an increase in firing of dopaminergic neurons (Bunney, Walters & others, 1973). In the present investigation we have studied the effect of metoclopramide on dopamine turnover by measuring dopamine and its principal metabolite homovanillic acid (HVA) in whole brain, and in corpus striatum and the mesolimbic area both of which contain large quantities of dopamine (Andén, 1972; Lloyd, Stadler & Bartholini, 1973). In addition, we have examined the effect of metoclopramide on whole brain levels of noradrenaline and its principal metabolite, 4-hydroxy-3-methoxy-phenylglycol sulphate (MOPEG-SO_4), and on 5-hydroxytryptamine (5-HT) and its principal metabolite, 5-hydroxyindoleacetic acid (5-HIAA).

Metoclopramide was injected intraperitoneally into Swiss "S" strain mice (approximately 30 g). The whole brains were quickly removed and deep-frozen. Brain parts were dissected on an ice-cold Petri-dish and then deep-frozen immediately. A transverse cut was made behind the striata, which were excised, and the cortex and the adhering part of the hypothalamus were removed. The forebrain tissue remaining contained the corpora amygdala, the olfactory tubercle and the nucleus accumbens (mesolimbic area). Parts from 3 animals were pooled for each determination. Dopamine was estimated by the method of Chang (1964), HVA by the method of Murphy, Robinson & Sharman (1969), noradrenaline by the method of Maickel, Cox & others (1968) and 5-HT and 5-HIAA by the method of Curzon & Green (1970). MOPEG-SO_4 was estimated in male Wistar rats according to Meek & Neff (1972) as this metabolite does not seem to be a major degradation product of noradrenaline in the mouse (Ceasar, Hague & others, 1974).

The results are summarized in Fig 1 and Table 1. Metoclopramide had no effect on whole brain dopamine concentrations, but caused a dose-dependent increase in whole brain HVA, which was maximal 1·5 h after injection. Metoclopramide increased HVA concentrations both in the corpus striatum and in the mesolimbic area, to approximately the same extent (i.e. by a factor of 4·5 and 5·9 respectively). Metoclopramide had no significant effect on whole brain noradrenaline, MOPEG-SO_4, 5-HT or 5-HIAA concentrations.

* Since this study was completed, Ahtee & Buncombe (*Acta pharm. tox.*, 1974, 35, 429-432) also have shown that metoclopramide causes a dose-dependent increase in mouse striatal HVA correlated with the intensity of catalepsy produced, and they suggest that metoclopramide blocks striatal dopaminergic receptors.

Table 1. *Effect of 50 mg kg^{-1} metoclopramide (1·5 h before death) on whole mouse brain concentrations of amines and their metabolites.* HVA was also measured in the corpus striatum (CS) and in the mesolimbic area (ML). MOPEG-SO_4 was measured in whole rat brain. The results are expressed as ng g^{-1} (± s.e.m.), figure in ( ) is the no. of estimations. $^{**}P<0{\cdot}001$.

Dopamine		HVA	
Saline	Metoclopramide	Saline	Metoclopramide
1241±273 (4)	1176±267 (4)	85±4 (19)	632±65 (8)**
		CS 766±126 (5)	3125±116 (5)**
		ML 170±28 (5)	895±63 (5)**
Noradrenaline		MOPEG-SO_4	
322±23 (4)	316±32 (4)	146±11 (6)	140±10 (6)
+5-HT		5-HIAA	
1100±49 (4)	1046±45 (4)	474±21 (4)	506±98 (4)

The data suggest that metoclopramide, like other neuroleptic agents, blocks dopamine receptors in the brain, but that it has little effect biochemically on noradrenaline or 5-HT systems. Other evidence also indicates that metoclopramide is a dopamine receptor antagonist. In rodents, metoclopramide causes catalepsy (Costall & Naylor, 1973), inhibits apomorphine-induced stereotypy (Janssen, Niemegeers & Schellekens, 1967; Hackman, Pentikäinen & others, 1973), inhibits apomorphine reversal of reserpine-induced locomotor suppression, and antagonizes apomorphine or amphetamine-induced circling behaviour in animals with a unilateral destruction of the nigro-striatal dopamine pathway (Dolphin, Jenner & others, 1975). In all these respects metoclopramide resembles pimozide which is believed to be a relatively specific dopamine receptor antagonist (Andén & others, 1970), although an approximately ten-fold greater dose of metoclopramide is required to achieve the same behavioural effects as pimozide (Dolphin & others, 1975). From all these data we conclude that metoclopramide is a cerebral dopamine receptor antagonist, and the present evidence suggests that this is so both in corpus striatum and mesolimbic area.

It is therefore surprising that metoclopramide has been used in patients with Parkinson's disease without obvious adverse action. Indeed, we have directly compared the effect of metoclopramide (up to 60 mg daily) and pimozide (up to 4 mg daily) in a group of patients with Parkinson's disease treated with L-dopa. Metoclopramide caused no increase in severity of the parkinsonian symptoms and did not affect the

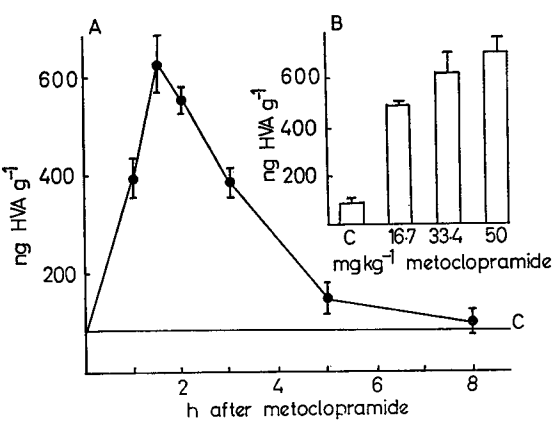

FIG. 1. Effect of metoclopramide on mouse whole brain concentration of HVA. A) Time response curve to 50 mg kg^{-1}, i.p. B) Dose response results for three doses of metoclopramide given i.p. 1·5 h before death. C) indicates HVA levels in saline pretreated animals.

intensity of L-dopa-induced dyskinesia. Pimozide caused a significant clinical deterioration, with increased akinesia, rigidity and tremor, and also reduced the intensity of L-dopa dyskinesias (Tarsy, Parkes & Marsden, 1975). It is also surprising that metoclopramide has little if any antipsychotic activity (Borenstein & Bles, 1965), in view of the current suggestion that this property is associated with the capacity to block cerebral dopamine receptors, particularly those in the mesolimbic area (van Rossum, Janssen & others, 1970; Andén, 1972; Costall & Naylor, 1973; Matthysse, 1973). The present results indicate that metoclopramide administered intraperitoneally substantially affects both striatal and mesolimbic dopamine turnover, so these clinical observations are unlikely to be due to a failure of metoclopramide to gain access to cerebral dopamine receptors. The failure of this action of the drug to be reflected in clinical practice may indicate that it possesses some other unrecognized pharmacological property, or that antiemetic doses used in man are insufficient to cause significant dopamine antagonism in corpus striatum and mesolimbic areas.

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REFERENCES

ANDÉN, N-E., BUTCHER, S. C., CORRODI, H., FUXE, K. & UNGERSTEDT, U. (1970). *Eur. J. Pharmac.*, **11**, 303–314.

ANDÉN, N-E. (1972). *J. Pharm. Pharmac.*, **24**, 905–906.

BORENSTEIN, P. & BLES, G. (1965). *Thérapie*, **20**, 975–995.

BUNNEY, B. S., WALTERS, J. R., ROTH, R. H. & AGHAJANIAN, G. K. (1973). *J. Pharmac. exp. Ther.*, **185**, 560–571.

CARLSSON, A. & LINDQVIST, M. (1963). *Acta pharmac. tox.*, **20**, 140–144.

CASTEELS-VAN DAELE, M., JAEKEN, J., VAN DER SCHUEREN, P., ZIMMERMAN, A. & VAN DEN BON, P. (1970). *Arch. Dis. Child*, **45**, 130–133.

CEASAR, P. M., HAGUE, P., SHARMAN, D. F. & WERDINIUS, B. (1974). *Br. J. Pharmac.*, **51**, 187–195.

CHANG, C. C. (1964). *Int. J. Neuropharmac.*, **3**, 643–649.

COSTALL, B. & NAYLOR, R. J. (1973). *Psychopharmacologia*, **32**, 161–170.

CURZON, G. & GREEN, A. R. (1970). *Br. J. Pharmac.*, **39**, 653–655.

DOLPHIN, A., JENNER, P., MARSDEN, C. D., PYCOCK, C. & TARSY, D. (1975). *Psychopharmacologia*, **41**, 133–138.

HACKMAN, R., PENTIKÄINEN, P., NEUVONEN, P. J. & VAPAATALO, H. (1973). *Experientia*, **34**, 1524–1525.

JANSSEN, P. A., NIEMEGEERS, C. J. & SCHELLEKENS, K. H. (1967). *Arzneimittel-forsch.*, **17**, 841–854.

LLOYD, K. G., STADLER, H. & BARTHOLINI, G. (1973). In: *Frontiers in catecholamine research.* p. 777. Editors Usdin, E. & Snyder, S. H. Oxford: Pergamon.

MAICKEL, R. P., COX, R. H. Jr., SAILLANT, J. & MILLER, F. P. (1968). *Int. J. Neuropharmac.*, **7**, 275–281.

MATTHYSSE, S. (1973). *Fedn. Proc. Fedn. Assoc. Socs exp. Biol.*, **32**, 200–205.

MEEK, J. L. & NEFF, N. M. (1972). *Br. J. Pharmac.*, **45**, 435–441.

MURPHY, C. F., ROBINSON, D. & SHARMAN, D. F. (1969). *Ibid.*, **36**, 107–115.

NYBÄCK, H. & SEDVALL, G. (1969). *Eur. J. Pharmac.*, **5**, 245–252.

ROBINSON, O. P. W. (1973). *Postgrad. med. J.*, **49**, Suppl. **4**, 77–80.

TARSY, D., PARKES, J. D. & MARSDEN, C. D. (1975). *J. Neurol. Neurosurg. Psychiat.* (in the press).

VAN ROSSUM, J. M., JANSSEN, P. A. J. & others (1970). In: *Modern Problems of Pharmacopsychiatry, The Neuroleptics*, Editors: Bobson, D. P., Janssen, P. A. J. & Bobon, J. Vol. 5, pp. 23–70. Basel: Karger.