Catalepsy and stereotyped behaviour in rats treated chronically with methadone: relation to brain homovanillic acid content

Acute administration of methadone and several other narcotic analgesics produces a dose-dependent catalepsy and increase of brain homovanillic acid (HVA) content in rats (Ahtee & Kääriäinen, 1973; Ahtee, Kääriäinen & Paasonen, 1972; Kuschinsky & Hornykiewicz, 1972; Sasame, Perez-Cruet & others, 1971, 1972). Fog (1970) found that chronic but not acute morphine administration produces stereotyped behaviour in rats. In the present work the behaviour and brain HVA content of rats treated chronically with methadone has been assessed.

(±)-Methadone hydrochloride (Leiras Oy, Turku, Finland; all doses refer to the base) was given to male Wistar rats gradually increasing the daily dose from 3 to 18 mg kg^{-1}, which dose was given from the 28th day of treatment to the 31st or 37th day. Methadone was administered subcutaneously twice daily, at 8 a.m. and 3 p.m., as well as in drinking water. The average daily consumption of methadone in drinking water was 1·5 mg kg^{-1} from the 4th to the 11th day of treatment, 3 mg kg^{-1} from the 12th to the 19th day and 6 mg kg^{-1} from the 20th to the 28th day when the administration in this way was stopped. Control rats were given 0·2 ml of 0·9 % NaCl solution subcutaneously twice daily. Before starting the treatment the rats weighed 220–280 g, during the 32 day treatment the control rats gained about 40 g and the methadone-treated rats lost about 20 g of the original weight.

Catalepsy was scored as described by Simon, Malatray & Boissier (1970). Four tests (3 cm high cork, 9 cm high cork, parallel bars and vertical grid) were used, each was scored from 0 to 2. To assess the stereotyped behaviour the rats were placed in transparent plastic cages, 18 × 22 × 14 cm. To detect gnawing the bottom of each cage was covered with corrugated paper, the corrugations facing upwards. The behaviour considered to be stereotyped consisted of standing or sitting in an abnormal posture, continuous jerking of head or jaw upwards, backwards locomotion and continuous movement of one or both front legs as if to grab unexisting objects.

On the 32nd or 38th day the rats were given 10 mg kg^{-1} of methadone or saline between 8 and 9 a.m. Two h later the rats were decapitated, the brain rapidly removed and dissected. The striata from two brains were pooled for the estimation of HVA by the method of Portig, Sharman & Vogt (1968). The rectal temperatures of the rats were measured just before the injection and 2 h later. Methadone slightly decreased the rectal temperature of the control rats (0·4 ± 0·3°, mean ± s.e., n = 14) but increased that of the rats treated chronically with methadone by 1·4 ± 0·3° (n = 17) on the 32nd day and by 1·8 ± 0·2° (n = 6) on the 38th day.

Fig. 1 shows the time course of catalepsy in rats after 10 mg kg^{-1} of methadone. In rats treated chronically with saline methadone-induced catalepsy started in 2–3 min and the maximum score, 8, was reached at 30 min after the injection. The rats remained maximally cataleptic for 3–4 h. Nearly all were fully recovered 5 h after the methadone injection. No stereotypies or gnawing were observed in these rats after the single methadone dose.

In rats treated chronically with methadone the methadone-induced catalepsy started about as quickly as in the saline-treated controls. These rats were felt to be more rigid than the controls when touched but the cataleptic score was not as high as in the controls and the rats fully recovered from catalepsy in 2·5–3 h. However, all these rats had gnawing and/or stereotyped behaviour which appeared about a week after starting methadone-treatment. Of the 13 rats watched on the 29th day, 11 had both stereotypies and gnawed the corrugated paper. Of the 2 remaining rats, one had

stereotypies and the other gnawed. On the 36th day 8 out of the 13 rats had both symptoms, 2 had only stereotypies and 3 only gnawed. Fig. 2 shows the percentage proportion of rats which gnawed and/or had stereotypies in eight subsequent half-hour periods after methadone injection. Both these effects were maximal at about 2 h after methadone injection and had almost disappeared at 4 h after methadone. The

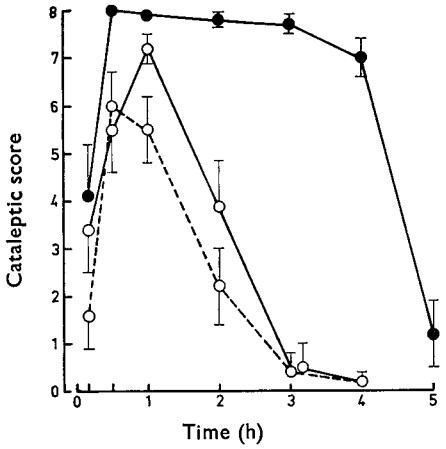

FIG. 1. The cataleptic score of rats at various times after methadone injection (10 mg kg^{-1}). The mean ± s.e. from 11 rats treated chronically with saline (●—●) and from 13 rats treated with gradually increasing doses of methadone (on the 29th (○—○) and 36th (○ --- ○) day of treatment).

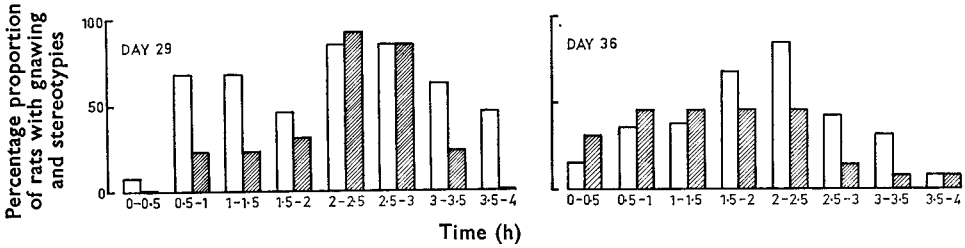

FIG. 2. The percentage proportion of rats with gnawing (open columns) and/or with stereotypies (hatched columns) during eight subsequent half-hour periods after methadone injection (10 mg kg^{-1}). Thirteen rats treated with gradually increasing doses of methadone were watched on the 29th and 36th day of treatment.

Table 1. *The effect of methadone (10 mg kg^{-1}, s.c.) on the homovanillic acid content in the striatum of rats treated chronically with saline or with methadone for 32 or 38 days.*

Treatment (days)		Homovanillic acid μg g^{-1}* 2 h after saline		2 h after methadone	
Chronic saline	(32)	0·71 ± 0·05	(6)	1·70 ± 0·16	(5)
,, ,,	(38)	0·48	(1)	1·25	(1)
Chronic methadone	(32)	0·52 ± 0·09	(4)	1·71 ± 0·09	(9)
,, ,,	(38)	0·41 ± 0·19	(3)	1·38 ± 0·22	(3)

* Mean ± s.e., number of estimations in brackets.

HVA content in the striatum of the rats treated chronically with methadone was slightly lower than in the striatum of the saline-treated controls. Two h after methadone (10 mg kg^{-1}) the HVA content was increased up to the same level in both groups (Table 1).

These results demonstrate that in rats treated chronically with methadone, tolerance develops towards the cataleptic effects of methadone, but simultaneously the rats start gnawing and having other stereotypies. The duration of abnormal behaviour (catalepsy and stereotypies) induced by a single dose of methadone in methadone-treated rats is about the same as that of catalepsy in control rats. Moreover, methadone increases the striatal HVA up to a similar amount in control and tolerant rats. On the basis of these results it is suggested that the primary effect of methadone could be catalepsy (possibly a blockade of dopamine receptors) which causes a compensatory increase in the production of dopamine. The additional dopamine then causes stereotyped behaviour because the methadone-induced catalepsy in tolerant rats lasts only for a short time.

I am indebted to Mrs. Pirkko Olkkonen and Mrs. Margareta Svartström-Fraser for skilful assistance. This work was supported by the National Research Council for Medical Sciences, Finland. The rats used were kindly donated by Leiras Oy, Turku, Finland.

Department of Pharmacology,
University of Helsinki,
Siltavuorenpenger 10, SF-00170 Helsinki 17,
Finland.

LIISA AHTEE

March 5, 1973

REFERENCES

AHTEE, L. & KÄÄRIÄINEN, I. (1973). *Eur. J. Pharmac.*, **22**, 206–208.

AHTEE, L., KÄÄRIÄINEN, I. & PAASONEN, M. K. (1972). *Annls Med. exp. Biol. Fenn.*, **50**, 180–185,

FOG, R. (1970). *Psychopharmacologia (Berl.)*, **16**, 305–312.

KUSCHINSKY, K. & HORNYKIEWICZ, O. (1972). *Eur. J. Pharmac.*, **19**, 119–122.

PORTIG, P. J., SHARMAN, D. F. & VOGT, M. (1968). *J. Physiol., Lond.*, **194**, 565–572.

SASAME, H. A., PEREZ-CRUET, J., DI CHIARA, G., TAGLIAMONTE, A., TAGLIAMONTE, P. & GESSA, G. L. (1971). *Rivista di Farmacologia e Terapia*, **11**, 99–105.

SASAME, H. A., PEREZ-CRUET, J., DI CHIARA, G., TAGLIAMONTE, A., TAGLIAMONTE, P. & GESSA. G. L. (1972). *J. Neurochem.*, **19**, 1953–1957.

SIMON, P., MALATRAY, J., & BOISSIER, J. R. (1970). *J. Pharm. Pharmac.*, **22**, 546–547.

Comparison of the blocking effects of antagonists of adrenaline and 5-hydroxytryptamine on their mutual receptors

When adrenoceptor and 5-HT receptor antagonist drugs are used as tools in the elucidation of the mechanism of action of other drugs, the antagonists are often regarded as specific irrespective of the dose employed. However, with the blockade of adrenoceptors and 5-HT receptors, most antagonists have the potential to influence both types of receptors and have therefore only a narrow dose range in which the antagonism can be regarded as specific for one or the other of these receptors. We decided therefore to determine the blocking effects of some adrenolytic and 5-HT antagonistic drugs to both types of receptors in the rat isolated fundus strip—which is specially sensitive to 5-HT—and on the isolated vas deferens—which is fairly sensitive to noradrenaline.