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.

Table 1. *pA_2 values of adrenaline- and 5-hydroxytryptamine antagonists against 5-hydroxytryptamine, noradrenaline and dopamine.*

	5-Hydroxytryptamine fundus strip	Noradrenaline vas deferens	Dopamine vas deferens	Ratio of inhib. concns 5-HT : NA
Methysergide	8·89 ± 0·20	5·79 ± 0·08	not tested	1 : 1260
Cyproheptadine	8·38 ± 0·07	6·28 ± 0·02	not tested	1 : 126
Haloperidol	5·77 ± 0·01	7·21 ± 0·02	7·50 ± 0·02	28 : 1
Chlorpromazine	5·74 ± 0·13	8·16 ± 0·08	8·35 ± 0·12	260 : 1
Phentolamine	<4·1	7·67 ± 0·05	7·97 ± 0·05	>3700 : 1

The isolated organs were taken from male rats of the Wistar II strain weighing about 250 g. The isolated fundus strip was prepared according to Vane (1957). Cumulative dose-response curves for 5-HT were set up by increasing the 5-HT concentrations in the bath every 90 s until maximal contraction was achieved. Between two dose-response curves an interval of 1 h was allowed for recovery.

The isolated vas deferens was prepared and mounted in the usual way. EDTA (10^{-5} M) was added to the Tyrode solution (Furchgott, 1955), the temperature was maintained at 30°. Cumulative dose-response curves were made by increasing the concentrations of noradrenaline or dopamine every 60 s until maximal contraction had occurred. An interval of 1 h was allowed between two dose-response curves. Antagonists were added 5 min before the agonist, cyproheptadine 30 min before.

All experiments were repeated 6–10 times. The pA_2 values were calculated according to Schild (1947), the pD_2 values by the method of van Rossum (1963). 5-HT was used as creatinine sulphate, dopamine as the hydrochloride which was dissolved in 0·01 N HCl. (−)-Noradrenaline was used as a dilution of Arterenol (Hoechst) which had previously been shown not to differ from prepared solutions of noradrenaline. Cyproheptadine HCl and methysergide–methanesulphonate were used as 5-HT antagonists and phentolamine–methanesulphonate, chlorpromazine (Megaphen, Bayer) and haloperidol (Janssen) as catecholamine antagonists.

On the fundus strip 5-HT had a pD_2 value of 7·89 ± 0·08, pD_2 values for noradrenline and dopamine on the vas deferens were 5·05 ± 0·05 and 4·24 ± 0·12, respectively. pA_2 values of the antagonistic drugs are summarized in Table 1.

The results show that at least 4 of the 5 drugs, commonly regarded as "specific" antagonists of either noradrenaline or 5-HT, are able to block both types of receptors when given in sufficiently high concentrations. The only exception was phentolamine which even at 10^{-4}M was devoid of a 5-HT antagonistic effect. The difference between the concentrations blocking the two types of receptors was especially narrow with haloperidol which is known to be a much more potent antagonist of dopamine than of noradrenaline (Janssen, Niemegeers & Schellekens, 1965), but was, on the vas deferens, about equally active against both catecholamines (Table 1). This apparent discrepancy suggests that in the vas both catecholamines influence the same receptor. Dopamine seems to behave here as a weak agonist for the noradrenaline receptor.

Also, cyproheptadine can only be considered to be a specific 5-HT antagonist when the concentrations necessary to block the 5-HT receptors are not unduly exceeded, and the same applies to chlorpromazine as an antagonist of α-adrenoceptors. Besides phentolamine, only methysergide had a margin of safety between 5-HT and α-adrenoceptors exceeding a factor of 1:1000.

The results thus point to a conformational similarity of α-adrenoceptor and 5-HT receptors. This makes a strict adjustment of doses or concentrations of the antagon-

ist necessary if misinterpretations of experimental results are to be avoided. We thank Prof. Dr. Schümann for allowing us to conclude these experiments in his institute.

Institute of Pharmacology,
Klinikum Essen, D-4300 Essen,
Hufelandstr. 55.

BERND-D. GÖRLITZ

Dept. of Pharmacology and Toxicology,
School of Veterinary Medicine,
Free University, D-1000 Berlin 33,
Koserstr. 20, Germany.

H.-H. FREY

January 15, 1973

REFERENCES

FURCHGOTT, R. F. (1955). *Pharmac. Rev.*, **7**, 183–265.
JANSSEN, P. A. J., NIEMEGEERS, C. J. E. & SCHELLEKENS, K. H. L. (1965). *Arzneimittel-Forsch.*, **15**, 104–117.
VAN ROSSUM, J. M. (1963). *Archs int. Pharmacodyn. Thér.*, **143**, 299–330.
SCHILD, H. O. (1947). *Br. J. Pharmac. Chemother.*, **2**, 189–206.
VANE, J. R. (1957). *Ibid.*, **12**, 344–349.

Arachidonic acid lowers and indomethacin increases the blood pressure of the rabbit

Studies on the effects of exogenous prostaglandins (PG) of the E and A-type on vascular resistance have shown them to be among the most potent of all naturally occurring vasodilatators (Karim & Somers, 1972) Normally, the prostaglandins do not act on a tissue after release into the blood stream but are formed locally. They are inactivated by the ubiquitous 15-hydroxy prostaglandin dehydrogenase (PGDH) and other enzymes, either close to the site of action or in the lung and other tissues following release into the blood (Änggård, 1971). It might therefore be more interesting from a physiological view point to study the effects of locally produced endogenous prostaglandins. It has been proposed that since the availability of the precursor acid at its site of formation appears to be the rate limiting factor in the formation of PG (Samuelsson, 1970), the endogenous formation of PG might be enhanced by the administration of large doses of the C_{20} polyenoic precursor acids (Änggård, 1970). Conversely the formation of endogenous prostaglandins can be blocked by indomethacin and related compounds (Smith & Willis, 1971; Vane, 1971; Hamberg & Samuelsson, 1972). We now report that intra-arterial infusion of arachidonic acid in rabbits lowers the blood pressure. This is prevented by indomethacin or 5,8,11,14-eicosatetraynoic acid (TYA), two PG synthesis inhibitors, which conversely produce an increase in the resting blood pressure.

Five male white New Zealand rabbits (2·5–3·5 kg) were anaesthetized with 1–2 g kg^{-1} of urethane. A polyethylene catheter was inserted from the femoral artery into the descending aorta above the origin of the renal arteries for infusion of arachidonic acid and indomethacin. Blood pressure was monitored from the right femoral artery, from which arterial blood was also sampled. Urine was collected from catheters inserted into the urethers. Arachidonic acid was stored frozen under nitrogen as the methyl ester. One to two hours before use the ester was hydrolysed, the acid purified by