indicate an important role for 5-HT in the regulation of the cataleptic effect of morphine and suggest that the activation of the central 5-hydroxytryptaminergic system has a facilitatory effect on the catalepsy induced by morphine, and our results with methysergide, which are in agreement with those of Scheel-Krüger et al (1977) and Costall & Naylor (1975), suggest that inhibition of the central 5-hydroxytryptaminergic system decreases the cataleptic effect of morphine.

Morphine in high doses induces immobility and catalepsy and simultaneously apparently induces a facilitation of some dopaminergic mechanisms in the rat. These behavioural effects of morphine depend in part on a balance between the dopaminergic system and an inhibitory 5-hydroxytryptaminergic system simultaneously activated by high doses of morphine (Buxbaum et al 1973; Costall & Naylor 1975). The mutual interdependence of the two systems has also been demonstrated morphologically. 5-Hydroxytryptaminergic fibres arising from the raphé nuclei have been shown to make synaptic contacts with dopaminergic cells in the substantia nigra (Parizek et al 1971).

In conclusion we would like to suggest that activation of the central 5-hydroxytryptaminergic mechanisms by morphine most probably results in inhibition of the central dopaminergic system, with resultant decrease in the amounts of dopamine at post synaptic striatal dopamine receptor sites and occurrence of catalepsy.

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REFERENCES

Aghajanian, G. K., Asher, I. M. (1971) Science 172: 1159–1161

Buxbaum, D. M., Yarbrough, G. G., Carter, M. E. (1973) J. Pharmacol. Exp. Ther. 185: 317–327

Costall, B., Naylor, R. J. (1975) J. Pharm. Pharmacol. 27: 67–69

Fog, R. (1970) Psychopharmacologia (Berl.) 16: 305–312

Hamon, M., Bourgoin, S., Enjalbert, A., Bockaert, J., Hery, F., Ternaux, J. P., Glowinski, J. (1976) Naunyn-Schmiedebergs Arch. Pharmacol. 294: 99–108

Iwatsubo, K., Clouet, D. H. (1975) Biochem. Pharmacol. 24: 1499–1503

Kuschinsky, K., Hornykiewicz, O. (1972) Eur. J. Pharmacol. 19: 119–122

Kuschinsky, K., Hornykiewicz, O. (1974) Ibid. 26: 41–50

Lal, H., Gianutsos, G., Puri, S. K. (1975) Life Sci. 17: 29–34

Medon, P. J., Leeling, J. L., Phillips, B. M. (1973) Ibid. 13: 685–691

Parizek, J., Hassler, R., Bak, I. J. (1971) Z. Zellforsch. 115: 137–148

Rodriguez, R., Rojas-Ramirez, J. A., Drucker-Colin, R. R. (1973) Eur. J. Pharmacol. 24: 164–171

Ross, S. B., Renyi, A. L. (1975) Acta Pharmacol. Toxicol. 36: 382–394

Scheel-Krüger, J., Golembiowska, K., Mogilnicka, E. (1977) Psychopharmacology 53: 55–63

The effect of levamisole on the cardiac responses to sympathomimetics and on the amine uptake process

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DL-Tetramisole (2,3,5,6-tetrahydro-6-phenylimidazol {2,1-b} thiazole hydrochloride) is a broad spectrum antihelmintic (Thienpont et al 1966) with reported antidepressant activity (Bobon et al 1974). Most antidepressant agents interfere with the peripheral adrenergic nerve endings mainly through a cocaine-like blockade of the neuronal uptake of noradrenaline (Trendelenburg 1968; Maxwell et al 1970; 1974). Recently Vanhoutte et al (1977) confirmed this type of action for the isomers of tetramisole on the saphenous vein strips of the dog; however, they observed that levamisole up to 4×10^{-5} M increased the contractile response to tyramine which is in disaccord with the proposed blockade of the amine uptake process. We have tested the influence of levamisole on the cardiac stimulation due to direct and indirectly acting sympathomimetics as well as on the uptake of tritiated noradrenaline.

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Guinea-pigs of either sex, 300–450 g, were killed by a blow on the head and exsanguinated. The hearts were rapidly removed, a cannula inserted into the aorta and the perfusion with a modified Ringer-Locke solution (mM: NaCl, 154; $CaCl_2$, 1·6; KCl, 5·6; NaH_2PO_4, 0·07; $NaHCO_3$, 1·7; glucose 5·5) continuously bubbled with O_2 and kept at 37 °C begun immediately. The hydrostatic pressure at the tip of the aortic cannula was 50 mm Hg. Cardiac contractility was registered through a lateral writing isotonic lever on a smoked drum. The total tension applied was of approximately 2 g. After equilibration for 30 min, agonists were injected as a bolus into the medium as it entered the heart in volumes that never exceeded 0·1 ml. Dose-response curves to the agonists were obtained before and 20 min after the addition of levamisole to the reservoir. Histamine, which increases the cardiac contractility independently of adrenergic nerve terminals or receptors (Trendelenburg 1960), was

used as the control inotropic agent in a single dose before and after levamisole. There was a significant inhibition of the tyramine effect and a potentiation of the inotropic action of noradrenaline by levamisole. The cardiac stimulation due to histamine was not significantly affected by levamisole which in the dose employed did not significantly alter the basal cardiac tension (Table 1).

Table 1. The effect of levamisole on the contractile responses of the isolated heart to noradrenaline (NA), tyramine (Ty) and histamine (Hi). The contractile responses are given as per cent increase in relation to the basal contractility at the moment of injection. Each value represents the mean ± s.e.m. of eight experiments.

Drug	Dose × 10^{-6} M	Force of contraction (as % of basal) Control	Levamisole 1.5×10^{-5} M
Ty	2·0	29·5 ± 4·5	3·5 ± 2·0*
	4·0	81·0 ± 15·0	20·8 ± 7·4*
	8·0	126·3 ± 24·2	32·0 ± 8·6*
NA	0·03	37·2 ± 3·6	66·6 ± 6·2*
	0·06	68·6 ± 10·9	116·5 ± 7·5*
	0·12	183·0 ± 22·8	358·7 ± 48·3*
Hi	1·0	90·0 ± 9·6	79·5 ± 7·2

* Significantly different from control ($P < 0.05$; Student's t-test).

In another group of experiments, right ventricle slices of about 10 mg each were pre-incubated with 3 ml of Ringer-Locke solution at 37 °C. After 10 min the tissues were exposed to (±)-[^{3}H]noradrenaline (^{3}H-NA), New England Nuclear, specific activity 9·8 Ci mmol^{-1}) with or without levamisole or cocaine for 20 min. The slices were then washed with ^{3}H-NA-free Ringer-Locke solution for an additional 10 min, after which they were blotted and weighed; 50 mg was then homogenized in 2 ml of 0·4 M $HClO_4$ and kept at 2 °C. After 30 min the homogenate was centrifuged at 1500 g for 15 min. Aliquots of 1 ml of the supernatant were transferred into vials containing 7 ml of scintillation mixture (PPO, POPOP, toluene and triton X-100) and read in a liquid scintillator spectrometer (Beckman LS 100 C). The counting efficiency was determined by external standardization. Fig. 1 shows that levamisole inhibits the neuronal uptake of noradrenaline. It can be seen that levamisole has about half the potency of cocaine on the guinea-pig cardiac muscle.

These observations suggest that the levamisole-induced blockade of the neuronal uptake of amines is responsible for the inhibition of the tyramine effect and the potentiation of the cardiostimulatory action

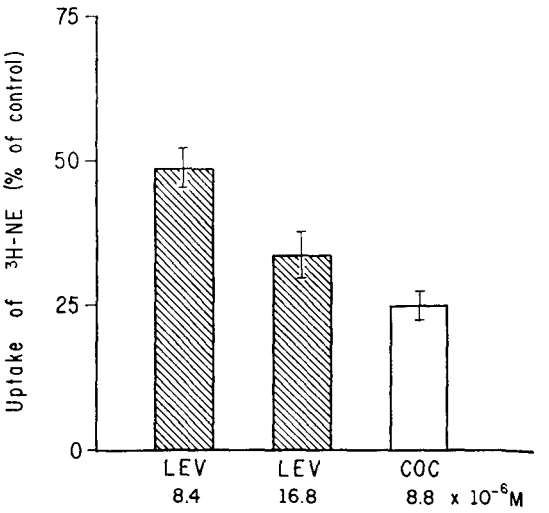

FIG. 1. The effects of levamisole (LEV) and cocaine (COC) on the uptake of ^{3}H-NA by ventricular slices of the guinea-pig heart. Each value represents the mean ± s.e.m. of 4 experiments.

of exogenously added noradrenaline. The explanation given by Vanhoutte et al (1977) for the unexpected potentiation of tyramine contractile action by levamisole on saphenous vein strip was an observed increase in noradrenaline overflow associated with an inhibition of monoamine oxidase activity. Such an enhanced outflow of ^{3}H-NA by levamisole does not seem to occur in the heart when the tyramine effect was inhibited rather than potentiated.

Our results also suggest that the antidepressant activity of levamisole (Bobon et al 1974) may be due to this cocaine-like activity which is a common property of the tricyclic antidepressants (Maxwell et al 1970).

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REFERENCES

Bobon, J., Bobon, D. P., Bourdouxhe, S., Pinchard, A. (1974) J. Int. Med. Res. 2: 171–174

Maxwell, R. A., Batmanglidj Eckhardt, S., Hite, G. (1970) J. Pharmacol. Exp. Ther. 171: 62–69

Maxwell, R. A., Ferris, R. M., Burcsu, J., Chaplin Woodward, E., Tang, D., Williard, K. (1974) Ibid. 191: 418–430

Thienpont, D., Van Parijs, O. F. J., Raeymaekers, A. H. M., Vandenberk, J., Demoen, P. J. A., Allewijn, F. T. N., Marsboom, R. P. H., Niemegeers, C. J. E., Schellekens, K. H. L., Janssen, P. A. (1966) Nature (London) 209: 1084–1086

Trendelenburg, U. (1960) J. Pharmacol. Exp. Ther. 130: 450–460

Trendelenburg, U. (1968) Ibid. 161: 222–231

Vanhoutte, P. M., Van Nueten, J. M., Verbeuren, T. J., Laduron, P. M. (1977) Ibid. 200: 127–140