alone. In contrast, the inhibition of phenethylamine oxidation by *N*-cyclopropyl-PCA was only slightly influenced by harmaline (68% inhibition compared to 80% inhibition in rats receiving *N*-cyclopropyl-PCA alone).

The concentrations of 5-HT and of 5-HIAA are also shown in Table 1. *N*-Cyclopropyl-PCA alone markedly reduced 5-HIAA concentration without affecting 5-HT concentration significantly at this time, in agreement with earlier data (Fuller & Perry 1977). Although harmaline is an inhibitor of type A monoamine oxidase, it is short-acting so that no inhibition of type A monoamine oxidase remained at 24 h; 5-HT concentration therefore was not changed in the group of rats that received harmaline alone, though a slight but statistically significant decrease in 5-HIAA persisted. In rats that received harmaline along with *N*-cyclopropyl-PCA, 5-HT was significantly depressed, and 5-HIAA concentration was lowered to about the same extent as in rats treated with *N*-cyclopropyl-PCA alone.

Considering these data in light of our previous studies on *N*-cyclopropyl-PCA, we make the following interpretations. At times up to 24 h after *N*-cyclopropyl-PCA injection into rats, the concentration of 5-HT in brain was not decreased because inhibition of monoamine oxidase prevented the expression of the depleting effect of the drug. The concentration of 5-HIAA was lowered since both monamine oxidase inhibition and the PCA-like inhibition of 5-hydroxyindole formation by *N*-cyclopropyl-PCA would lower that metabolite. Prevention of type A monoamine oxidase inhibition through co-administration of harmaline, a short-acting reversible inhibitor that acts preferentially on type A MAO, revealed the 5-hydroxyindole-depleting effect of *N*-cyclopropyl-PCA. Both 5-HT and 5-HIAA concentrations were lowered in rats receiving this drug combination. Earlier we had shown that the PCA-like depleting effect of *N*-cyclopropyl-PCA could be prevented by inhibition of its uptake into 5-HT-containing neurons (Fuller & Perry 1977), resulting in expression of monoamine oxidase inhibition (an increase in 5-HT concentration). Thus the two major components of the action of *N*-cyclopropyl-PCA on 5-HT-containing neurons in brain can be dissociated pharmacologically.

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REFERENCES

Fuller, R. W. (1978) Ann. N.Y. Acad. Sci. 305: 147–159

Fuller, R. W., Hemrick, S. K. (1978) Life Sci. 22: 1083–1086

Fuller, R. W., Hemrick, S. K., Mills, J. (1978) Biochem. Pharmacol. in the press

Fuller, R. W., Molloy, B. B. (1973) Res. Commun. Chem. Pathol. Pharmacol. 6: 407–418

Fuller, R. W., Molloy, B. B. (1974) Adv. Biochem. Psychopharmacol. 10: 195–205

Fuller, R. W., Perry, K. W. (1977) Neuropharmacology 16: 495–497

Fuller, R. W., Roush, B. W. (1972) Arch. Int. Pharmacodyn. Ther. 198: 270–276

Miller, F. P., Cox, R. N., Jr., Snodgrass, W. R., Maickel, R. P. (1970) Biochem. Pharmacol. 19: 435–442

Metoclopramide reverses inhibitions of electrically-induced contractions of guinea-pig isolated ileum by anti-inflammatory drugs

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Metoclopramide stimulates peristaltic movements of the stomach, duodenum and small intestine leading to gastric emptying in man (Justin-Besançon et al 1964; Duret & Arguello 1969; Howells et al 1971) and animals (Guerrin et al 1967; Jacoby & Brodie 1967; Johnson 1971) but its mode of action is not well understood. Besides a central and anti-emetic action, the drug seems to have a peripheral action (Jacoby & Brodie 1967; Duret & Arguello 1969; Johnson 1971). It stimulates various preparations of the gastrointestinal tract (Reuse 1973) including the guinea-pig isolated ileum (Fontaine & Reuse 1973). It is also able to increase the response of the guinea-pig ileum to the electrical transmural stimulation (Fontaine & Reuse 1972) and to reverse the inhibition of these electrically-induced contractions by procaine, morphine and atropine (Fontaine & Reuse 1973).

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Non-steroidal anti-inflammatory drugs (NSAID) and steroidal anti-inflammatory drugs (SAID) inhibit electrically-induced contractions of guinea-pig isolated ileum and this is reversed by prostaglandins (PG), nicotine and caerulein, a polypeptide with gastrointestinal stimulating properties (Famaey et al 1975; Fontaine 1976). Thus the inhibition and its reversal seems to be non-specific. We therefore examined the effects of the drug on these inhibitions.

Segments of ileum (4 cm) at least 10 cm from the caecum were suspended under an initial load of 1 g in Krebs-Henseleit solution maintained at 37° C and gassed with a mixture of 5% CO_2 in oxygen. Isometric contractions (registered by a force transducer) were elicited by coaxial electrical stimulation (pulse width 0·5 ms, pulse strength 5–25 V, frequency 0·1 Hz; Paton 1955).

At concentrations known to induce approximately 50% inhibitions of these contractions one of 11 NSAID

(mefenamic, flufenamic and niflumic acids ibuprofen, indomethacin, clopirac, bufexamac and amidopyrine at 10 or 40 μg ml^{-1}, phenylbutazone, oxyphenbutazone and alclofenac at 200 μg ml^{-1}) or 6 SAID (hydrocortisone, dexamethasone, betamethasone, paramethasone, prednisone and prednisolone at 40 μg ml^{-1}) was added to the bath after 5 min of constant contractions. The induced inhibitions are easily reversed by PGE_2, E_1 or $F_{2\alpha}$ and nicotine (Famaey et al 1975) or caerulein (Fontaine 1976).

When the inhibition was well established and stabilized (10 to 15 min) metoclopramide was added to the bath at various concentrations.

A reversing effect was observed on all inhibitions at a metoclopramide concentration of 3 μg ml^{-1} (Fig. 1A, B), and even at 0·3 μg ml^{-1} in some experiments.

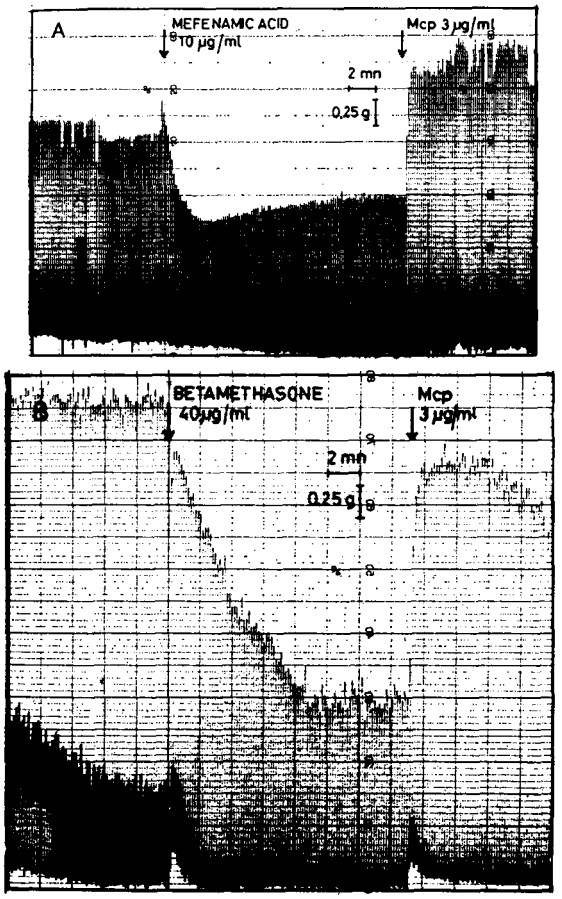

FIG. 1. Inhibitory effects of A: one NSAID (mefenamic acid) and B: one SAID (betamethasone) on the electrically-induced contractions of the guinea-pig isolated ileum and reversing effect of metoclopramide (3 μg ml^{-1}, Mcp) added subsequently.

The reversal obtained with 30 μg ml^{-1} was not greater than with 3 μg ml^{-1}.

A few experiments were conducted with higher NSAID or SAID concentrations able to induce almost total inhibition of electrically-induced contractions and thus metoclopramide was still able to reverse but to a lesser degree than the partial inhibitions.

In conclusion, it appears (i) that metoclopramide is able to reverse NSAID and SAID inhibitions of electrically-induced contractions of the guinea-pig ileum as it does in the presence of morphine, procaine or atropine. This is most probably due to the sensitizing action of metoclopramide on the ileal smooth muscle to acetylcholine-like agonists (Fontaine & Reuse 1972, 1973); (ii) that NSAID and SAID inhibitions of electrically-induced contractions can be reversed by compounds other than PG, nicotine and caerulein (Famaey et al 1975; Fontaine 1976) which confirms our suggestion (Famaey et al 1975) that the inhibitions are only partly related to inhibition of endogenous PG-synthetase production and largely due to non-specific spasmolytic action of the anti-inflammatory compounds.

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REFERENCES

Duret, R. L., Arguello, M. (1969) Sem. Hop. Paris 45: 1678–1690

Famaey, J. P., Fontaine, J., Reuse, J. (1975) Agents and Actions 5: 354–358

Fontaine, J. (1976) These d'agrégation de l'enseignement superieur, Université Libre de Bruxelles

Fontaine, J., Reuse, J. (1972) Arch. Int. Pharmacodyn. Ther. 197: 396–398

Fontaine, J., Reuse, J. (1973) Ibid. 204: 293–305

Guerrin, F., Milbled, G., Merveille, P., Hequet, B. (1967) C.r. Seanc. Soc. Biol. 161: 1318–1322

Howells, T. H., Khanam, T., Kreel, L., Seymour, C., Olivier, B., Davis, J. A. H. (1971) Br. Med. J. 2: 558–560

Jacoby, H. I., Brodie, D. A. (1967) Gastroenterology 52: 676–684

Johnson, A. G. (1971) Gut 12: 158–163

Justin-Besançon, L., Grivaux, M., Laville, C. (1964) Arch. Fr. Mal. App. Dig. 53: 1273–1286

Paton, W. D. M. (1955) J. Physiol. Lond. 27: 40P–41P

Reuse, J. (1973) Bull. Acad. r. Med. Belg. 128: 331–352