REFERENCES

Bannon, M. J., Grace, A. A., Bunney, B. S., Roth, R. H. (1980) Naunyn-Schmiedeberg's Arch. Pharmacol. 312: 37–41

Coyle, J. T., McGeer, E. G., McGeer, P. L., Schwarcz, R. (1978) in: McGeer, E. G., Olney, J. W., McGeer, P. L. (eds) Kainic Acid as a Tool in Neurobiology. Raven Press, New York, pp 139–160

McGeer, E. G., McGeer, P. L., Singh, K. (1978a) Brain Res. 139: 381–383

McGeer, P. L., McGeer, E. G., (1976) J. Neurochem. 26: 65–76

McGeer, P. L., McGeer, E. G., Hattori, T. (1978b) in: McGeer, E. G., Olney, J. W., McGeer, P. L. (eds) Kainic Acid as a Tool in Neurobiology. Raven Press, New York, pp 123–138

Mitchell, P. R., Doggett, N. S. (1980) Life Sci. 26: 2073–2081

Rowlands, G. J., Roberts, P. J. (1980) Eur. J. Pharmacol. 62: 241–242

Sanberg, P. R., Johnston, G. A. R. (1981) Med. J. Aust.

Sanberg, P. R., Pisa, M., Fibiger, H. C. (1979) Pharmacol. Biochem. Behav. 10: 137–144

Schwarcz, R., Creese, I., Coyle, J. T., Snyder, S. H. (1978) Nature (London) 271: 765–768

Stoof, J. C., Thieme, R. E., Vrijmoed-de Vries, M. C., Mulder, A. H. (1979) Nauyn-Schmiedeberg's Arch. Pharmacol. 309: 119–124

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Antidiarrhoeal effects of quipazine and 1-(*m*-trifluoromethylphenyl)piperazine in mice

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Quipazine (1-[2-quinolyl]piperazine) and 1-(*m*-trifluoromethylphenyl)-piperazine (TFMPP) are thought to be agonists at 5-hydroxytryptamine (5-HT) receptors. Quipazine stimulates contraction of the rat uterus and other peripheral smooth muscles, and these effects are antagonized by 5-HT antagonists (Hong & Pardo 1966; Hong et al 1969). In addition, various in vivo effects suggest that quipazine stimulates 5-HT receptors in brain. These effects include antagonism of reserpine-induced sedation and hypothermia in mice and rats (Rodriguez & Pardo 1971), antagonism of muricidal activity in rats (Rodriguez & Pardo 1971), sham-rage reactions and other behavioural changes in cats (Rodriguez et al 1973), inhibition of sexual activity in male rats (Grabowska 1975), decreased brain 5-HT turnover in rats (Grabowska et al 1974), a behavioural syndrome associated with 5-HT stimulation in rats (Green et al 1976), elevation of serum corticosterone (Fuller et al 1978a) and prolactin (Meltzer et al 1976) in rats, antinociception in rats (Samanin et al 1976), head twitch in mice (Malick et al 1977), potentiation of the flexor reflex of the hind limb in spinal rats (Palider & Rawlow 1977), and decreased food intake in rats (Samanin et al 1977).

Quipazine competes for the binding of tritiated 5-HT to rat brain membrane receptors in vitro (Whitaker & Seeman 1978). Another substituted piperazine, TFMPP, also competes for the binding of tritiated 5-HT to rat brain membrane receptors in vitro (Fuller et al 1978b) and causes many of the same in vivo effects as quipazine (Fuller et al 1978b; Fuller & Clemens 1979). Since the 5-HT precursor 5-hydroxytryptophan (5-HTP) causes diarrhoea in mice that is antagonized by 5-HT antagonists (Woolley 1958), and since quipazine has been reported to cause increased gastrointestinal motility and diarrhoea in humans (Parati et al 1980), it might be expected that quipazine and TFMPP would cause diarrhoea in mice but they proved to be potent antagonists of the diarrhoea induced by 5-HTP.

Cox standard mice (Laboratory Supply, Indianapolis, Indiana), 20–25 g, were given i.p. injections of drugs dissolved in distilled water. Each mouse was placed in a glass beaker and observed continuously for the character of its faecal excretion during the first 30 min after injection and again at 1 h. Quipazine maleate (Miles Laboratories) was injected at doses equivalent to 10, 15, 20, 25, 32 and 10 mg kg^{-1} of the free base. TFMPP (Aldrich Chemical) was injected at doses of 10, 15, 20, 25, 32 and 40 mg kg^{-1}. 5-HTP was injected at 25 mg kg^{-1}. Control mice received injections of distilled water. Each treatment group contained 5 mice.

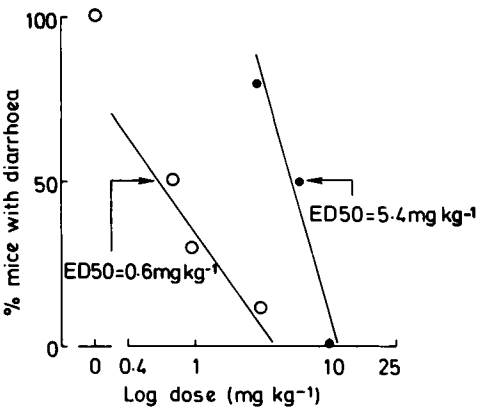

FIG. 1. Antagonism of 5HTP-induced in mice by TFMPP (○) and quipazine (●) in mice.

* Correspondence.

In the first experiment all mice treated with 5-HTP developed diarrhoea. In contrast, no diarrhoea was noted among 30 mice treated with various doses of quipazine except in one mouse at the lowest and one at the highest dose, and only one mouse of 30 treated with TFMPP developed diarrhoea. Instead, at the three higher doses of quipazine, two-thirds of the mice showed evidence of constipation (no faecal material excreted) and two-thirds of all mice treated with TFMPP showed constipation.

These observations led to a second experiment in which 5-HTP was injected at 25 mg kg^{-1} along with either quipazine or TFMPP at various doses. Both compounds caused a dose-related antagonism of the diarrhoea induced by 5-HTP (Fig. 1). From these data the ED50 values for antidiarrhoeal properties of these compounds were calculated by linear regression analysis to be 5·4 mg kg^{-1} for quipazine and 0·6 mg kg^{-1} for TFMPP. No mice given doses of 10 or 25 mg kg^{-1} of either quipazine or TFMPP developed diarrhoea after 5-HTP injection.

These results indicate differences between the 5-HT receptors mediating diarrhoea in mice (presumably located in the gut) and those brain 5-HT receptors mediating various central 5-hydroxytryptaminergic effects in rats and mice. Quipazine induces head twitches in mice (similar to those induced by 5-HTP) that are blocked by methiothepin, methysergide and cinanserin (Malick et al 1977), evidence that quipazine activates central 5-HT receptors in mice as it has been shown to do in more diverse studies in rats. Quipazine, TFMPP and 5-HTP produce several effects including elevation of serum corticosterone and prolactin, suppression of food intake, and lowering of blood pressure in genetically hypertensive rats, and in each case there is evidence that central 5-HT receptors mediate the effect (Samanin et al 1977; Krulich et al 1979; Fuller 1981; Fuller et al 1981; R. W. Fuller & J. E. Owen, unpublished data on TFMPP). Thus both quipazine and TFMPP seem to mimic the effect of 5-HT at brain receptors mediating these various actions. On the other hand, these two compounds do not mimic, rather antagonize, the action of 5-HT on (gut?) receptors mediating diarrhoea in mice. The relative potency of the two compounds is similar in both situations; TFMPP is more potent than quipazine both as a central 5-HT agonist and as an antidiarrhoeal compound. Evidence for heterogeneity of 5-HT receptors has been presented (Snyder & Goodman 1980), and our results reveal that compounds acting as 5-HT agonists in brain may be antagonists on some peripheral 5-HT receptors. Antagonism of peripheral 5-HT receptors by quipazine has also been reported by Lansdown et al (1980), who made in vitro studies with the rat stomach.

REFERENCES

Fuller, R. W. (1981) Neuroendocrinology 32: 118

Fuller, R. W., Clemens, J. A. (1979) IRCS Med. Sci. 7: 106

Fuller, R. W., Snoddy, H. D., Clemens, J. A. (1978a) Endocrinol. Res. Commun. 5: 161–171

Fuller, R. W., Snoddy, H. D., Mason, N. R., Molloy, B. B. (1978b) Eur. J. Pharmacol. 52: 11–16

Fuller, R. W., Yen, T. T., Stamm, N. B. (1981) Clin. Exp. Hypertension in the press.

Grabowska, M. (1975) in: Sandler, M., Gessa, G. L. (eds) Sexual Behavior: Pharmacology and Biochemistry. Raven Press, New York, pp 59–62

Grabowska, M., Antkiewicz, L., Michaluk, J. (1974) Biochem. Pharmacol. 23: 3211–3212

Green, A. R., Youdim, M. B. H., Grahame-Smith, D. G. (1976) Neuropharmacology 15: 173–179

Hong, E., Pardo, E. G. (1966) J. Pharmacol. Exp. Ther. 153: 259–265

Hong, E., Sancilio, L. F., Vargas, R., Pardo, E. G. (1969) Eur. J. Pharmacol. 6: 274–280

Krulich, L., Vijayan, E., Coppings, R. J., Giachetti, A., McCann, S. M., Mayfield, M. A. (1979) Endocrinology 105: 276

Lansdown, M. J. R., Nash, H. L., Preston, P. R., Wallis, D. T., Williams, R. G. (1980) Br. J. Pharmacol. 68: 525–532

Malick, J. B., Doren, E., Barnett, A. (1977) Pharmacol. Biochem. Behav. 6: 325–329

Meltzer, H. Y., Fang, V. S., Paul, S. M., Kaluskar, R. (1976) Life Sci. 19: 1073–1078

Palider, W., Rawlow, A. (1977) Pol. J. Pharmacol. Pharm. 29: 367–376

Parati, E. A., Zanardi, P., Cocchi, D., Caraceni, T., Muller, E. E. (1980) Br. J. Pharmacol. 68: 525–532

Rodriguez, R., Pardo, E. G. (1971) Psychopharmacologia 21: 89–100

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

Samanin, R., Bendotti, C., Miranda, F., Garattini, S. (1977) J. Pharm. Pharmacol. 29: 53–54

Samanin, R., Bernasconi, S., Quattrone, A. (1976) Psychopharmacologia 46: 219–222

Snyder, S. H., Goodman, R. R. (1980) J. Neurochem. 35: 5–15

Whitaker, P. M., Seeman, P. (1978) Psychopharmacology 59: 1–5

Woolley, D. W. (1958) Proc. Soc. Exp. Biol. Med. 98: 367–370