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The Central Antiserotonergic Action of Mianserin*

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Abstract. The central antiserotonergic action of mianserin (MS) was tested in mice, rats, and rabbits. MS, like cyproheptadine, to which it was compared, inhibits the head-twitch response to 5-hydroxytryptophan in mice and rats without affecting the pinna reflex. MS does not change the flexor reflex of the hind limb of the spinal rat; it antagonizes its stimulation induced by fenfluramine, LSD, and quipazine, but not that induced by clonidine. The hyperthermia in rabbits caused by the serotonergic stimulants cited above is also antagonized by pretreatment with MS. Unlike cyproheptadine, MS is not active in the oxotremorine test. The results indicate that at low doses MS is a central serotonergic-receptor blocker.

Key words: Mianserin – Fenfluramine – Quipazine – LSD – Clonidine – Cyproheptadine – 5-Hydroxytryptophan – Hyperthermia – Flexor reflex – Pinna reflex

Clinical data indicate that mianserin (1,2,3,4,10,14b-hexahydro-2-methyldibenzo [c,f] [pyrazino-1,2-a]-azepine monohydrochloride, Org GB-94, Tolvon, Tolvin, MS) is an effective antidepressant (Itil et al., 1972; Fell et al., 1973). Pharmacologically, MS does not induce effects characteristic of classical antidepressant drugs: it does not antagonize the action of reserpine, does not significantly inhibit the uptake of noradrenaline (NA) or 5-hydroxytryptamine (5-HT), and does not inactivate monoamine oxydase (MAO) (van Riezen, 1972; Kafoe and Leonard, 1973; Leonard, 1974).

The peripheral antiserotonergic (anti-5-HT) and antihistaminic effects of MS are evident (Vargaftig et al., 1971; van Riezen, 1972). The central anti-5-HT activity of MS is indicated by its antagonism toward the behavioral syndrome brought about by D,L-5-hydroxytryptophan (D,L-5-HTP) and toward convulsions induced by tryptamine (see Discussion). In this study we looked for pharmacological data further confirming the central anti-5-HT action of MS, which is of interest particularly because danitracen (WA-335), a clinically effective antidepressant (Matussek et al., 1976), was found to be a potent 5-HT antagonist practically devoid of the features of the tricyclic antidepressant drugs (TAD) (Engelhardt, 1975; Kähling et al., 1975; Maj et al., 1976a,b,c).

To determine the central anti-5-HT action of MS we used the following three tests.

1. *Antagonism to the behavioral syndrome induced by L-5-HTP.* This was assessed quantitatively according to Corne et al. (1963) by measuring the inhibition of characteristic head twitches. To determine the degree of specificity of this antagonism, the effect of MS on the pinna reflex (Corne et al., 1963) was also tested. For the sake of comparison, cyproheptadine (CPH), a potent 5-HT receptor-blocking agent (Vargaftig et al., 1971; van Riezen, 1972), was used.

2. *The flexor reflex of the hind limb of the spinal rat,* found to be useful for the assessment of the central serotonergic and serotoninolytic actions (Maj et al., 1976b, 1977c; Palider and Rawłów, 1977).

3. *Antagonism to hyperthermia induced in the rabbit by 5-HT-mimetic agents* (Horita and Hill, 1972; Quock and Beal, 1976; Quock et al., 1976).

In addition, we tested MS for the central anticholinergic effect found in many TADs.

Materials and Methods

The experiment were performed on male Wistar rats, 130–180 g, male Albino Swiss mice, 18–22 g, and male White Danish rabbits,

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1.8–3 kg. All animals had free access to food and water before the experiments. MS was injected in saline (0.9% NaCl). The control animals received an appropriate volume of the solvent. All the experiments were carried out at room temperature (20–22°C). Statistical significance was verified with Student's *t*-test.

The Effect on the Head-Twitch Response to 5-HTP. L-5-HTP was administered as homogenized suspension in 1% aqueous solution of Tween 80. It was given i.p. (at a dose of 270 mg/kg to rats, 280 mg/kg to mice) 1 h after i.p. injection of MS or CPH. CPH was administered as a suspension in 1% aqueous solution of Tween 80. Each group consisted of 6–8 rats or 8–10 mice. Head twitches were counted six times at the following periods after administration of L-5-HTP: 4–6, 14–16, 24–26, 34–36, 44–46, 54–56 min, according to the method described by Corne et al. (1963). ED_{50}'s for MS and CPH were determined according to Litchfield and Wilcoxon (1949).

The effects of MS on the pinna reflex in mice and rats was studied according to Corne et al. (1963) at 15-min intervals, starting the measurements 1 h after i.p. injection of MS or CPH. Pinna reflex was tested by stimulation of the ear meatus with a fine hair; the appearance of a head twitch was regarded as a positive response. The reflexes were tested five times in both ears. The maximum number of positive responses was 10 and this was assumed to be 100%.

The Effect on the Flexor Reflex of the Hind Limb of the Spinal Rat. Rats were anaesthetized with ethyl ether (only for a short period of time needed for surgery), and the spinal cord was transsected between the 8th and 9th thoracic vertebrae. The distal tendon of the tibial anterior muscle was exposed and the contractions of the muscle were recorded. The rat paw was stimulated with electric impulses (approx. 10V, 30 ms) with a frequency of 1/min. Both the voltage and duration of impulses were consistent throughout the experiment. The following agents stimulating the flexor reflex were injected into the femoral vein, as solutions in saline: fenfluramine (FF), LSD, quipazine (QP), and clonidine. MS was given i.v. 20 min before administration of a stimulant.

The Effect on the Hyperthermia in the Rabbit. Rabbits were immobilized in special cages and adapted to room temperature for 2 h. Body temperature was measured in the rectum using an Ellab thermistor thermometer. Each group consisted of 6–10 rabbits. After two initial measurements of body temperature, taken at 30-min intervals, MS was given s.c., and 1 h later the hyperthermic agents dissolved in saline were administered i.v. The compounds used were QP, FF, and LSD. The temperature was measured for 3 h at half-hour intervals, starting 30 min after the administration of the hyperthermic agent.

The Effect on the Action of Oxotremorine. Oxotremorine (OX) was injected i.p. (dissolved in saline) at a dose of 2 mg/kg to rats and 1 mg/kg to mice, 1 h after i.p. injection of MS or CPH. Tremor, salivation, and lacrimation were assessed 15, 30, 45, and 60 min after the injection of OX, using an arbitrary three-point scale (0, no signs; 3, maximum intensity of signs). The ED_{50} was determined with the method of Litchfield and Wilcoxon (1949).

Drugs. Clonidine hydrochloride (Boehringer Ingelheim), cyproheptadine hydrochloride (Merck, Sharp & Dohme), L-5-hydroxytryptophan (Sigma), fenfluramine hydrochloride (Les Laboratoires Servier), Lysergamid (Spofa), mianserin hydrochloride (Organon), oxotremorine hydrochloride (Merck-Schuchardt), and quipazine hydrochloride (Miles Laboratories) were used.

Results

The Effect on Head-Twitch Response to L-5-HTP. MS and CPH inhibited the head-twitch response to L-5-HTP in rats and mice. The ED_{50} of MS for rats was 0.84 mg/kg (0.186–3.780), and for mice 0.094 mg/kg (0.052–0.169); the ED_{50} of CPH for rats was 0.26 mg/kg (0.140–0.336), and for mice 0.038 mg/kg (0.026–0.055).

MS in doses up to 80 mg/kg in mice and rats did not affect the pinna reflex. Higher doses were lethal for some animals.

The Effect on the Flexor Reflex of the Hind Limb of the Spinal rat. FF (1 mg/kg), LSD (1 µg/kg), QP (0.2 mg/kg), and clonidine (0.2 mg/kg) stimulated the flexor reflex of the hind limb of the spinal rat. Previous administration of MS (0.5 mg/kg) prevented the stimulatory action of FF (Fig. 1), LSD (Fig. 2), and QP (Fig. 3). MS at a dose of 1 mg/kg did not influence the stimulation induced by clonidine; at a dose of 10 mg/kg, it depressed the flexor reflex counteracted by clonidine (Fig. 4).

The Effect on Hyperthermia in the Rabbit. QP (10 mg/kg), FF (10 mg/kg), and LSD (150 µg/kg) produced considerable hyperthermia in the rabbit. It was antagonized by pretreatment with MS. The antagonis-

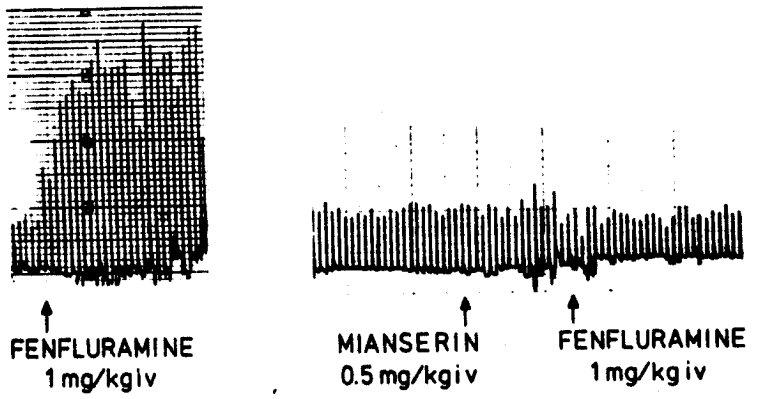


Fig. 1
The effect of fenfluramine on the flexor reflex of the hind limb of spinal rat after pretreatment with mianserin

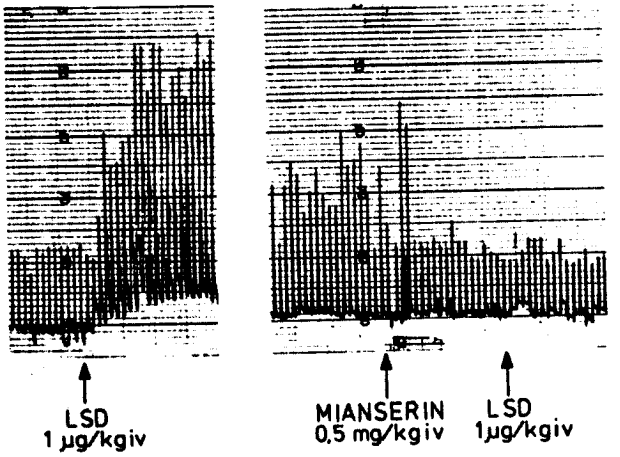


Fig. 2. The effect of LSD on the flexor reflex of the hind limb of spinal rat after pretreatment with mianserin

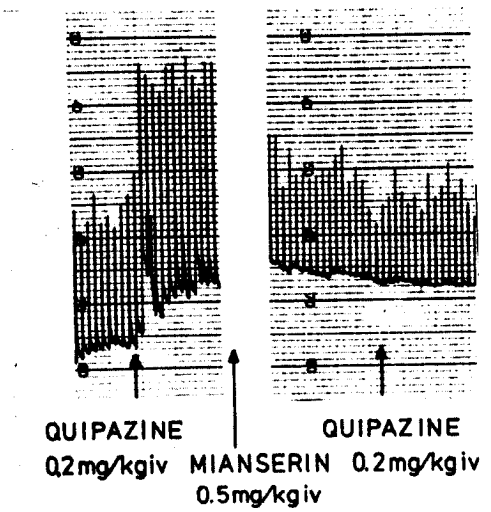
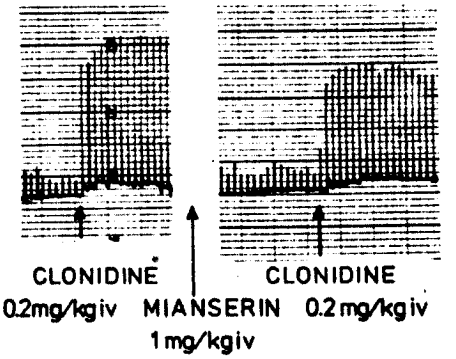


Fig. 3. The effect of quipazine on the flexor reflex of the hind limb of spinal rat after pretreatment with mianserin

tic effect was apparent throughout the 3-h observation period (Figs. 5–7).

The Effect on the Action of Oxotremorine. MS given to rats and mice at doses up to 20 mg/kg did not influence the syndrome induced by OX (tremor, salivation, and lacrimation). CPH had the antagonistic effect; its ED_{50} values in mice were as follows: for tremor, 0.66 mg/kg (0.47–0.92); for salivation, 1.6 mg/kg (1.16–2.21); and for lacrimation, 1.46 mg/kg (1.12–1.87). Approximate ED_{50} values in rats are, for tremor, about 0.5 mg/kg and, for salivation and lacrimation, about 1 mg/kg.



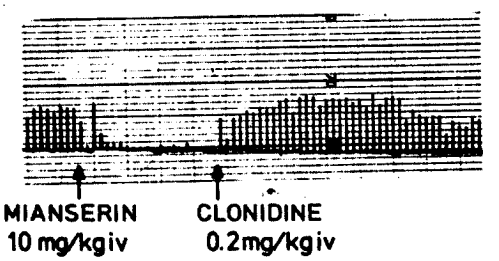


Fig. 4. The effect of clonidine on the flexor reflex of the hind limb of spinal rat after pretreatment with mianserin

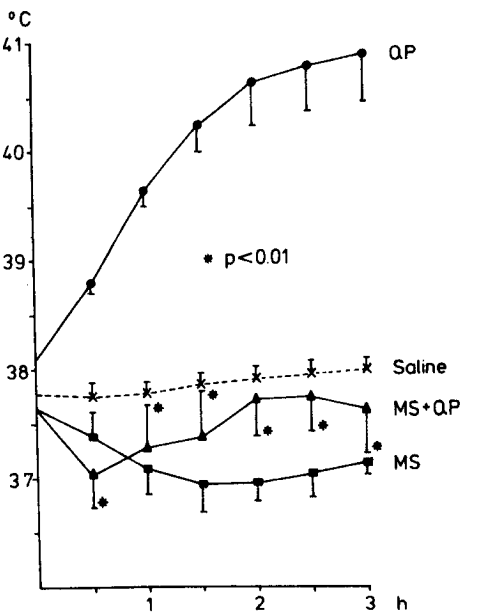


Fig. 5. The effect of mianserin (*MS*) on hyperthermia induced by quipazine (*QP*) in rabbits. MS (5 mg/kg s.c.) was given 1 h before QP (10 mg/kg i.v.). Statistical analysis: MS + QP vs. QP group

Discussion

Mianserin (MS) at low doses, like cyproheptadine (CPH), to which it was compared, counteracted the head-twitch response to L-5-HTP in rats and mice

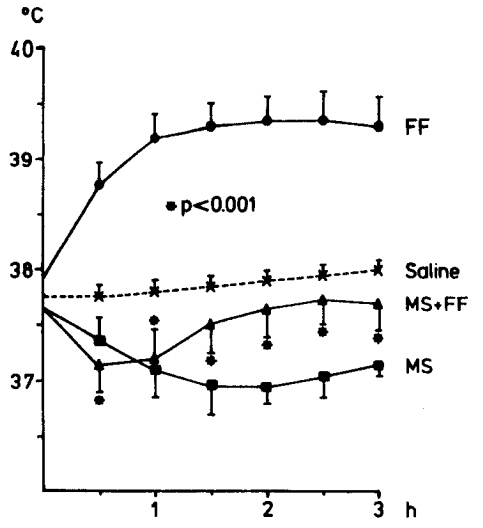


Fig. 6. The effect of mianserin (*MS*) on hyperthermia induced by fenfluramine (*FF*) in rabbits. MS (5 mg/kg s.c.) was given 1 h before FF (10 mg/kg i.v.). Statistical analysis: MS + FF vs. FF group

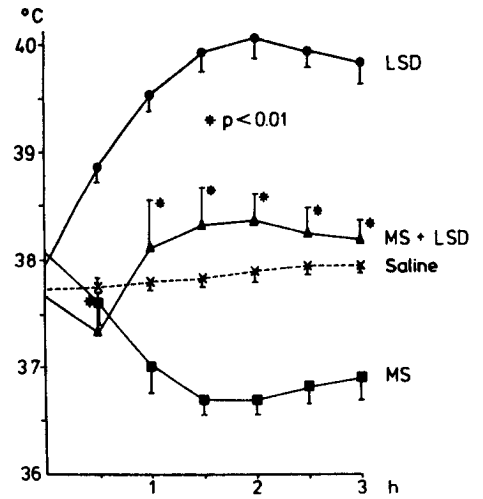


Fig. 7. The effect of mianserin (*MS*) on hyperthermia induced by LSD in rabbits. MS (4 mg/kg s.c.) was given 1 h before LSD (150 µg/kg i.v.). Statistical analysis: MS + LSD vs. LSD group

without influencing the pinna reflex (up to lethal doses). That indicates, according to the supposition of Corne et al. (1963), as well as to the data given by Jacobs (1976). that the antagonism of MS to L-5-HTP results from its central anti-5-HT action.

The partial antagonism of MS to D,L-5-HTP-syndrome in mice (van Riezen, 1972), as well as antagonism toward convulsions induced by tryptamine (Vargaftig et al., 1971), have been found previously. Recently, Przegaliński et al. (1977) have reported that MS, without affecting the pinna reflex, specifically counteracts (ED_{50} = 1 mg/kg) the head-twitches produced in rats by 5-methoxytryptamine.

CPH (Vargaftig et al., 1971; van Riezen, 1972) and danitracen (Engelhardt, 1975; Kähling et al., 1975; Maj et al., 1976b) exert cholinolytic activity. It cannot be relevant for anti-5-HTP effect as well as for other effects of MS, since the drug does not influence the oxotremorine (OX) syndrome, as might be expected according to other data (Vargaftig et al., 1971; van Riezen, 1972).

The 5-HT-receptor blockers (CPH, danitracen, metergoline) do not affect the flexor reflex of the hind limb of the spinal rat, but prevent the stimulation of this reflex induced by such 5-HT-mimetic agents as 5-HTP, tryptophan, LSD, fenfluramine (FF), p-chloroamphetamine, and quipazine (QF) (Maj et al., 1976b; Palider and Rawłów, 1977). The stimulation produced by NA agonists was not modified. In our experiments MS behaved like 5-HT-receptor blockers tested previously: it did not change the flexor reflex, but inhibited its stimulation produced by FF, LSD, and QP.

At doses 10–20 times higher than those inhibiting the effect of 5-HT-mimetics, MS depressed the flexor reflex and attenuated the stimulatory effect of clonidine (a NA agonist). This indicates that at higher doses MS has noradrenolytic action, as found previously on the periphery (Vargaftig et al., 1971).

5-HT-mimetics such as LSD, FF, and QP produced hyperthermia in the rabbit, which is antagonized by 5-HT-receptor blockers, including CPH (Horita and Hill, 1972; Quock and Beal, 1976; Quock et al., 1976). In our experiments MS has shown similar antihyperthermic effect. It also inhibits the hyperthermia induced in rabbits by N,N-dimethyltryptamine, regarded as similar to that produced by LSD (Domino et al., 1977).

Thus the results obtained in three tests and in three animal species seem to indicate that MS blocks the central 5-HT receptors. The effective doses of MS are lower than those active in the majority of other tests for the central action (Vargaftig et al., 1971; van Riezen, 1972), including two tests recently proposed for the assessment of the antidepressant effect – behavior of bulbectomized rats (van Riezen et al., 1976; Wren et al., 1977) and immobility induced in rats forced to swim (Persolt et al., 1977).

The central anti-5-HT action of MS may also be indicated by its potentiating effect on ponto-geniculo-occipital waves in the cat (Jalfre et al., 1974) and CPH- and methysergide-like inhibition of ovulation in the rat (Markó and Flückiger, 1976).

It should be added that the effect of MS on central 5-HT has also been found in biochemical experiments (see Leonard, 1974; Maj et al., 1977b), but the results are far from unequivocal.

FF is a serotonergic agent that acts presynaptically (Duhault and Verdavainne, 1967; Costa et al., 1971). Therefore the antagonism to FF revealed in these experiments might result from the presynaptic action of MS. It seems unlikely, however, since MS neither influences the 5-HT depletion induced by FF (Maj et al., 1977a) nor inhibits in vivo the 5-HT uptake (see Leonard, 1977).

There are some data suggesting that FF, LSD, and QP induce dopaminergic stimulation (Jori et al., 1973; Grabowska et al., 1974; Pieri et al., 1974; Da Prada et al., 1975). It seems unlikely, however, that it might be important in the preparation of the flexor reflex under study, because apomorphine in doses up to 5 mg/kg i.v. has no effect on this preparation (unpublished data). Also, hyperthermia in the rabbit, induced by FF or QP, does not result from dopaminergic stimulation, since it is not antagonized by neuroleptics (Quock and Beal, 1976; Quock et al., 1976).

MS and danitracen, both clinically effective antidepressants, are 5-HT antagonists. The central anti-5-HT activity has also been recently foud for doxepin, another antidepressant (Maj et al., 1977a). Tricyclic antidepressants (TADs) produce as 5-HT uptake inhibitors the serotonergic stimulation which produces an effect opposite to that of MS and danitracen. The question arises if inhibition of 5-HT uptake or, generally speaking, serotonergic activation is necessary for antidepressant action, at least in certain kinds of depression. As has been recently found (Ghose et al., 1977), FG 4969, a potent 5-HT uptake inhibitor that does not affect NA uptake, is clinically a much weaker antidepressant than amitriptyline.

It is not yet clear whether the central anti-5-HT action of MS is important for the clinical antidepressant effect. A number of data point out that there may exist two types of neurons or 5-HT receptors (e.g., Haigler and Aghajanian, 1974), yet their importance for the antidepressant action is unknown.

Besides, it is not unlikely that the mechanism of action of MS or of TADs when given chronically may differ from that in acute experiments.

Like danitracen, MS does not produce pharmacological effects characteristic of TADs. It seems, therefore, that the screening of new compounds for their antidepressant action should be modified or extended. Two new proposals have already been quoted (Porsolt et al., 1977; Wren et al., 1977). On the basis of our experiments, we think that the investigation into possible central anti-5-HT action should also be taken into account. A positive result in the three tests used in this paper, i.e., the antagonism to the behavioral syndrome induced by 5-HTP, the antagonism to 5-HT-mimetics in the preparation of the flexor reflex of the spinal rat (with no own effect on the reflex) and in the hyperthermia-test in rabbits, indicates the central anti-5-HT action of a compound tested and possibly its potential clinical antidepressant activity.

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