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The Central Action of Pizotifen

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Abstract. The central action of the potential antidepressant drug pizotifen (Sandomigran) was studied in mice, rats and rabbits. Pizotifen in doses up to 10 mg/kg i.p. was ineffective in classic tests for antidepressant activity. It neither antagonized the effects of reserpine in rats (hypothermia, ptosis) nor potentiated the effects of amphetamine (in mice and rats), nialamide or L-dopa (in mice) on locomotor activity. However, its antidepressant activity was found in the 'despair test' in rats.

On the other hand, pizotifen inhibited the head twitch reaction induced by L-5-hydroxytryptophan in mice (ED_{50} = 0.009 mg/kg, i.p.) and by 5-methoxytryptamine(+ tranylcypromine)inrats(ED_{50} = 0.45mg/kg, i.p.). It also antagonized tryptamine-induced clonic convulsions of fore-paws in rats (ED_{50} = 0.35 mg/kg, i.p.), and in doses of 5–10 mg/kg s.c. inhibited hyperthermia produced by LSD in rabbits. Finally, pizotifen (0.1–0.3 mg/kg, i.v.) inhibited or abolished LSD- or quipazine-induced stimulation of the hind limb flexor reflex of spinal rats; the above effect was not due to noradrenolytic action of the drug. These results suggest that pizotifen strongly blocks the central postsynaptic serotonin receptors.

Key words: Pizotifen – Antidepressant activity – Central antiserotonin effect

Pizotifen (Sandomigran) has been used for a few years in the prophylaxis of migraine (Ryan, 1968; Hughes and Foster, 1971; Sicuteri et al., 1976), the beneficial effect being possibly due to its potent peripheral antiserotonin and antihistamine activity (see Speight and Avery, 1972; Fozard, 1975). Numerous studies have revealed that it also produces a marked antidepressant effect, not necessarily connected with its antimigraine action (Krumholz et al., 1968; Olgiati and Calobrisi, 1974; Standal, 1977; Banki, 1978); however, the mechanism of this antidepressant action is not clear. On the basis of pharmacological studies, Dixon et al. (1977) suggested that pizotifen possesses properties both of classic, tricyclic imipramine-like drugs, and of new non-typical antidepressants, such as mianserin.

We examined pizotifen in a few classic tests for antidepressant action (interaction with reserpine, amphetamine, nialamide, L-dopa), as well as in the recently described (Porsolt et al., 1977) 'despair test', in which both tricyclic drugs and non-typical antidepressants, and also electro-shocks, exert a similar effect. In addition, we studied extensively the central antiserotonin activity of pizotifen, as such properties are revealed by non-typical antidepressants such as mianserin and danitracen (Van Riezen, 1972; Vargaftig et al., 1971; Engelhardt, 1975; Maj et al., 1976a, 1976b). These are clinically active antidepressants (Itil et al., 1972; Fell et al., 1973; Coppen et al., 1976; Matussek et al., 1976), but they do not display pharmacological properties characteristic of imipramine-like drugs (Kafoe and Leonard, 1973; Leonard, 1974; Engelhardt, 1975; Leonard and Kafoe, 1976; Maj et al., 1976a).

Materials and Methods

The experiments were carried out at ambient temperature, 20°–21° C, on male Wistar rats (150–170 g), male Albino-Swiss mice (20–25 g) and male rabbits (1.5–3 kg).

Pizotifen (Sandoz), *d*-amphetamine sulphate (Smith Kline and French), benserazide (Ro 4-4602, Hoffmann-La Roche), lysergic acid diethylamide tartrate (LSD, Spofa), tranylcypromine sulphate (Smith Kline and French), 5-methoxytryptamine hydrochloride (5-MT, Sigma) and tryptamine hydrochloride (Polfa) were dissolved in saline. Dihydroxyphenylalanine (L-dopa, Sigma), nialamide (Sigma) and L-5-hydroxytryptophan (5-HTP, Sigma) were suspended in 1% aqueous solution of Tween 80. Reserpine (Serpasil, Ciba) was given from original ampoules.

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The locomotor activity was measured with photoresistor actometers (two light beams and two photoresistors). The effect of pizotifen on the activity of (1) untreated mice and rats and (2) animals treated with amphetamine was recorded during 30-min sessions. Pizotifen's effect on the activity of mice treated with L-dopa (+ Ro 4-4602) or nialamide was recorded during 2-h sessions. The substances were given at the following doses and intervals before the test: amphetamine, 2.5 mg/kg s.c. in mice or 1.25 mg/kg s.c. in rats, 30 min; L-dopa, 200 mg/kg i.p., 60 min; Ro 4-4602, 25 mg/kg i.p., 90 min; nialamide, 100 mg/kg i.p., 18 h. Pizotifen was administered i.p. 1 h before the test, except for the experiment with L-dopa (+ Ro 4-4602), when it was injected 2 h before the test.

Body temperature was measured with an Ellab T-3 thermometer in the oesophagus (rats) or rectum (rabbits). The effects of pizotifen on hypothermia induced by reserpine (5 mg/kg, s.c., 18 h before pizotifen, i.p.) in rats and on hyperthermia produced by LSD (0.15 mg/kg, i.v., 1 h after pizotifen, s.c.) in rabbits were examined. Its effect on body temperature in normal animals was also studied. In the rats treated with reserpine, the influence of pizotifen on ptosis was estimated according to Rubin et al., (1957).

The head twitch reaction was induced by 5-HTP in mice (Corne et al., 1963) or by 5-MT (+ tranylcypromine) in rats (Przegaliński et al., 1977). Individual mice were observed at six 2-min periods (4–6, 14–16, 24–26, 34–36, 44–46, 54–56 min) after 5-HTP, whereas individual rats were observed for 45 min, beginning 15 min after 5-MT. Pizotifen was given i.p. 1 h before 5-HTP (280 mg/kg, i.p.) or 5-MT (2.5 mg/kg, i.p.) and tranylcypromine (20 mg/kg, i.p.) was given 30 min before 5-MT. In both tests, the dose of pizotifen required to decrease by 50% the mean frequency of head twitch reactions (ED_{50}) was estimated. Eight animals were used at each of four or more dose levels of pizotifen.

Clonic convulsions of fore-paws in rats were induced according to Tedeschi et al. (1959) by tryptamine (50 mg/kg, i.v.). The effect was assessed for 5 min after tryptamine using a 3-point scale (Niemegeers et al., 1977). Pizotifen was administered i.p. 1 h before tryptamine and the dose required to decrease by 50% the mean rating score (ED_{50}) was estimated. Eight rats were used at each of four dose levels of pizotifen.

The effect on the hind limb flexor reflex of spinal rats was examined according to the method described by Maj et al. (1976b).

The effect of pizotifen itself and its influence on the stimulatory action of LSD (3 µg/kg), quipazine (0.05 mg/kg) and clonidine (0.1 mg/kg) was estimated, all the drugs having been administered i.v. The effect of pizotifen on neuro-muscular transmission was also assessed (Maj et al., 1976b).

The effect of pizotifen on behavioural despair was investigated in rats. According to the method described by Porsolt et al., (1977), the animals were forced to swim in a narrow cylinder from which they could not escape. After an initial period of vigorous activity the rats assumed a characteristic immobile posture that was easily identified. In rats exposed for 15 min to the test situation 24 h earlier, pizotifen was administered i.p. 1 h before a 5-min session. The duration of immobility was measured.

Student's *t*-test was used for the statistical analysis of data. ED_{50} values were calculated according to Litchfield and Wilcoxon (1949).

Results

As shown in Table 1, pizotifen inhibited locomotor activity in mice and rats, and statistically significant effects were observed at a dose of 10 mg/kg in mice and at doses of 5 and 10 mg/kg in rats. At doses up to 10 mg/kg, pizotifen had no effect on the amphetamine-induced locomotor stimulation in rats, whereas at doses of 5 and 10 mg/kg it inhibited the activity in amphetamine-treated mice. The same doses of pizotifen also inhibited the L-dopa (+ Ro 4-4602)-induced locomotor stimulation in mice. In nialamide-treated mice, 0.5 and 10 mg/kg pizotifen exerted no effect, whereas at a dose of 5 mg/kg activity was significantly inhibited.

Pizotifen at a dose of 2 mg/kg did not affect body temperature in rabbits, while at doses of 5 and 10 mg/kg it produced a slight hypothermia (0.5° – 1° C decreases in body temperature, observed 60 – 180 min

Table 1. Effect of pizotifen on locomotor activity in mice treated with amphetamine, L-dopa (+ Ro4-4602) or nialamide, and in rats treated with amphetamine. The figures represent the mean number of activity counts ± SE. The number of animals in each group is shown in brackets

Drugs mg/kg	–	Amphetamine	L-Dopa (+ Ro 4-4602)	Nialamide
Mouse				
Saline	274.7 ± 45.1 (9)	327.6 ± 45.2 (10)	1245.6 ± 317.1 (9)	1021.9 ± 181.3 (9)
Pizotifen 0.5	256.5 ± 36.5 (10)	247.8 ± 25.1 (9)	882.8 ± 231.6 (10)	824.6 ± 202.7 (9)
Pizotifen 5	206.9 ± 45.1 (10)	188.6 ± 30.3[a] (10)	407.2 ± 166.2[a] (9)	576.4 ± 63.7[a] (10)
Pizotifen 10	117.9 ± 30.4[a] (9)	134.9 ± 28.3[b] (9)	153.7 ± 42.9[a] (9)	929.6 ± 167.8 (9)
Rat				
Saline	63.7 ± 11.9 (10)	248.7 ± 61.6 (10)		
Pizotifen 2.5	70.7 ± 11.5 (10)	191.6 ± 49.8 (8)		
Saline	63.7 ± 11.9 (10)	309.4 ± 76.4 (10)		
Pizotifen 5	30.0 ± 8.3[a] (10)	310.7 ± 68.1 (9)		
Saline	63.7 ± 11.9 (10)	388.6 ± 70.1 (7)		
Pizotifen 10	36.0 ± 6.2[a] (10)	505.4 ± 101.7 (7)		

[a] $P < 0.05$

[b] $P < 0.01$

The substances were given at the following doses and intervals before the test: amphetamine, 2.5 mg/kg, s.c. in mice or 1.25 mg/kg, s.c. in rats, 30 min; L-dopa, 200 mg/kg, i.p., 60 min; Ro 4-4602, 25 mg/kg, i.p., 90 min; nialamide, 100 mg/kg, i.p., 18 h. Pizotifen was administered i.p. 1 h before the test, except for the experiment with L-dopa (+ Ro 4-4602), when it was injected 2 h before the test

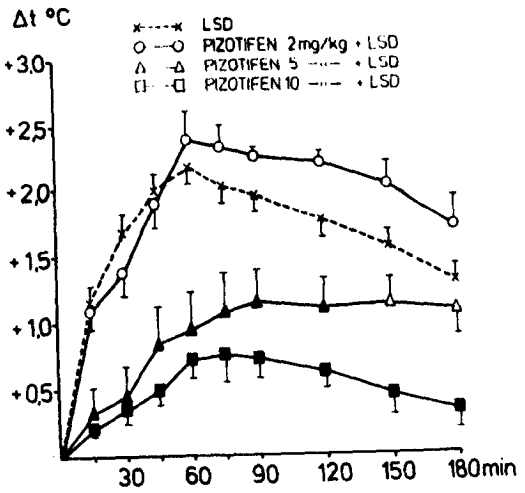

Fig. 1. Effect of pizotifen on hyperthermia induced by LSD (0.15 mg/kg, i.v., 1 h after pizotifen, s.c.) in rabbits. Symbols represent the means, and vertical bars SE, determined from 4–12 animals. Solid symbols indicate values that are significantly different ($P<0.05$) from those obtained for the group treated with LSD only

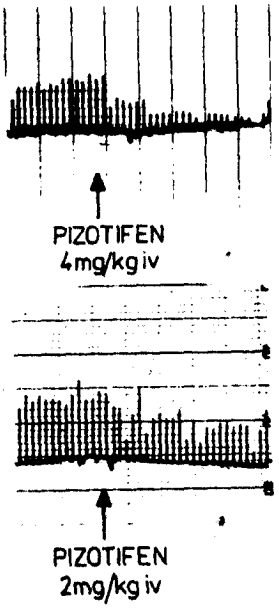

Fig. 2. Effect of pizotifen on the hind limb flexor reflex of spinal rats

Table 2. Inhibitory effect of pizotifen on head twitch reaction induced by 5-HTP in mice or 5-MT (+ tranylcypromine) in rats and on tryptamine-induced clonic convulsions of fore-paws in rats

Test	ED_{50} (mg/kg, i.p.); 95% confidence limits	
5-HTP	0.009	(0.002–0.03)
5-MT	0.45	(0.21–0.95)
Tryptamine	0.35	(0.14–0.89)

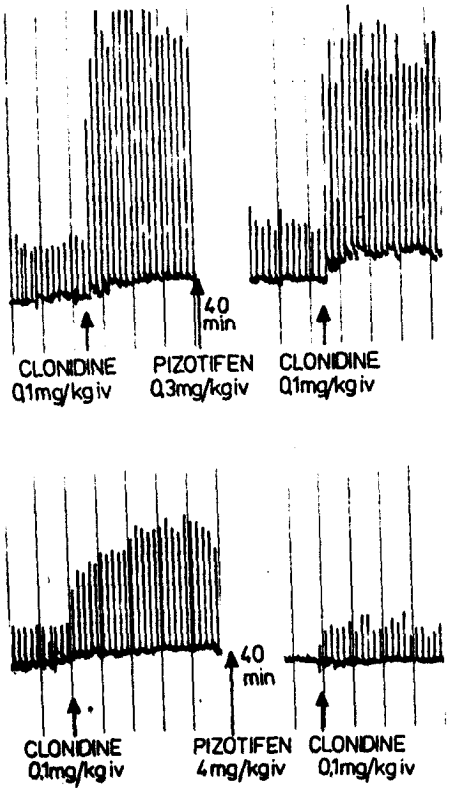

Fig. 3. Effect of pizotifen on the stimulatory action of clonidine on the hind limb flexor reflex of spinal rats

after administration) both in rabbits and rats (results not shown).

Reserpine-induced hypothermia and ptosis in rats were not affected by pizotifen at doses of 5 and 10 mg/kg (results not shown).

Pizotifen at a dose of 2 mg/kg had no effect on the LSD-induced hyperthermia in rabbits, whereas at doses of 5 and 10 mg/kg it produced a marked antagonistic effect that persisted for 120 and 180 min, respectively, after LSD administration (Fig. 1).

Pizotifen was a potent antagonist of the head witch reactions induced by 5-HTP or 5-MT, and of tryptamine-induced clonic convulsions (Table 2). Its ED_{50} values were: 0.009 mg/kg in the 5-HTP test in mice, or 0.45 mg/kg and 0.35 mg/kg in the 5-MT and tryptamine tests in rats, respectively.

Pizotifen at doses of 0.1 and 0.3 mg/kg exerted no effect on the flexor reflex (results not shown). A slight inhibitory effect was observed after only 2 mg/kg, while an almost complete inhibition of the reflex was effected by 4 mg/kg (Fig. 2). The stimulatory action of clonidine in this test was not affected by 0.3 mg/kg pizotifen, but was markedly reduced by a 4 mg/kg dose (Fig. 3). Pizotifen at a dose of 0.3 mg/kg, given 10 or 40 min

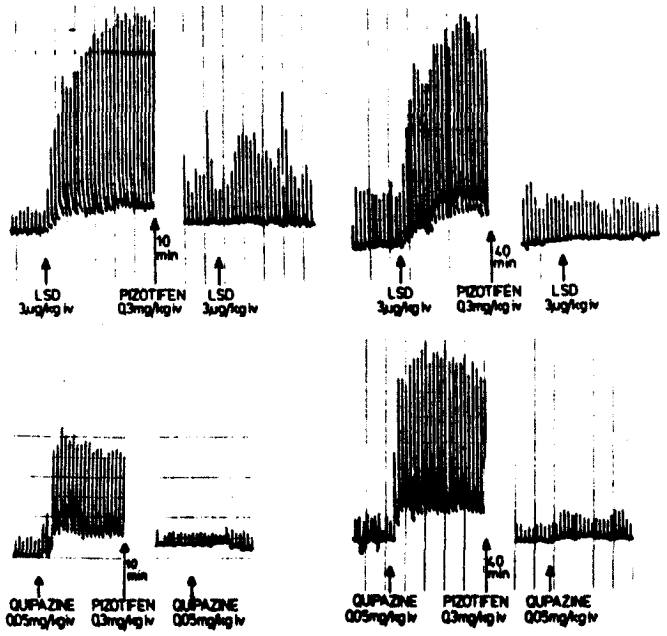

Fig. 4
Effect of pizotifen on the stimulatory action of LSD and quipazine on the hind limb flexor reflex of spinal rats

Table 3. Effect of pizotifen in the despair test in rats

Pizotifen mg/kg	*N*	Duration of immobility in s (mean ± SE)	% of control	*P*
–	20	185.0 ± 12.0	100.0	–
2.5	10	181.8 ± 18.4	98.3	n.s.
5	10	179.0 ± 16.8	96.8	n.s.
10	10	131.8 ± 24.7	71.3	<0.05
20	8	156.6 ± 15.6	84.7	n.s.

N = the number of animals per group

previously, blocked the stimulatory action of LSD and quipazine, although in the case of LSD administered 10 min after pizotifen the blockade was not complete (Fig. 4). Given at a dose of 0.1 mg/kg it also reduced the stimulatory action of LSD and quipazine on the flexor reflex, but this effect was weaker and a complete blockade was never observed (results not shown). Pizotifen up to 4 mg/kg did not affect neuro-muscular transmission (results not shown).

As shown in Table 3, pizotifen at doses of 2.5, 5 and 20 mg/kg had no effect on the duration of immobility in the despair test, but reduced it significantly (by almost 30%) at a dose of 10 mg/kg.

Discussion

It many classic tests used for assessment of antidepressant activity, pizotifen at doses up to 10 mg/kg proved ineffective. It neither enhanced the effects of amphetamine and L-dopa on the locomotor activity, nor produced stimulation after nialamide pretreatment. On the other hand, when used at doses 5–10 mg/kg, pizotifen antagonized the effects of all the three substances in mice. It should be stressed, however, that high doses (5–10 mg/kg) of pizotifen produced sedation in mice and rats. No significant effect of pizotifen on the reserpine-induced hypothermia and ptosis in rats was observed.

The above findings do not wholly agree with the results reported by other authors. Dixon et al. (1977) found that pizotifen antagonizes the reserpine-induced hypothermia in mice, as well as the tetrabenazine-induced sedation and ptosis in rats, and enhances the amphetamine-induced stereotypy in rats. Colpaert et al. (1975) studied the effect of pizotifen on the syndrome produced by a reserpine-like benzoquinolizine derivative, Ro 4-1284, and observed its antagonism towards ptosis and hypothermia, but no effect on sedation. It should be noted, however, that all these effects have been observed, as a rule, after doses higher than 10 mg/kg, and that in the experiment of Dixon et al., (1977) imipramine, used for comparison, had a much stronger antagonistic action, especially towards reserpine and tetrabenazine.

Searching for other pharmacological evidence of the antidepressant activity of pizotifen we also examined it in the despair test. Similar to many classic and non-typical antidepressants (Porsolt et al., 1977), pizotifen in a certain dose range significantly reduced the duration of immobility induced in the rats forced to swim.

Interestingly, pizotifen displayed a very strong central antiserotonin activity. It inhibited the head twitch reactions induced by 5-HTP in mice or by 5-MT in rats, counteracted the tryptamine-induced clonic convulsions of fore-paws in rats, blocked the stimulatory action of LSD and quipazine on the flexor reflex in spinal rats, and also antagonized the LSD-induced hyperthermia in rabbits. Almost all these effects were produced by doses lower than 0.5 mg/kg. The relatively weak effect of pizotifen in rabbits may be due to the fact that the LSD-induced hyperthermia in this species does not depend solely upon serotonin stimulation (Carino and Horita, 1977).

It is noteworthy that the antagonism to the stimulatory action of LSD and quipazine in the flexor reflex preparation was observed after doses of pizotifen (0.1 – 0.3 mg/kg) considerably lower than those (2 – 4 mg/kg) inhibiting the reflex itself or reducing the stimulatory action of clonidine. Furthermor, pizotifen at doses up to 4 mg/kg did not affect the neuromuscular transmission. This permits a suggestion (Maj et al., 1976b) that the antiserotonin action of this drug – at least in the flexor reflex preparation – is specific, being connected neither with its noradrenolytic properties nor with the effect on the neuro-muscular transmission.

The central antiserotonin activity of pizotifen, demonstrated in the present paper and also reported by other authors (Dixon et al., 1977; Niemegeers et al., 1977), may be due to the blockade of postsynaptic 5-HT receptors. This hypothesis is supported by the antagonism to effects of several direct agonists of 5-HT receptors (e.g., LSD, 5-MT, quipazine), as well as by the fact that a number of 5-HT receptor blockers (e.g., cyproheptadine, methysergide, metergoline, cinanserin) have been reported as acting similarly to pizotifen. They antagonize head twitch reactions induced by 5-HTP (Corne et al., 1963; Clineschmidt and Lotti, 1974) or 5-MT (Przegaliński et al., 1977), tryptamine-induced convulsions (Clineschmidt and Lotti, 1974), LSD-induced hyperthermia (Horita and Hill, 1972) and the stimulatory action of 5-HT receptor agonists on the flexor reflex (Maj et al., 1976b). Moreover, pizotifen increases appetite and causes a rise in body weight in man (see Speight and Avery, 1972). Similar effects have been observed in the case of cyproheptadine (Silverstone and Schuyler, 1975). The latter drug, as well as danitracen, also enhances food intake in animals (Kähling et al., 1975), this effect being attributed to the blockade of central 5-HT receptor. Finally, pizotifen is a peripheral antagonist of 5-HT (see Speight and Avery, 1972; Fozard, 1975).

On the other hand, we found that the antagonism of pizotifen towards 5-HTP in mice was 40 – 50 times stronger than towards 5-MT or tryptamine in rats. This might suggest that mice are more sensitive to pizotifen than rats and/or that a presynaptic mechanism is also involved in the antiserotonin action of the drug.

Our findings allow a suggestion that pizotifen, as regards its pharmacological profile, resembles non-typical antidepressants – especially mianserin and danitracen (see Introduction) – rather than classic tricyclic drugs. At higher doses (not examined in this study) pizotifen reveals some characteristics of the latter group (Dixon et al., 1977; Colpaert et al., 1975). Yet in view of its action being much weaker than that of imipramine (Dixon et al., 1977), which is effective at considerably lower doses in the treatment of depression (Krumholz et al., 1968; Olgiati and Calobrisi, 1974; Standal, 1977; Banki, 1978), the impramine-like properties do not seem of much importance for the clinical effect of pizotifen. Such a conclusion is also supported by the fact that unlike tricyclic antidepressants, pizotifen does not affect the uptake of monoamines or noradrenaline in the brain (Dixon et al., 1977). On the other hand, the importance of the central antiserotonin activity of pizotifen for its clinical effect is obscure. It should be stressed, however, that besides mianserin and danitracen, doxepin, another clinically active antidepressant (see Pinder et al., 1977), apart from its ability to inhibit the brain monoamine uptake (Buus Lassen et al., 1975), displays a central antiserotonin activity (Maj et al., 1977).

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