J. Neural Transmission 43, 113—120 (1978)

Journal of
Neural Transmission


# The Effect of Haloperidol, Spiperone and Pimozide on the Flexor Reflex of the Hind Limb of the Spinal Rat*

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With 3 Figures

Received March 20, 1978

## Summary

It was found that spiperone and pimozide in doses which themselves do not influence the flexor reflex of the hind limb of the spinal rat inhibit stimulation of this reflex induced by serotoninomimetic drugs (LSD and fenfluramine). Higher doses of spiperone depress the flexor reflex and inhibit the stimulating effect of clonidine. Pimozide has no such effect. Haloperidol in doses which do not influence the action of LSD and fenfluramine produces a depression of the flexor reflex and antagonizes the action of clonidine. Our findings indicate that, irrespective of their antidopamine action, spiperone has a central antiserotonin effect and an antinoradrenaline one, pimozide—an antiserotonin one and haloperidol—an antinoradrenaline one.

## Introduction

In our previous paper we observed that a number of neuroleptics, *e.g.* haloperidol, spiperone and pimozide antagonize the L-5-hydroxytryptophan (L-5-HTP)-induced behavioural syndrome in rats and mice (*Maj et al.*, 1978). This fact seems to indicate that they have a central antiserotonin action. In other experiments we proved that the flexor reflex of the hind limb of the spinal rat is a good model for

* The results of this paper were presented at the Polish-Hungarian Symposium on "Monoaminergic mechanisms" in Tihany, June 21—23, 1977.

0300-9564/78/0043/0113/$ 01.60

evaluation of the central antiserotonin activity (*Maj et al.*, 1976). 5-Hydroxytryptamine (5-HT) antagonists, such as cyproheptadine, mianserin, danitracen and metergoline do not affect this reflex, yet they inhibit its stimulation evoked by 5-HT-mimetics *e.g.* tryptophan, L-5-HTP, LSD, fenfluramine, quipazine (*Maj et al.*, 1976; *Maj et al.*, in press; *Palider et al.*, 1977). Therefore we decided to study the effect of haloperidol, spiperone and pimozide on the flexor reflex, using LSD and fenfluramine to induce serotoninergic stimulation.

The preparation of the flexor reflex of the spinal rat makes it possible, at the same time, to find a noradrenolytic activity. In this case it is especially important since, on the one hand, the noradrenolytic activity has been observed in a number of neuroleptics (*Janssen et al.*, 1965) and, on the other hand, typical noradrenolytics as phenoxybenzamine and phentolamine antagonize distinctly the L-5-HTP-induced behavioural syndrome (*Maj et al.*, 1978). Therefore, we also assessed the examined neuroleptics with respect to their effect on noradrenaline (NA) neurons, although they had been already studied in this regard by other authors (*Janssen et al.*, 1965).

## Materials and Methods

We carried out the experiments on male Wistar rats, 170—230 g, using the technique previously described. A rat's paw was stimulated by means of an electric impulse, released from the stimulator every 1 min and a contraction of the musculus tibialis anterior was registered (*Maj et al.*, 1976).

Clonidine, fenfluramine, LSD and haloperidol dissolved in 0.9 % NaCl, and spiperone—in 1.5 % aqueous solution of tartaric acid, were injected i.v. Pimozide, suspended in 1 % aqueous solution of Tween 80, was injected i.p. Haloperidol and spiperone were administered 1 hour before drugs stimulating the flexor reflex, while pimozide— 4hours before them.

### *Substances Used*

Clonidine hydrochloride (Boehringer, Ingelheim), fenfluramine hydrochloride (Servier), haloperidol (Gedeon Richter), LSD (Delysid, Sandoz), pimozide (Janssen Pharmaceutica), spiperone (Janssen Pharmaceutica).

## Results

The results are summarized in Table 1.

Table 1. *The effect*

| Neuroleptics |
|---|
| Haloperidol (i.v.) |
| Spiperone (i.v.) |
| Pimozide (i.v.) |

Explanations: — (in case no effect was an effect was observed

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Table 1. *The effects of neuroleptics on the flexor reflex of the hind limb of the spinal rat*

| Neuroleptics | Anti-5-HT effect | | Anti-NA effect | |
|---|---|---|---|---|
| | Antagonism to fenfluramine | Antagonism to LSD | Depression of the reflex | Antagonism to clonidine |
| Haloperidol (i.v.) | — (≤ 0.4) | — (≤ 0.4) | + (0.5) | + (0.5) |
| Spiperone (i.v.) | + (0.4) | + (0.4) | + (1.2) | + (1.2) |
| Pimozide (i.v.) | + (4.0) | + (4.0) | — (≤ 16.0) | — (≤ 16.0) |

Explanations: — no effect; + effect observed. In brackets—doses in mg/kg (in case no effect was observed—the dose up to which no effect occurred; in case an effect was observed—the lowest effective dose).

## *Haloperidol*

Haloperidol in doses of 0.05—0.4 mg/kg does not influence the flexor reflex, nor changes the reflex stimulation induced by LSD (5 μg/kg) or by fenfluramine (1 mg/kg). A dose of 0.5 mg/kg and higher depress the flexor reflex and inhibit partly or totally the stimulating effect of clonidine (0.1 mg/kg) (Fig. 1).

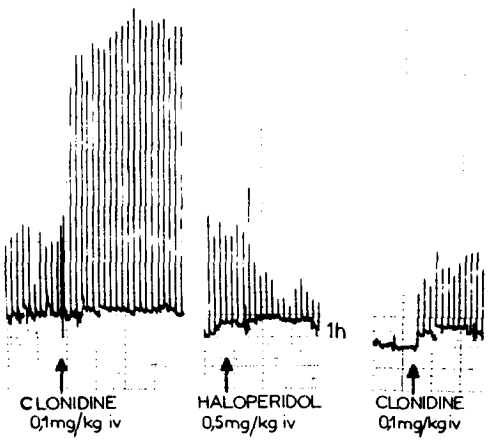


Fig. 1. The influence of clonidine and haloperidol on the flexor reflex (the musculus tibialis anterior) of the hind limb of the spinal rat

### *Spiperone*

Spiperone in doses up to 1 mg/kg has no effect on the flexor reflex. A dose of 1.2 mg/kg and higher doses cause a depression of the flexor reflex which is not antagonized by clonidine (0.1 mg/kg).

Spiperone in a dose of 0.4 mg/kg, not affecting the flexor reflex, prevents its stimulation evoked by LSD (5 μg/kg) or by fenfluramine (1 mg/kg). A dose of 0.4 mg/kg does not influence the stimulation induced by clonidine (0.1 mg/kg) (Fig. 2).

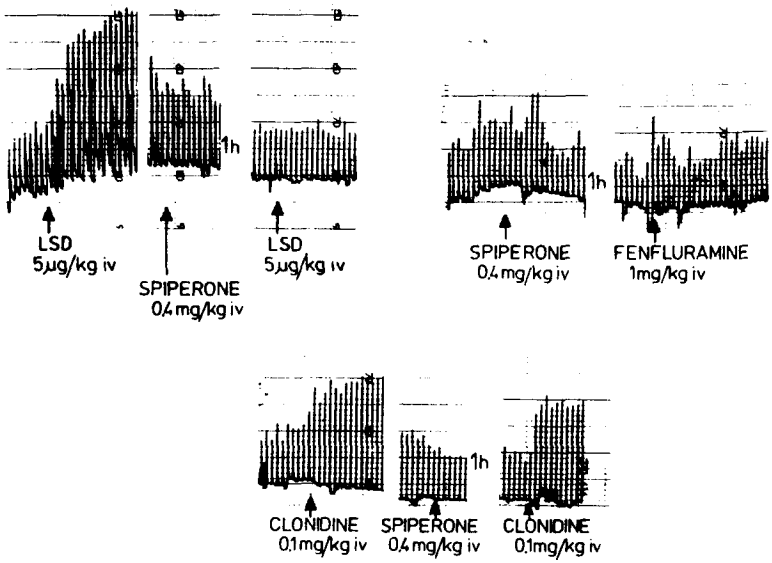


Fig. 2. The influence of spiperone on the action of LSD, fenfluramine and clonidine on the flexor reflex (the musculus tibialis anterior) of the hind limb of the spinal rat

### *Pimozide*

Pimozide administered in doses up to 16 mg/kg has no effect on the flexor reflex and does not change the stimulating action of clonidine (0.1 mg/kg). A dose of 4 mg/kg prevents the reflex stimulation evoked by LSD (5 μg/kg) (Fig. 3) or by fenfluramine (1 mg/kg).

## Discussion

As it has been already mentioned in the introduction, the preparation of the flexor reflex of the hind limb of the spinal rat makes it possible to show the effect on central 5-HT neurons and NA neurons

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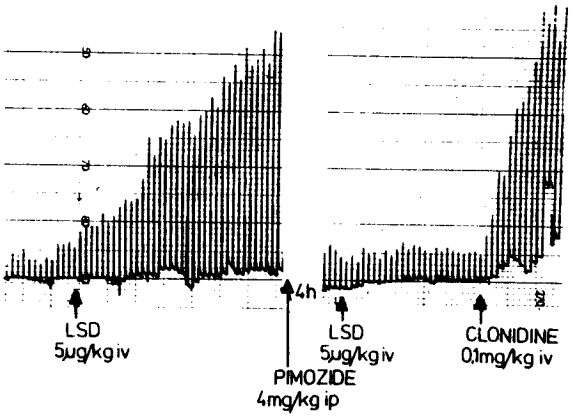


Fig. 3. The influence of pimozide on the action of LSD and clonidine on the flexor reflex (the musculus tibialis anterior) of the hind limb of the spinal rat

(*Maj et al.*, 1976). 5-HT receptor blockers administered alone have no effect on the flexor reflex, yet they prevent its stimulation caused by 5-HT mimetics, such as LSD or fenfluramine and, at the same time, do not change the stimulation induced by NA agonists, such as clonidine. NA receptor blockers given alone depress the flexor reflex and antagonize the stimulatory effect of NA agonists.

Our findings indicate that haloperidol acts as a NA antagonist. Lower doses have no anti-5-HT effect. The anti-NA action of haloperidol (the antagonism to clonidine) in the preparation of the flexor reflex was also previously observed (*Andén et al.*, 1970 b).

Spiperone in lower doses exerts an anti-5-HT activity, as it blocks LSD- or fenfluramine-induced stimulation. Higher doses produce a noradrenolytic effect. Pimozide also reveals an anti-5-HT action, having no anti-NA effect.

The anti-NA action of the three neuroleptics in the preparation of the flexor reflex was also studied by *Andén et al.* (1970 a), and the results obtained by them were similarly as regards the anti-NA activities of haloperidol and spiperone at higher doses, and the lack of such an activity for pimozide. The active doses of haloperidol and spiperone were much higher (5 and 10—20 mg/kg respectively) than those observed in our experiments. This fact may be due to a few factors: (1) a lower sensitivity of the model used by *Andén et al.* (1970 a); (2) a different route of administration of the neuroleptics (i.p. in their experiments, in ours i.v.); (3) the stimulation of the flexor reflex by L-Dopa (together with nialamide) and not by clonidine. However, similar dose ratios should be noted. The effective

doses of spiperone are 2—4 times higher than the effective doses of haloperidol in the experiments of *Andén et al.* (1970 a) and 2.4 times higher in our experiments.

The active noradrenolytic doses of haloperidol and spiperone, assessed by us, are considerably higher than the doses producing effects regarded as typical of neuroleptics. It applies chiefly to spiperone and is in agreement with functional and biochemical data of *Andén et al.* (1970 a), as well as with the data given by *Janssen et al.* (1965) on the basis of antagonism to the lethal i.v. dose of NA. Lack of the pimozide antagonism to NA administered i.v. was also observed by *Niemegeers et al.* (1977).

These findings allow us to conclude that spiperone and pimozide have a central antiserotonin activity, at least in rats. This fact was already indicated by our previous experiments in which we had observed antagonism of both neuroleptics to the L-5-HTP-induced behavioural syndrome (*Maj et al.*, 1978). Antagonism of spiperone to the behavioural syndrome induced by tryptophan (*Jacobs*, 1974; *Heal et al.*, 1976), as well to convulsions induced by tryptamine (*Janssen et al.*, 1965) have been also described. However, antagonism of pimozide to both agents has not been observed (*Jacobs*, 1974; *Heal et al.*, 1976; *Niemegeers et al.*, 1977).

The anti-5-HT doses of spiperone and pimozide found in the flexor reflex preparation, are a few times higher than those producing the cataleptic effect (*Maj et al.*, 1978), regarded as typical of neuroleptics. Therefore it is difficult to judge whether the anti-5-HT action of spiperone and pimozide is of practical value in the clinic. On the other hand, it is well-known that in the treatment of schizophrenia doses considerably higher than average initial therapeutic ones are often applied.

The observed antagonism of spiperone and pimozide to LSD indicates that they may have antihallucinogenic action. It should be added here that in the preparation of the flexor reflex 5-HT antagonists (cyproheptadine, mianserin, danitracen) also antagonize the action of other hallucinogens, such as mescaline (*Maj et al.*, 1977) or bufotenine (own data—unpublished).

Despite the fact that the anti-5-HT activity of haloperidol has not been observed in the model of the flexor reflex, it is not unlikely that this drug may produce such an effect when administered in doses higher than noradrenolytic ones. However, depression of the flexor reflex induced by the noradrenolytic action in this model makes impossible to find out an effect on 5-HT neurons. Antagonism of high doses of haloperidol to tryptophan (*Heal et al.*, 1976) and to tryptamine (*Janssen et al.*, 1965) has been already described.

More recent data indicate that, contrary to earlier opinions, dopamine neurons or terminals may be present in the spinal cord (*Commissiong* and *Sedgwick*, 1975; *Magnusson*, 1973; *Zivin et al.*, 1975; *Reid et al.*, 1975; *Bingham et al.*, 1975). It seems unlikely, however, that they might be of importance for the flexor reflex preparation used in our experiments. The above assumption may be evidenced by the fact that apomorphine injected i.v. in doses up to 5 mg/kg exerts no effect on this reflex (own data—unpublished).

## Acknowledgements

We would like to thank Boehringer, Ingelheim, for supplying clonidine; Laboratoires Servier for supplying fenfluramine; Janssen Pharmaceutica for supplying pimozide and spiperone.

## References

*Andén, N.-E., Butcher, S. G., Corrodi, H., Fuxe, K., Ungerstedt, U.:* Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. Eur. J. Pharmacol. *11*, 303—314 (1970 a).

*Andén, N.-E., Corrodi, H., Fuxe, K., Hökfelt, T., Rydlin, C., Swensson, T.:* Evidence for a central noradrenaline receptor stimulation by clonidine. Science *9*, 513—523 (1970 b).

*Bingham, W. G., Ruffolo, R., Goodman, J. H., Knofel, J., Friedman, S.:* Norepinephrine and dopamine levels in normal dog and monkey spinal cord. Life Sci. *16*, 1521—1526 (1975).

*Commissiong, J. W., Sedgwick, E. M.:* Dopamine and noradrenaline in humany spinal cord. The Lancet *1*, 347 (1975).

*Heal, D. J., Green, A. R., Boullin, D. J., Grahame-Smith, D. G.:* Single and repeated administration of neuroleptic drugs to rats: Effect on striatal dopamine-sensitive adenylate cyclase and locomotor activity produced by tranylcypromine and L-tryptophan or L-dopa. Psychopharmacology *49*, 287—300 (1976).

*Jacobs, B. L.:* Effect of two dopamine receptor blockers on a serotonin-mediated behavioral syndrome in rats. Eur. J. Pharmac. *27*, 363—366 (1974).

*Janssen, P. A. J., Niemegeers, C. J. E., Schellekens, K. H. L.:* Is it possible to predict the clinical effects of neuroleptic drugs (major tranquillizers) from animal data? Arzneim.-Forsch. *15*, 104—117 (1965).

*Magnusson, T.:* Effect of chronic transection on dopamine, noradrenaline and 5-hydroxytryptamine in the rat spinal cord. Naunyn-Schmiedeberg's Arch. Pharmacol. *278*, 13—22 (1973).

*Maj, J., Palider, W., Baran, L.:* The effect of serotonergic and antiserotonergic drugs on the flexor reflex of spinal rat: a proposed model to

evaluate the action on the central serotonin receptor. J. Neural Transm. *38*, 131—147 (1976).

*Maj, J., Palider, W., Rawłów, A.:* The influence of mescaline on the flexor reflex of the hind limb of the spinal rat. J. Pharm. Pharmac. *19*, 177—178 (1977).

*Maj, J., Baran, L., Bigajska, K., Rogóż, Z., Skuza, G.:* The effect of neuroleptics on the central action of 5-hydroxytryptophan. Pol. J. Pharmacol. Pharm. (in press, 1978).

*Maj, J., Sowińska, H., Baran, L., Gancarczyk, L., Rawłów, A.:* The central antiserotonergic action of mianserin. Psychopharmacology (in press, 1978).

*Niemegeers, C. J. E., Lenaerts, F. M., Artois, K. S. K., Janssen, P. A. J.:* Interaction of drugs with apomorphine, tryptamine and norepinephrine. A new "in vivo" approach: the ANT-test in rats. Arch. int. Pharmacodyn. *227*, 238—253 (1977).

*Palider, W., Rawłów, A.:* Effect of serotonin uptake blocking agents on the flexor reflex of hind limb of the spinal rat. Pol. J. Pharmacol. Pharm. *29*, 367—376 (1977).

*Reid, J. L., Zivin, J. A., Foppen, F. H., Kopin, I. J.:* Catecholamine neurotransmitters and synthetic enzymes in the spinal cord. Life Sci. *16*, 975—984 (1975).

*Zivin, J. A., Reid, J. L., Saavedra, J. M., Kopin, I. J.:* Quantitative localization of biogenic amines in the spinal cord. Brain Res. *99*, 293—301 (1975).

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