Psychopharmacologia (Berl.) 40, 123—127 (1974)

Antipsychotic Drugs Stimulate Prolactin Release

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Received June 4, 1974

Abstract. Antipsychotic drugs have been found to markedly stimulate prolactin secretion in male and female rats. The amount of prolactin released was greater in females than in males. Most non-antipsychotic phenothiazines failed to alter prolactin. These results imply that the dopamine receptor that inhibits prolactin release may be similar to the dopamine receptor involved in the action of antipsychotic drugs.

Key words: Antipsychotic Drugs — Prolactin — Dopamine.

Several lines of evidence implicate catecholamines, especially dopamine, in mediating drug effects in schizophrenic patients. Of the several biochemical effects of antischizophrenic drugs, their apparent blockade of dopamine receptors most closely parallels their therapeutic efficacy (Horn and Snyder, 1971). The evidence connecting dopamine transmission with schizophrenia has been reviewed recently by Matthysse (1974). In his review he pointed out an apparent contradiction to the dopamine hypothesis of the antipsychotic action of phenothiazines. Thioridazine, a well-recognized antipsychotic drug approximately equal in potency to chlorpromazine was considerably less effective in increasing brain dopamine turnover and blocking apomorphine-induced stereotypy than chlorpromazine and other antipsychotic drugs. Thiethylperazine, a non-antipsychotic drug, was able to increase brain dopamine turnover and block apomorphine-induced stereotypy similar to known antipsychotics. The explanation offered for this apparent paradox was that there probably were regional differences in the effect of phenothiazines on opamine receptors.

Prolactin release is another process which is linked to dopamine. It is well known that the release of prolaction from the adenohypophysis is tonically inhibited by dopamine neurons (Meites and Clemens, 1972). Dopamine agonists markedly inhibit prolactin release (Smalstig *et al.*, 1973; Macleod and Lehmeyer, 1974) while dopamine synthesis inhibitors and antagonists all stimulate prolactin release (Lu and Meites, 1970; Dickerman *et al.*, 1972). Clinically, galactorrhea is a well documented side effect of antipsychotic agents. Because of these interesting relationships we decided to study the effects of some antipsychotic and structurally related non-antipsychotic drugs on prolaction release in rats.

Materials and Methods

Normal adult male Sprague-Dawley rats were used in the present study. The following antipsychotic drugs were examined for effects on prolactin release: pimozide, haloperidol, chlorpromazine, thioridazine, sulpiride and fluphenazine. Non-antipsychotic; phenothiazines examined were as follows: promethazine, an antihistamine; thiethylperazine, an antiemetic (Donovan, 1963); pyrathiazine, an antihistamine (Vander Brook *et al.*, 1948); methdilazine, an antihistamine (Weikel *et al.*, 1960); and ethopropazine, an antispasmodic (Timberlake and Schwab, 1952). Tartaric acid was used as a vehicle for pimozide and haloperidol while other drugs were dissolved in saline. All drugs were administered i.p., and the rats were killed by decapitation 2 hrs after drug administration. Serum was collected and assayed for prolactin by a double antibody radioimmunoassay using the kit distributed by the National Institutes of Arthritis and Metabolic Diseases (NIAMD) Pituitary Hormone Distribution Program. The assay was performed according to the instructions supplied with the kit. All results were expressed in terms of NIAMD-RP-1 prolactin. Each serum sample was assayed for prolactin at two different dilutions, and the average of the two was taken as representative of the true prolactin concentration of the sample.

The activity of some of the above drugs was compared in adult male and female rats to determine if there was a sex difference in the prolaction response to antipsychotic drugs. Female rats were used while in diestrus as indicated by daily vaginal smears. The same treatment schedule as indicated above was used.

Table 1. Effects of some antipsychotic and non-antipsychotic drugs on prolactin secretion in male rats

Treatment	*N*	Serum prolactin concentration (ng/ml)[c]
0.1 M Tartaric Acid vehicle	10	19.3 ± 2.5[b]
Pimozide[d] (2.5 mg/kg)	10	40.5 ± 2.2 ($P < 0.001$)[a]
Haloperidol[d] (2.5 mg/kg)	11	35.6 ± 4.4 ($P < 0.02$)
Saline, control	10	27.6 ± 2.7
Sulpiride[d] (30 mg/kg)	9	159.8 ± 9.7 ($P < 0.0001$)
Chlorpromazine[d] (8.0 mg/kg)	12	50.6 ± 5.7 ($P < 0.001$)
Promethazine (8.0 mg/kg)	10	14.7 ± 1.0 ($P < 0.02$)
Saline, control	10	20.6 ± 1.3
Thioridazine[d] (8.0 mg/kg)	10	64.8 ± 6.7 ($P < 0.001$)
Fluphenazine[d] (8.0 mg/kg)	10	73.3 ± 3.8 ($P < 0.001$)
Thiethylperazine (8.0 mg/kg)	10	75.8 ± 2.5 ($P < 0.001$)
Pyrathiazine (8.0 mg/kg)	10	20.1 ± 2.8
Methdilazine (8.0 mg/kg)	10	24.8 ± 4.1
Ethopropazine (8.0 mg/kg)	10	22.1 ± 1.4

[a] ng NIAMD-RP-1 prolactin/ml.
[b] Mean $\pm$ standard error.
[c] Level of significance (treated vs control).
[d] Antipsychotic drug.

Results

Table 1 shows the effects of antipsychotic and non-antipsychotic drugs on prolaction release in male rats. Every antipsychotic drug significantly stimulated prolactin release. Thiethylperazine was the only non-antipsychotic drug that showed a prolactin-releasing effect. Promethazine inhibited while the other non-antipsychotic phenothiazines had no effect on prolactin release. Table 2 indicates that antipsychotic drugs produced a much greater stimulation of prolactin release in females than in males suggesting that there is a sex difference in response to these drugs.

Table 2. Effects of some psychoactive drugs on prolactin release in male and female rats

Treatment	Serum Prolactin levels (ng/ml)[a]	
	Females	Males
0.1 M Tartaric acid controls	25.4 ± 4.5[b] (8)[c]	19.3 ± 2.4 (10)
Pimozide[f] (2.5 mg/kg)	239.0 ± 25.6 (8)[e]	40.5 ± 2.1 (10)[e]
Chlorpromazine[f] (9.2 mg/kg)	343.5 ± 17.1 (10)[e]	56.1 ± 3.0 (10)[e]
Promethazine (8.0 mg/kg)	14.4 ± 3.6 (8)	14.7 ± 1.0[d] (10)

[a] Expressed as ng NIAMD-RP-1 prolactin/ml.
[b] Mean ± standard error.
[c] ( ) = number of rats.
[d] $P < 0.02$.
[e] $P < 0.001$.
[f] Antipsychotic drug.

Discussion

Our results indicate that drugs possessing antipsychotic activity are able to stimulate prolactin release. In this study thioridazine appeared to be of the same order of potency as chlorpromazine in stimulating prolactin release. They also appear to be of about the same order of potency as antipsychotics (Matthysse, 1974). If the dopamine hypothesis (Horn and Snyder, 1971) is valid, the dopamine receptor that is concerned with the action of antipsychotic drugs may be more similar to the one controlling prolactin release than the dopamine receptors involved in other studies (Cook and Kelleher, 1962; Janssen *et al.*, 1967) attempting to correlate various behaviorial or biochemical phenomena with antipsychotic activity. Our observation that thiethylperazine stimulates prolactin release indicates that there may be some difference between the dopamine receptor involved in the neuroleptic action of antipsychotic drugs and

the one inhibiting prolactin release. Perhaps thiethylperazine should be evaluated for antipsychotic activity.

In view of recent studies from our laboratory (Smalstig *et al.*, 1974) and others (MacLeod and Lehmeyer, 1974) suggesting that dopamine is the natural prolaction inhibiting factor and that dopamine receptors are present in the anterior pituitary, it is not surprising that antipsychotic drugs can stimulate prolactin release. Some antipsychotic phenothiazines have been reported to elevate prolactin levels in humans (Frantz, 1973). At the present time it is unclear if the elevated prolactin levels influence the effectiveness of antipsychotic drugs. Fuxe and Hokfelt (1970) reported that prolactin administration to rats increased dopamine turnover in the tuberoinfundibular dopaminergic tract. The increase in tuberoinfundibular dopamine turnover observed after prolactin administration is similar to the increased dopamine turnover in other brain areas noted after the administration of neuroleptics. In addition, Clemens *et al.*, 1971, have shown that prolactin administration to rabbits alters the firing rate of brain stem neurons. Thus, the possibility exists that prolactin may participate in the behavioral modifications noted after the administration of antipsychotic drugs.

Another finding of significance is that the antipsychotic drugs are able to stimulate prolactin release to a significantly greater extent in females than in males. This suggests that there may be some interaction between ovarian steroids and antipsychotic drugs. The interaction in the case of prolaction results in potentiation of prolaction release, but we are unaware of any human studies suggesting a sex difference in antipsychotic properties.

Further studies are needed to determine the nature of the antipsychotic drug-dopamine receptor interaction and the sex linked responses to these drugs.

Acknowledgements. We thank the National Institutes of Arthritis and Metabolic Diseases, Rat Pituitary Hormone Distribution Program for radioimmunoassay materials. We also thank the following companies for generous samples of drugs: Smith Kline and French (chlorpromazine and trimeprazine), Wyeth (promethazine), Sandoz (thiethylperazine and thioridazine), Warner-Lambert Research Institute (ethopropazine HCl), Squibb Institute for Medical Research (fluphenazine HCl), Upjohn (pyrathiazine), Mead Johnson (methdilazine) and Delagrange, Paris (sulpiride).

References

Clemens, J. A., Gallo, R. V., Whitmoyer, D. I., Sawyer, C. H.: Prolactin-responsive neurons in the rabbit hypothalamus. Brain Res. **25**, 371—379 (1971)

Cook, L., Kelleher, R.: Drug effects on the behavior of animals. Ann. N.Y. Acad. Sci. **96**, 315—335 (1962)

Dickerman, S., Clark, J., Dickerman, E., Meites, J.: Effects of Haloperidol on serum and pituitary prolactin and on hypothalamic PIF in rats. Neuroendocrinology **9**, 332—340 (1972)

Donovan, J.: Radiation sickness and its control with thiethylperazine ("Torecan"): A preliminary evaluation. Med. J. Australia **1**, 614—615 (1963)

Frantz, A. G.: The regulation of prolactin secretion in humans. In: Frontiers in neuroendocrinology. W. F. Ganong and L. Martini, eds., pp. 337—374. New York: Oxford University Press 1973

Fuxe, K., Hokfelt, T.: Central monoaminergic systems and hypothalamic function. In: The hypothalamus. L. Martini, M. Motta and F. Fraschini, eds., pp. 123—138. New York: Academic Press 1970

Horn, A. S., Synder, S. H.: Chlorpromazine and dopamine: Conformational similarities that correlate with the antischizophrenic activity of phenothiazine drugs. Proc. nat. Acad. Sci. (Wash.) **68**, 2325—2328 (1971)

Janssen, P., Niemegeers, C., Schellekens, K., Lenaerts, F.: Is it possible to predict the clinical effects of neuroleptic drugs (major tranquillizers) from animal data? Arzneimittel-Forsch. **17**, 841—854 (1967)

Lu, K. H., Amenomori, Y., Chen, C. L., Meites, J.: Effects of central acting drugs on serum and pituitary prolactin levels in rats. Endocrinology **87**, 667—672 (1970)

Lu, K. H., Meites, J.: Inhibition by L-Dopa and monoamine oxidase inhibitors of pituitary prolactin release: stimulation by methldopa and *d*-amphetamine. Proc. Soc. exp. Biol. (N.Y.) **137**, 480—483 (1971)

Macleod, R. M., Lehmeyer, J. E.: Studies on the mechanism of dopamine-mediated inhibition of prolactin secretion. Endocrinology **94**, 1077—1084 (1974)

Matthysse, S.: Dopamine and the pharmacology of schizophrenia. State of the evidence. J. psychiat. Res. **11**, in press (1974)

Meites, J., Clemens, J.: Hypothalamic control of prolactin secretion. Vitam. and Horm. **30**, 165—221 (1972)

Smalstig, E. B., Clemens, J. A.: Inhibition of serum prolactin by apomorphine in chlorpromazine treated and lactating rats. Fed. Proc. **32**, 308 (1973)

Smalstig, E. B., Sawyer, B. D. Clemens, J. A.: Inhibition of rat prolactin release by apomorphine. Endocrinology **95**, 123—129 (1974)

Timberlake, W. H., Schwab, R.: Experimental preparation W-483 in the treatment of Parkinson's disease. New Engl. J. Med. **247**, 98—100 (1952)

VanderBrook, M., Olson, K., Richmond, M., Kuizenga, M.: Pharmacology of a new antihistamine, β-pyrrolidine-ethyl-phenothiazine (pyrrolazote). J. Pharmacol. exp. Ther. **94**, 197—208 (1948)

Weikel, J., Wheeler, A., Joiner, P.: Metabolic fate and toxicology of methdilazine (10-(l-methyl-3-pyrrolidylmethyl)phenothiazine]. Toxicol. appl. Pharmacol. **2**, 68—82 (1960)

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