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Reduction in blood pressure in normal and spontaneously hypertensive rats by lergotrile mesylate

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The acute administration of lergotrile mesylate to normal or spontaneously-hypertensive rats (SHR) causes a prompt reduction in blood pressure. In SHR, doses as small as 0·05 mg kg^{-1} are effective; maximal reductions in blood pressure are obtained at a dose of 0·25 mg kg^{-1}. Lergotrile may be administered intraperitoneally or orally. Its efficacy as an anti-hypertensive agent in rats does not diminish significantly when administered twice daily for 7 days. Although lergotrile has been reported to be a dopamine agonist, the present data do not establish the mechanism by which the drug lowers blood pressure.

Lergotrile (2-chloro-6-methyl-8β-acetonitrile), an ergoline derivative originally developed as a direct-acting inhibitor of prolactin secretion at the pituitary level (Clemens et al 1975; Lemberger et al 1974), has been shown to be effective in the treatment of galactorrhoea, amenorrhoea, and prolactin-dependent breast carcinomas (Cleary et al 1975; Kleinberg et al 1977; Teller et al 1977). The drug is believed to act, at least in part, as a dopamine agonist (Fuxe et al 1978a; Silbergeld & Pfeiffer 1977; Tye et al 1977), and thus it has been of limited use in treating Parkinson's disease (Lieberman et al 1975; Klawans et al 1977). In determining whether lergotrile might be used to lower high serum titres of prolactin in hypertensive subjects taking methyldopa (Steiner et al 1976), we discovered a new, unreported action of the drug in hypertensive animals in which it proved potent in lowering blood pressure.

MATERIALS AND METHODS

Male spontaneously hypertensive rats (SHR) of the Okamoto strain, and normotensive Sprague-Dawley rats were obtained from Charles River Breeding Laboratories (Wilmington, Mass.), and housed two per cage in our animal facilities. Food (Charles River Rat, Mouse, and Hamster Maintenance Formula) and water were freely available. The animals were exposed to light (Vita-Lite, Duro Test Corp., North Bergen, N.J.; 300 μw cm^{-2}) for 12 h each day.

Experiments were begun when animal body weights were between 250 and 350 g. Resting blood pressures of rats in this weight range were 180–220 mm Hg for SHR, and 100–130 mm Hg for the normotensive animals.

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Arterial blood pressure was estimated by the tail-cuff method (Udenfriend 1976) using a Narco Biosystems Pneumatic Pulse Transducer (Narco Biosystems, Houston, Tex.). The animals were warmed at 37 °C for 20 min before each reading; 8 measurements per animal were then made at each time, and the averaged value taken as the blood pressure. Before their use, all animals were acclimatized to this procedure daily for four days to minimize stress-induced fluctuations in blood pressure. The rats were used in different experiments with at least four days between experiments.

Lergotrile mesylate (2-chloro-6-methyl-8-β-acetonitrile) was kindly provided by the Eli Lilly Company (Indianapolis, Ind.). The drug was dissolved in water immediately before injection, and was administered intraperitoneally to rats at a volume of 1 ml kg^{-1}. The specific doses and times are indicated in the Figures. The data were analysed by analysis of variance, and by the Neuman-Keuls test (Zivin & Bartko 1976).

RESULTS

In normotensive rats, lergotrile produced a significant reduction in blood pressure. Following injection of 1 mg kg^{-1}, the maximal decrease occurred 1·0 h later, and by 3·0 h blood pressure had returned to baseline (Fig. 1). A dose-response curve was then generated (Fig. 2), by measuring the change in pressure 1·0 h after lergotrile injection. 0·1 mg kg^{-1} was the smallest dose that elicited a significant reduction in blood pressure. The 1·0 mg kg^{-1} dose produced the maximal hypotensive response; higher doses (up to 10 mg kg^{-1}) yielded no further decreases (data not shown).

In SHR lergotrile, given intraperitoneally, also

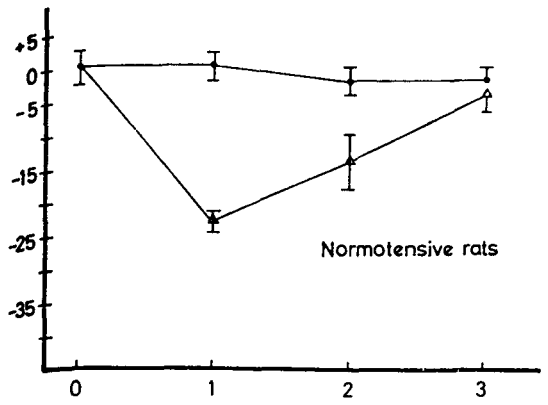

FIG. 1. Lergotrile-induced fall in blood pressure (ordinate: change in b.p. (mm Hg)) in normotensive rats. Groups of 6 male rats received lergotrile, 1·0 mg kg^{-1} i.p., immediately after baseline blood pressure determination. Further measurements were then taken at the indicated times. Data are presented as the means ± s.e. in mm Hg of the change in pressure from control values for each time. The reductions in blood pressure at 1 and 2 h are statistically significant ($P < 0.05$). Abscissa: hours after lergotrile administration.

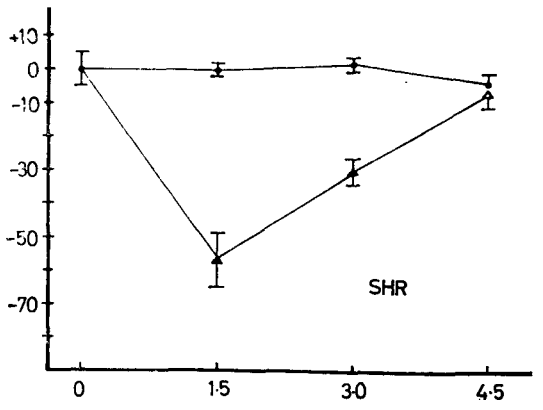

FIG. 3. Lergotrile-induced reduction in blood pressure in spontaneously-hypertensive rats. Groups of 6 male SHR received 0·5 mg kg^{-1} lergotrile, i.p., or its vehicle, immediately after baseline blood pressure determination. At 1·5 h intervals thereafter, blood pressures were re-measured. The data are expressed as the means ± s.e. of the change in blood pressure from control values at each time point. The reductions in blood pressure at 1·5 and 3 h are statistically significant ($P < 0.05$). Axes as in Fig. 1.

lowered blood pressure; the reduction was greatest 1·5 h after drug injection (Fig. 3). Lergotrile by mouth was also effective (see Table 1). The dose-response relationship for this effect is presented in Fig. 4. Lergotrile caused larger decreases in blood pressure in SHR than in normal animals (cf. Figs 2 and 4). Moreover, the drug was effective in SHR at a lower dose, 0·05 mg kg^{-1}, than in normals; the maximal response (a fall in blood pressure of about 60 mm Hg) was produced by 0·25 mg kg^{-1} lergotrile. (In normal rats, the maximal reduction, 30 mm Hg, required a dose of 1 mg kg^{-1}.) When administered orally twice a day for one week to SHR, lergotrile (1 mg kg^{-1}) continued to be as effective in lowering blood pressure after the last dose as it was following the first administration (see Table 1).

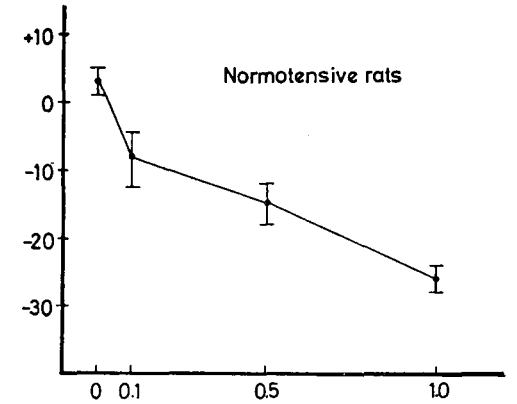

FIG. 2. Dose-response curve for the hypotensive action of lergotrile in normotensive rats. The drug was administered to groups of 6 rats, at the doses indicated, immediately after baseline blood pressure determination; blood pressures (ordinate: mm Hg) were then measured 1 h later. The data are expressed as the means ± s.e. of the change in blood pressure from the control values, in mm Hg. Each dose of lergotrile produced a statistically-significant reduction in blood pressure ($P < 0.05$). Abscissa: dose of lergotrile (mg kg^{-1}).

DISCUSSION

Our data show that lergotrile, administered intraperitoneally or orally, substantially lowers blood

Table 1. Effect of chronic lergotrile administration on blood pressure in SHR. Groups of 6 SHR received lergotrile (1 mg kg^{-1}, orally) every 12 h for one week. The changes in blood pressure were recorded after the first and last administration of the drug. Baseline measurements were made just before drug or vehicle administration, and then 2 and 4 h later. Data are presented as the mean ± s.e. of the change in pressure from control values obtained at the same time point. Both the first and last administration of lergotrile significantly reduced blood pressure ($P < 0.05$) at both times, and these changes were statistically indistinguishable.

Day	Change in pressure (mm Hg)	
	2 h	4 h
0	—35 ± 7	—34 ± 6
7	—21 ± 8	—27 ± 7

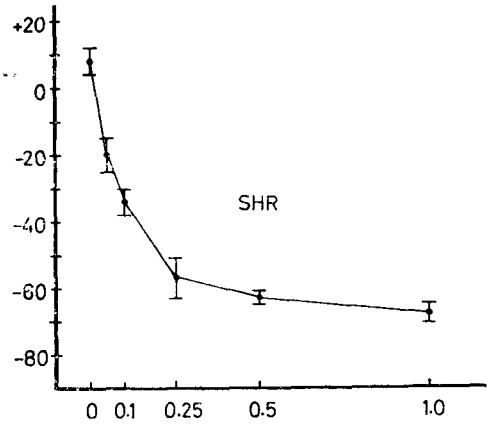

FIG. 4. Dose-response curve for the antihypertensive action of lergotrile in SHR. Groups of 6 animals received lergotrile at the indicated doses, immediately after baseline blood pressure determination; 1·5 h later, blood pressures were remeasured. The data are presented as the means ± s.e. of the change in blood pressure, compared to control values, in mm Hg. Each dose of the drug produced a statistically-significant decrease in blood pressure ($P < 0.05$). Ordinate: b.p. mm Hg. Abscissa: dose of lergotrile (mg kg^{-1}).

pressure in both normal and hypertensive rats. The effective dose range appears to be quite low (the minimal effective dose in SHR was 0·05 mg kg^{-1}), which would seem to make lergotrile a potent antihypertensive agent.

The drug is generally thought to act at least in part as a dopamine agonist (Fuxe et al 1978a; Clemens et al 1975; Silbergeld & Pfeiffer 1977). Consistent with this notion, we have obtained preliminary evidence showing that haloperidol pretreatment can block the ability of lergotrile to lower blood pressure (Sved, A. F., and Fernstrom, J. D., unpublished observations). The notion that activation of dopamine receptors (peripherally or centrally) can reduce blood pressure is not new. For example, bromocriptine, another ergoline derivative (like lergotrile) which stimulates dopamine receptors (Fuxe et al 1978b), has also been reported to lower blood pressure in man (Kaye et al 1976; Nilsson & Hokfelt 1978; Stumpe et al 1977) and in experimental animals (Clark et al 1978). Moreover, the antihypertensive action of bromocriptine can be blocked by pretreatment with a dopamine antagonist (Clark et al 1978).

If compounds such as lergotrile and bromocriptine do act via dopamine receptors to reduce blood pressure, then there are at least three possible sites at which a dopamine agonist could act. First, the drug might stimulate dopamine receptors on the smooth muscle of some vascular beds (Goldberg 1972), causing vasodilatation and a subsequent reduction in blood pressure. A second peripheral mechanism might involve a lergotrile-mediated activation of dopamine receptors on post-ganglionic sympathetic neurons, thereby causing a reduction in noradrenaline release onto effector organs (Starke et al 1977) and thus a fall in blood pressure. Third, lergotrile might stimulate dopamine receptors in the central nervous system, thereby activating central mechanisms involved in lowering blood pressure (Heise 1975). It is difficult to choose among these possibilities. It might well be that the drug acts at all three potential loci to induce a fall in blood pressure; indeed, results of studies on bromocriptine and blood pressure suggest that this may be so (Clark et al 1978).

Some data also suggest that lergotrile might influence blood pressure by acting directly within the noradrenergic synapse. That is, the drug has been shown to displace WB-4101*, a compound that binds specifically to α-adrenoceptors, in preparations of cerebral cortical membranes (Lew et al 1977). It has also been observed that the administration of lergotrile to animals increases the brain concentrations of methoxyhydroxyphenylethylglycol-sulphate (MOPEG-SO_4) (Fuller & Perry 1978), a finding that suggests that noradrenaline release is stimulated, which in turn indicates that lergotrile may function as an α-blocker (Fuller & Perry 1978). Blockade of *peripheral* α-noradrenoceptors should decrease blood pressure, but no data are presently available to confirm the possibility that lergotrile might have such a pharmacologic action. Peripheral blockade would seem important, since the ventricular administration of an α-noradrenoceptor blocker appears to produce only a small reduction in blood pressure, and this effect may not be due to a central action of the drug (Buccafusco & Brezenoff 1977).

Regardless of its ultimate mechanism of action, however, lergotrile is clearly a potent antihypertensive agent in the rat.

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* 2-(*N*-[2,6-dimethoxyphenoxyethyl])aminomethyl-1,4-benzodioxane.

REFERENCES

Buccafusco, J. J., Brezenoff, H. E. (1977) Neuropharmacology 16: 775–780

Clark, B. J., Scholtysik, G., Fluckinger, E. (1978) Acta Endocrinol. (Suppl. 216) 88: 75–81

Cleary, R. E., Crabtree, R., Lemberger, L. (1975) J. Clin. Endocrinol. Metab. 40: 830–833

Clemens, J. A., Smalstig, E. B., Shaar, C. J. (1975) Acta Endocrinol. 79: 230–237

Fuller, R. W., Perry, K. W. (1978) J. Neural Transm. 42: 23–35

Fuxe, K., Fredholm, B. B., Ogren, S. O., Agnati, L. F., Hokfelt, T., Gustafsson, J. A. (1978a) Fedn. Proc. Fedn. Am. Soc. Exp. Biol. 37: 2181–2191

Fuxe, K., Fredholm, B. B., Ogren, S. O., Agnati, L. F., Hokfelt, T., Gustafsson, J. A. (1978b) Acta Endocrinol. (Suppl. 216) 88: 27–56

Goldberg, L. I. (1972) Pharmacol. Rev. 24: 1–30

Heise, A. (1975) in: Scriabine, A., Sweet, C. S. (eds), New antihypertensive drugs, pp. 135–145 Spectrum: New York

Kaye, S. B., Shaw, K. M., Ross, E. J. (1976) Lancet 1: 1176

Klawans, H. L., Weiner, W. J., Nausieda, P. A., Volkman, P., Goetz, C., Lupton, M. D. (1977) Neurology 27: 390

Kleinberg, D. L., Noel, G. L., Frantz, A. G. (1977) N. Engl. J. Med. 296: 589–600

Lemberger, L., Crabtree, R., Clemens, J., Dyke, R. W., Woodburn, R. T. (1974) J. Clin. Endocrinol. Metab. 39: 579–584

Lew, J. Y., Hata, F., Ohashi, T., Goldstein, M. (1977) J. Neural Transm. 41: 109–121

Lieberman, A., Miyamoto, T., Battista, A. F., Goldstein, M. (1975) Neurology 25: 459–462

Nilsson, A., Hokfelt, B. (1978) Acta Endocrinol. (Suppl. 216) 88: 83–96

Silbergeld, E. K., Pfeiffer, R. F. (1977) J. Neurochem. 28: 1323–1326

Starke, K., Taube, H. D., Borowski, E. (1977) Biochem. Pharmacol. 26: 259–268

Steiner, J., Cassar, J., Mashiter, K., Dawes, I., Fraser, T. R. (1976) Br. Med. J. 1: 1186–1188

Stumpe, K. O., Kolloch, R., Higuchi, M., Kruck, F., Vetter, H. (1977) Lancet 2: 211–213

Teller, M. N., Stock, C. C., Helman, L., Mountain, I. M., Bowie, M., Rosenberg, B. J., Boyar, R. M., Budinger, J. M. (1977) Cancer Res. 37: 3932–3938

Tye, N. C., Horsman, L., Wright, F. C., Large, B. T., Pullar, I. A. (1977) Eur. J. Pharmacol. 45: 87–90

Udenfriend, S., Chairman, Committee on the care and use of spontaneously hypertensive (SHR) rats. (1976) ILAR News 19 G1–G20

Zivin, J. A., Bartko, J. J. (1976) Life Sci. 18: 15–26