J. Pharm. Pharmacol. 1983, 35: 536–537
Communicated October 26, 1982

The effects of dopamine on mean arterial blood pressure in the spontaneously hypertensive rat

P. DENNIS DEPALMA*, DENNIS M. ACKERMAN, *Smith Kline & French Labs. 1500 Spring Garden Street, Philadelphia, PA 19101 U.S.A.*

Dopamine has a complex cardiovascular profile resulting from a summation of its agonist activity at α-adrenergic, β-adrenergic and dopaminergic receptors (Goldberg 1972). Its α-adrenoceptor activity results in a pressor response, which can be partially counteracted by its activity at both vascular β_2-adrenergic and dopaminergic receptors which would tend to reduce blood pressure. In addition, a cardiac stimulant effect via β_1-receptor activation occurs (Weiner 1980).

Most of the measurements on the cardiovascular effects of dopamine in the rat have been made with normotensive animals. There is evidence to suggest that the responsiveness of the spontaneously hypertensive rat (SHR) to catecholamines and other vasoactive agents differs from that in the normotensive rat (Shibata et al 1973; Walsh 1981). Moreover, dopamine agonist-like drugs are being suggested for use as antihypertensive agents (Ackerman et al 1982). We have investigated the blood pressure response to dopamine in the SHR and the effect of selective receptor antagonists on this response.

Male SHRs, 18–22 weeks of age, 270–370 g, were anaesthetized with pentobarbitone sodium, 60 mg kg^{-1}, i.p. (preferred to urethane for this purpose in our laboratory since results with urethane were negative). The trachea was cannulated to facilitate respiration. The right external jugular vein and a tail vein were cannulated for drug administration. Systemic blood pressure was measured with a Statham pressure transducer (P23AA) connected to a cannula in the left carotid artery. Mean arterial blood pressure (MABP) was calculated as diastolic blood pressure +1/3 pulse pressure. Body temperature was maintained at 37·5 °C with a Thermistemp Temperature Controller (Yellow Springs Instrument Co.).

Drugs were dissolved in 0·9% NaCl (saline) containing 0·02% ascorbic acid. Dopamine hydrochloride (3 mg kg^{-1}) was administered i.v. over 1 min before and again 10 min post propranolol (1 mg kg^{-1}, i.v., over 5 min) and also before and during sulpiride infusion (2·4 mg kg^{-1} i.v. over 10 min). Isoprenaline hydrochloride (1 μg kg^{-1}) was administered before and during sulpiride administration. Histamine diphosphate (300 μg kg^{-1}) and acetylcholine chloride (1 μg kg^{-1}) were given before and after propranolol. Each test group consisted of 4 or 5 animals. The rats were pretreated 19–24 h previously with phenoxybenzamine, 45 mg kg^{-1} s.c. (a dose causing maximum α-blockade with minimum blood pressure lowering). Blood pressure effects of dopamine (30 μg kg^{-1}–3 mg kg^{-1}) were also determined in SHRs not pretreated with phenoxybenzamine. All drug doses are expressed as free base.

The data were analysed with a paired Student's *t*-test.

* Correspondence.

Results

MABP of anaesthetized SHRs was 179 ± 6. Pressure 19–24 h after phenoxybenzamine was 148 ± 6 mmHg.

In the untreated SHR, dopamine, 30 μg kg^{-1} to 1 mg kg^{-1}, i.v., produced a dose-related increase in blood pressure. This response ranged from 30 mmHg at 30 μg kg^{-1} to 75 mmHg at 1 mg kg^{-1}. At 3 mg kg^{-1} MABP increased by 55 mmHg but death ensued 5 min after dosing. After α-receptor blockade with phenoxybenzamine, the pressor response to dopamine was reversed, and the 3 mg kg^{-1} dose could be given without toxicity.

Sulpiride, a dopamine receptor blocker, caused a slight but significant attenuation of the depressor response to dopamine in the phenoxybenazmine-pretreated SHR (Table 1). However, a more effective blockade of this response was produced by propranolol, a β-adrenergic antagonist. Sulpiride did not block the depressor response to the β-receptor agonist isoprenaline; likewise, propranolol did not block the depressor response induced by histamine or acetylcholine.

Discussion

In normotensive rats pretreated with phenoxybenzamine, Blackwell & Marley (1967) abolished the

Table 1. Effects of the test drugs vs challenge drugs on MABP in phenoxybenzamine-pretreated SHRs. Test drugs given before then either 10 min after propranolol (1 mg kg^{-1} i.v.) or during sulpiride infusion (2.4 mg kg^{-1} i.v.). Values are expressed as mean ± s.e. mean; n = number of animals per group.

			Δ mmHg MABP		
Test drug	Dose (μg kg^{-1})	n	Before challenge drug	After or during challenge drug	Challenge drug
Dopamine	3000	5	−56 ± 3	−14 ± 2**	Propranolol
"	"	4	−54 ± 4	−45 ± 6*	Sulpiride
Isoprenaline	1	5	−72 ± 6	−72 ± 7	Sulpiride
Histamine	300	4	−57 ± 4	−75 ± 3*	Propranolol
Acetylcholine	1	4	−48 ± 4	−61 ± 7	Propranolol

* Significantly different ($P < 0.05$) from response before the challenge drug.
** Significantly different ($P < 0.001$) from response before the challenge drug.

depressor response to dopamine with propranolol alone. In contrast, Day & Blower (1975) reported no antagonism with propranolol but dose-related reductions in the depressor response to dopamine with metoclopramide. Wardell et al (1979) showed that although the dopamine receptor antagonists bulbocapnine and metoclopramide exerted a slight inhibition of the dopamine-induced depressor response, this blockade could be explained by the weak β-receptor antagonist activity of these agents. They concluded, in agreement with Blackwell & Marley (1967), that stimulation of β-receptors is primarily responsible for dopamine's depressor response in phenoxybenzamine-pretreated normotensive rats. Chapman et al (1980) by using sulpiride, a more selective dopaminergic antagonist, concluded that the depressor response to dopamine in normotensive rats is partly due to an action on β-receptors and partly due to an action on specific dopamine receptors.

Our results in the SHR although with small numbers of animals were in the same direction and to the same degree among animals and show that as in the normotensive rat, dopamine's pressor response is due to an α-receptor stimulation, and that the depressor response after α-receptor blockade is caused by an action on both β-adrenergic and dopamine receptors. The more effective blockade by propranolol vis-a-vis sulpiride suggests that the dopamine induced depressor response is primarily a result of β-receptor stimulation. Thus, the SHR may not be the ideal model in which to explore selective dopamine agonists.

The authors wish to thank Dr Paul Hieble for his suggestions in the preparation of this paper.

REFERENCES

Ackerman, D. M., Weinstock, J., Wiebelhaus, V. D., Berkowitz, B. (1982) Drug Dev. Res. 2: 283–297

Blackwell, B., Marley, E. (1967) Nature (London) 213: 840

Chapman, B. J., Horn, N. M., Munday, K. A., Robertson, M. J. (1980) J. Physiol. (London) 298: 437–452

Day, M. D., Blower, P. R. (1975) J. Pharm. Pharmacol. 27: 276–278

Goldberg, L. I. (1972) Pharmacol. Rev. 24: 1–29

Shibata, S., Kurahashi, K., Kuchii, M. (1973) J. Pharmacol. Exp. Ther. 185: 407–417

Walsh, G. M. (1981) Fed. Proc. Fed. Am. Socs. Exp. Biol. 40: 528

Wardell, J. R., Hahn, R. A., Stefankiewicz, J. S. (1979) in. Imbs, J. L., Schwartz, J. (eds) Advances in Biosciences. Pergamon Press, Oxford, pp 389–399

Weiner, N. (1980) in: Gilman, A. G., Goodman, L. S., Gilman, A. (eds) The Pharmacological Basis of Therapeutics. 6th Ed. Macmillan, New York, pp 138–175

J. Pharm. Pharmacol. 1983, 35: 537–539
Communicated January 31, 1983

Reconstituted collagen nanoparticles, a novel drug carrier delivery system

M. S. EL-SAMALIGY†, P. ROHDEWALD, *Inst. für Pharm. Chemie der Universität Münster, W. Germany, and Faculty of Pharmacy, Cairo University, Egypt*†

Recent colloidal drug delivery systems (Marty et al 1978; Kreuter 1978; El-Samaligy & Rohdewald 1982) have shown promise for optimal drug activity. Cross-linked coacervated gelatin and human serum albumin systems have been used as carriers for carcinogenic agents (Oppenheim & Stewarts 1979) and flukicides (Marty 1977). Gelatin, even in extremely dilute solutions, is capable of aggregate formation (Boedtker & Doty 1954; Engel 1962). This aggregation is temperature-dependent at all temperatures below the equilibrium melting point. The aggregate size, however, is dependent not only on temperature, but also on the process thermal path. It was concluded by Boedtker & Doty (1954) and Beyer (1954) that the crystallites in the gel aggregates appear as multiple chain segments in the collagen-fold configuration.

Such a property has been used to prepare aggregates in the nanometer range to act as colloidal drug-delivery carriers. The nanoparticles have also been investigated for their particle size distribution, biodegradability and their drug-holding capacity. The in-vitro release of the sorbed drugs from such nanoparticle products was also studied.

† Correspondence.

Methods

Materials. Gelatin, type II from swine skin (IEP 5.6): adriamycin and dactinomycin (Sigma Chemical Co., W. Germany), triamcinolone diacetate (Cyanamide GmbH, W. Germany), Tween 20 (Atlas Chemical Industries Inc., W. Germany). Sephadex G-25m, and Sephadex G-10f (Pharmacia Fine Chemicals, Sweden).

Methods. To determine the pH most suitable for the preparation of the colloidal nanoparticle system, 0·25% aqueous gelatin solution containing 0·5% Tween 20 was prepared and adjusted to different pH values in the range 3–9 using ammonia or HCl (to avoid the effect of ionic strength of buffer solution). The solutions were left at 25 °C for 48 h. The colloidal solutions obtained were examined for colloidal stability and particle size distribution at 5 day intervals for one month.

Accordingly the nanoparticles were prepared by dissolving 0·25 g gelatin and 0·5 g Tween 20 in 100 ml of bidistilled water, adjusting the solution to the optimum pH determined using dilute HCl solution, then centrifuging the solution at 14 000 rev min^{-1} for 15 min. The clear solution was heated at 40 °C for 1 h, quenched to 4 °C for one day, and then left at 25 °C for 48 h. The