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Effects of 3′,4′-dihydroxynomifensine on the dopamine vascular receptor

JAI D. KOHLI*, LEON I. GOLDBERG, *Committee on Clinical Pharmacology, Departments of Pharmacological and Physiological Sciences and Medicine, The University of Chicago, 947 East 58th Street, Chicago, Il 60637 U.S.A.*

Poat et al (1978) reported that 3′,4′-dihydroxynomifensine was a potent agonist of dopamine (DA) receptors in the rat striatum and nucleus accumbens, being approximately two to four times less active than DA in stimulating DA-sensitive adenylate cyclase in these brain areas. More recently, Woodruff & Sumners (1979) reported that 3′,4′-dihydroxynomifensine resembled DA in reducing blood pressure of the guinea-pig and this hypotensive action was not antagonized by propranolol, but was attenuated, like DA, by sulpiride. The present study was designed to determine the activity of 3′,4′-dihydroxynomifensine as a DA vascular agonist in the canine renal vascular bed. The effects of 3′,4′-dihydroxynomifensine on α- and β-adrenergic receptors were also studied.

All experiments were conducted in pentobarbitone-anaesthetized dogs (18–25 kg). Details of the surgical procedure and the proctocols used have been described previously (Goldberg et al 1978). In brief, renal or femoral blood flow was measured by an electromagnetic flowmeter; agonists or antagonists were injected intra-arterially, unless otherwise stated; and carotid blood pressure was recorded simultaneously with a pressure transducer.

Comparison of the effects of intra-arterial injections of DA and 3′,4′-dihydroxynomifensine on renal blood flow is shown in Fig. 1. DA and 3′,4′-dihydroxynomifensine produced dose-related increments in renal blood flow in the phenoxybenzamine-treated dog. Like DA, the vasodilation caused by 3′,4′-dihydroxynomifensine was not significantly attenuated by propranolol, 2·5 to 5 mg kg^{-1} (n = 5). This dose of propranolol was sufficient to abolish the effects of an equivasodilator dose of isoprenaline (3–12 nmol). Vasodilation by DA and 3′,4′-dihydroxynomifensine was attenuated to a similar extent (60–100%) by (±)-sulpiride in a dose of 0·5 mg intra-arterially (n = 3). In a separate experiment hexamethonium, 10 mg kg^{-1} given intravenously, abolished the effect of 25 μg kg^{-1} of 1,1-dimethyl-4-phenylpiperazinium but had no effect on renal vasodilation caused by DA or 3′,4′-dihydroxynomifensine. These experiments demonstrated that 2′,4′-dihydroxynomifensine was causing renal vasodilation by acting on DA vascular receptors.

Dose-response curves (n = 7) of increase in renal blood flow in phenoxybenzamine treated dogs produced by DA and 3′,4′-dihydroxynomifensine expressed as percent of the effect produced by 190 nmol of DA are shown in Fig. 2. The threshold dose of 3′,4′-dihydroxynomifensine was about 16-fold higher than that of DA; however, the dose-response curve of 3′,4′-dihydroxynomifensine was flatter than that of DA and the effect produced by the highest dose (12 000 nmol) of 3′,4′-dihydroxynomifensine was only 65% of the effect produced by 190 nmol of DA. Since the dose-response curves of the two compounds were not parallel, their

* Correspondence.

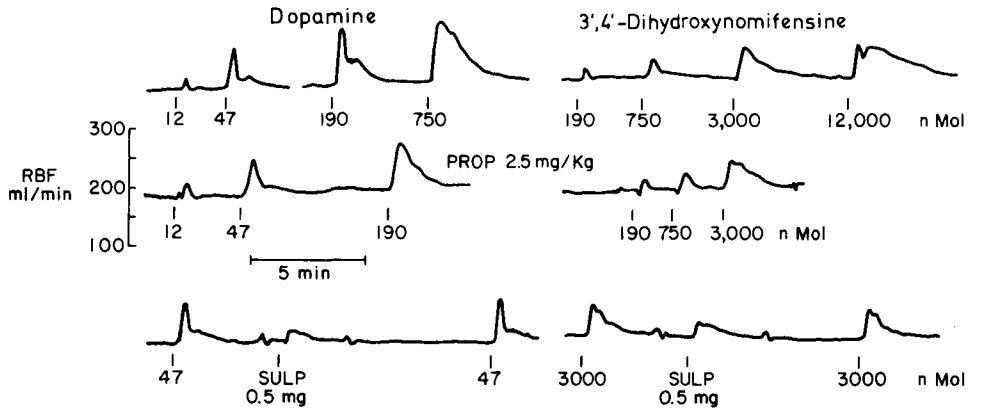

FIG. 1. Effect on renal blood flow (RBF) of increasing doses of dopamine and 3′,4′-dihydroxynomifensine injected into the renal artery in a pentobarbitone-anaesthetized dog. Top panel: after phenoxybenzamine (5 mg kg^{-1}) pretreatment, i.a. Middle panel: after subsequent administration of propranolol (Prop), 2·5 mg kg^{-1}, i.a. Bottom panel: effect of agonists alone compared with simultaneous administration of the agonist and (±) sulpiride, 0·5 mg.

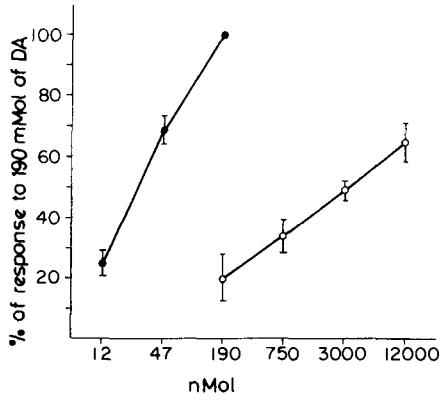

FIG. 2. Dose-response curves of increase in renal blood flow by dopamine (●——●) and 3′,4′-dihydroxynomifensine (○——○) expressed as (mean ± s.e.) percent of response to 190 nmol of dopamine (DA), (n = 7).

potencies could not be compared precisely. However, at the 50% effect level 3′,4′-dihydroxynomifensine appeared to be about 100 times weaker than DA.

The dose response curve of 3′,4′-dihydroxynomifensine indicated that it was not a full agonist. Accordingly, two experiments were performed in which minimal effective doses of 3′,4′-dihydroxynomifensine (190–750 nmol) were injected simultaneously with 47 nmol of DA and the response compared with the effects of DA alone. In one experiment 3′,4′-dihydroxynomifensine attenuated the vasodilating effects of DA by 35% and in the other experiment by 40%.

In two experiments 3′,4′-dihydroxynomifensine, in doses of 0·5 and 1 mg kg^{-1} administered intravenously, did not significantly affect right ventricular contractile force as measured by a Walton-Brodie strain gauge arch. In the same experiments DA, in doses ranging from 8–16 $\mu g\ kg^{-1}$ intravenously, increased contractile force by 30–50%.

In the final series of experiments (n = 4) 3′,4′-dihydroxynomifensine was injected into the femoral artery to study its effects on that vascular bed. Before administration of antagonists, 3′,4′-dihydroxynomifensine displayed weak vasoconstrictor effects. In these experiments DA caused dose-related decrease in femoral blood flow in doses ranging from 3–750 nmol, as previously described. The minimum effective dose of 3′,4′-dihydroxynomifensine in the same experiments ranged from 47·5 to 190 nmol and at the highest tested dose (12 000 nmol) the vasoconstriction was less than that produced by 47·5 nmol of DA. Vasconstriction caused by 3′,4′-dihydroxynomifensine and DA was blocked by phenoxybenzamine.

Our results suggest that 3′,4′-dihydroxynomifensine is a partial DA vascular agonist. In this regard it resembles apomorphine which also appears to be a

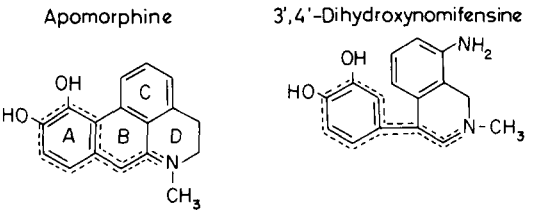

FIG. 3. Structure of apomorphine and 3′,4′-dihydroxynomifensine. The dopamine portion of each molecule is outlined by the dotted lines.

partial DA vascular agonist (Crumly et al 1976). As shown in Fig. 3, 3′,4′-dihydroxynomifensine exhibits a close structural resemblance to apomorphine. The major difference in the two compounds is that the ring B of apomorphine has been broken in 3′,4′-dihydroxynomifensine. Another difference is that there is an NH_2 substitution in ring C. An interesting difference in the actions of apomorphine and 3′,4′-dihydroxynomifensine is that whereas apomorphine has been shown to be a weak partial agonist of the DA receptor in stimulating adenylate cyclase in rat striatal homogenates (Miller et al 1974), 3′,4′-dihydroxynomifensine is almost as potent as DA in stimulating striatal DA sensitive adenylate cyclase (Poat et al 1978). However, both compounds are rather weak and only partial agonists of the DA vascular receptor.

Finally, although 3′,4′-dihydroxynomifensine is a weak DA agonist, it exhibits interesting qualitative differences from DA in that it does not possess a positive inotropic action (β_1-adrenergic) and is an even weaker α-adrenergic agonist than DA. Accordingly, it is possible that further modification of the nomifensine molecule may yield a more potent DA agonist with relatively little effect on α- and β-adrenergic receptors.

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