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Dihydrexidine: a new potent peripheral dopamine D_1 receptor agonist

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Dihydrexidine (trans-10,11-dihydroxyhexahydrobenzo-[a]phenanthridine) was found to be a full dopamine D_1 receptor agonist with a potency five times that of dopamine. Dihydrexidine showed no agonist activity at peripheral dopamine D_2 receptors, α- or β-adrenoceptors at the doses which produced near maximal stimulation of dopamine D_1 receptors. The chemical structure of dihydrexidine shows that addition of a phenyl ring to a benzo[f]quinoline moiety bestows potent D_1 activity upon a structure which had no such activity previously. This observation introduces a new factor in structure-activity considerations for dopamine receptor ligands.

Dihydrexidine; Dopamine receptor ligands; Dopamine receptors (peripheral)

1. Introduction

Dopamine receptor ligands continue to be of interest to clinicians, pharmacologists, and medicinal chemists. It is important to determine precisely the structural requirements for agonist and antagonist activity at the various dopamine receptor subtypes, which in turn can guide receptor modelling. Selective agonists at peripheral dopamine D_1 have been limited to the benzazepine series (SK&F 38393 and fenoldopam – SK&F 82526). However, these compounds have limitations both as biological probes and as therapeutic agents. We were therefore interested in dihydrexidine (trans-10,11-dihydroxyhexahydrobenzo-[a]phenanthridine), reported to be a potent and full-efficacy central dopamine D_1 receptor agonist (Lovenberg et al., 1989; Brewster et al., 1990), and undertook to study its cardiovascular effects in the in vivo model used in our laboratory for the study of peripheral dopamine receptors.

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This work was presented in part at the 1990 IUPHAR meeting in Amsterdam (Kohli et al., 1990).

2. Materials and methods

2.1. Vascular effects of dihydrexidine

Adult dogs were anesthetized and prepared for measurement of renal blood flow, heart rate and blood pressure as has been described (Goldberg and Kohli, 1979; Goldberg et al., 1978). Injections into the renal artery were carried out before and after phenoxybenzamine (15 mg/kg i.v.) and propranalol (2 mg/kg i.v.). Blockade of α- and β-adrenoceptors was confirmed by the absence of effects of norepinephrine (12 nmol) and isoproterenol (3 nmol). SCH 23390 (10 μg/kg i.v.) was used for blockade of dopamine D_1 receptors. Domperidone (10 μg/kg i.v.) was given to produce selective blockade of dopamine D_2 receptors.

Effects of dihydrexidine on renal vascular resistance were studied by i.v. infusion and compared with those of dopamine. Each dose of either drug was infused for 10 min. The renal blood flow and carotid blood pressure were recorded at the end of each infusion period. The infusion rate was then increased. The order of drugs in each dog was determined randomly. After the effects in untreated dogs were observed, α- and β-adrenoceptor blockade was produced as above and the drug administrations repeated.

2.2. Neuronal effects of dihydrexidine

Dopamine D_2 receptor activity of dihydrexidine was determined by its effect on the postganglionic sympathetic cardiac nerve in the dog (for details, see Horn et al., 1982). Frequency-heart rate response curves were generated before and after the administration of dihydrexidine up to 5 μg/kg per min i.v. infusion for up to a total of 50 μg/kg.

2.3. Drugs

The following drugs were used in this study: atropine sulfate, hexamethonium bromide, d,l-propranolol hydrochloride, l-isoproterenol-d-bitartrate, l-norepinephrine-d-bitartrate (Sigma Chemical Company); dopamine hydrochloride (3-hydroxy-tyramine hydrochloride (Calbiochem). Dihydrexidine hydrochloride was synthesized at Purdue University, West Lafayette, IN. The authors thank the following companies for generous gifts of drugs: Janssen Pharmaceuticals for domperidone; Schering Corporation for SCH 23390; Smith, Kline and French Laboratories for phenoxybenzamine; and Sandoz Ltd. for bromocryptine mesylate.

2.4. Statistical methods

Reported values are the means ± S.E.M. Blood pressure is reported as the mean arterial pressure, calculated as diastolic pressure plus one third of the pulse pressure. When comparing the responses produced by different drugs, Student's t-test was used.

TABLE 1

Basal renal blood flow and response to dihydrexidine (188 nmol) before and after antagonist administration.

Antagonist	N	Untreated		After antagonist	
		RBF [a]	Response [b]	RBF	Response
Atropine	3	119± 8	58± 7	117±12	61± 6
Propranolol	5	116± 7	70±14	103±13	66±10
Domperidone	4	127±12	61± 5	117±19	58± 7
SCH 23390	7	105±10	64± 3	100± 8	2± 1

[a] Basal renal blood flow in ml/min. [b] Increase in blood flow (ml/min) produced by a bolus injection of 188 nmol dihydrexidine into the renal artery.

Comparisons of the responses to a given dose of a drug before and after treatment with an antagonist were made using the Wilcoxon signed rank test. Differences were considered statistically significant when the P value was < 0.05.

3. Results

3.1. Renal vascular effects

Given i.a. into the renal artery dihydrexidine produced dose-related increases in renal blood flow which were not accompanied by changes in systemic blood pressure, indicating a selective decrease in renal vascular resistance. Renal vasodilation by dihydrexidine was not antagonized by acetylcholine receptor (atropine 1 mg/kg i.v.), β-adrenoceptor (propranolol 2 mg/kg i.v.) or dopamine D_2 receptor (domperidone 10 μg/kg i.v.) antagonists but was completely blocked by SCH 23390

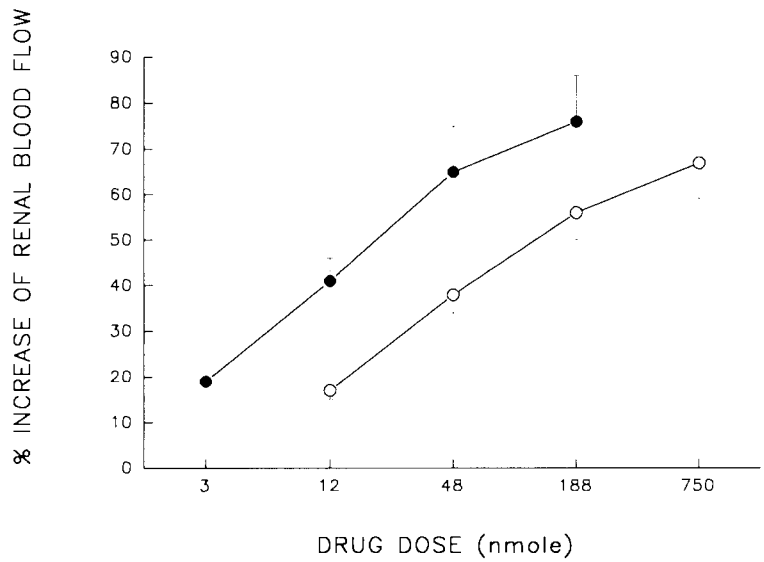

Fig. 1. Dose-response curves of increase in renal blood flow produced by injection of dihydrexidine (●) and dopamine (○) into the arterial blood supply of the right kidney (n = 6). The animals had been treated with phenoxybenzamine (15 μg/kg i.v.) and propranolol (2 μg/kg i.v.) to produce α-adrenoceptor and β-adrenoceptor blockade, respectively. The resting blood flow in these animals before and after adrenoceptor blockade was 152±21, and 136±24 ml/min, respectively.

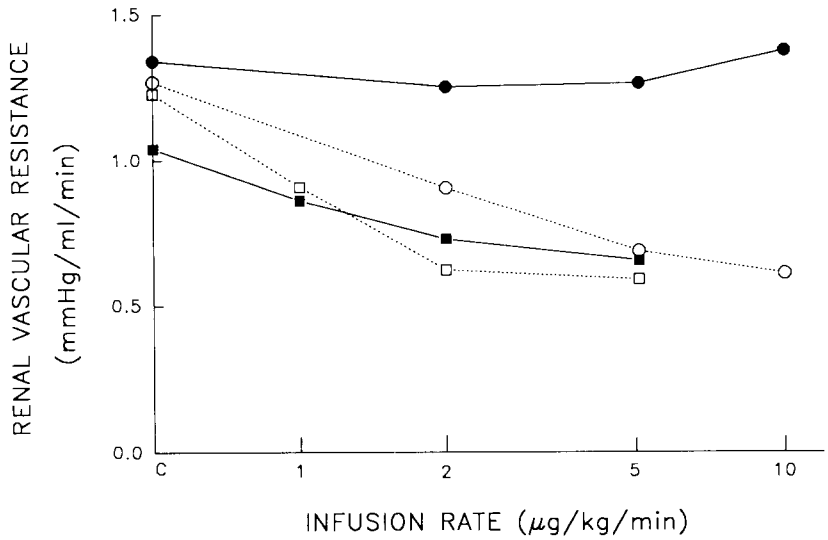

Fig. 2. Effect of i.v. infusions of dihydrexidine (squares) and dopamine (circles) on renal vascular resistance in pentobarbital-anesthetized dogs (n = 4). Filled symbols represent the response prior to and open symbols represent the response following α- and β-adrenoceptor blockade. In these animals renal blood flow was 124 ± 20 ml/min before and 115 ± 14 ml/min following adrenoceptor blockade.

(10 μg/kg i.v.), a selective dopamine D_1 receptor antagonist (table 1). Dose-response curves for increases in renal blood flow produced by dopamine and dihydrexidine are shown in fig. 1 (n = 6). The EC_{50} (dose causing a 50% increase over the predrug basal flow) of dihydrexidine was 17 ± 3 and that of dopamine was 89 ± 17 nmol. Based on these experiments dihydrexidine appears to be a full agonist at dopamine D_1 receptors, approximately 5-fold more potent than dopamine.

Dihydrexidine was compared with dopamine by the i.v. route, again using renal vascular resistance as the index (n = 4). Results are shown in fig. 2. Mean arterial pressure in these dogs was 135 ± 4 mm Hg. Infusion of dopamine at 10 μg/kg per min increased mean arterial pressure by 42 ± 5 mm Hg while dihydrexidine (5 μg/kg per min) reduced it by 39 ± 7 mm Hg. After the administration of phenoxybenzamine and propranolol the mean arterial pressure was 127 ± 5 mm Hg. Infusions of dopamine or dihydrexidine at the rates used above reduced mean arterial pressure by 34 ± 8 or 43 ± 5 mm Hg, respectively. At these infusion rates neither dopamine nor dihydrexidine significantly altered heart rate which was 137 ± 12 beats/min prior to, and 111 ± 14 beats/min following α- and β-adrenoceptor blockade. Note that dopamine had little effect on renal vascular resistance before adrenoceptor blockade, but produced dose-related vasodilation after the blockade. With dihydrexidine however, there was a similar decrease in renal vascular resistance before or after adrenoceptor blockade, suggesting dihydrexidine was devoid of α- or β-adrenoceptor activity. Further, as with i.a. administration, dihydrexidine was also somewhat more potent than dopamine by the i.v. route.

3.2. Dopamine D_2 receptor activity

Frequency-heart rate response curves are shown in fig. 3. There was a frequency related increase in heart rate at nerve stimulation frequencies of 0.25 to 4 Hz. Bromocryptine, infused at 1 μg/kg per min i.v. (10 μg/kg total dose), produced inhibition of nerve stimulation. This action of bromocryptine is known to be mediated by neuronal dopamine D_2 receptors (Lokhandwala, 1979). However, even at a 5 × higher dose (50 μg/kg total dose), dihydrexidine had no effect in

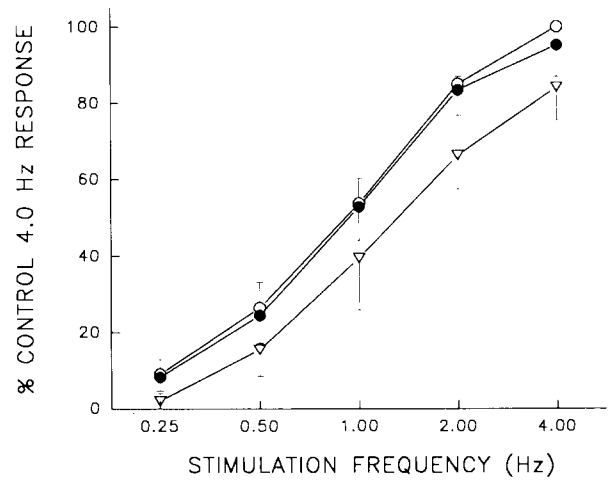

Fig. 3. Increases in heart rate produced by electrical stimulation of the postganglionic sympathetic cardiac nerve (n = 6). In these animals the resting heart rate was 116 ± 8 beats/min and was increased by 98 ± 19 beats/min by electrical stimulation a 4.0 Hz (100%). Control response (○); during dihydrexidine infusion at 5 μg/kg per min i.v. (●) and during bromocryptine infusion at 1.0 μg/kg per min i.v. (▽).

this model, indicating lack of dopamine D_2 receptor agonist activity at the doses used.

4. Discussion

The present results show that dihydrexidine is a potent renal vasodilator by both the i.a. and i.v. routes. Pharmacological analysis further demonstrated that this effect was mediated by peripheral D_1 dopamine receptors. The dose-response curve of dihydrexidine is parallel and to the left of the dopamine curve throughout the dose-range studied, indicating relatively higher full range potency. In this respect our results are similar to those reported in the CNS; dihydrexidine being 80 × more potent than dopamine in rat striatal membranes (Lovenberg et al., 1989). It is interesting to note that at the infusion rate (5 μg/kg per min) at which dihydrexidine showed near maximal dopamine D_1 receptor activity, it had no dopamine D_2 receptor activity. Higher doses of dihydrexidine could not be studied without profound reduction of systemic blood pressure produced by i.v. administration.

Contradictions in the structure-activity relationships of dopamine receptor agonists continue to hamper rationalization of the structural determinants of agonist activity at the two subtypes ot peripheral dopamine receptors, D_1 and D_2. For example, it first appeared that the β- and not α-rotameric conformation of dopamine was required for D_1 agonist activity (Volkman et al., 1977). But finding potent renal vasodilator activity (D_1) in the N,N-di-n-propyl analog of the α-rotamer of the 2-aminotetralin (A-5,6-DTN) appeared to make rotameric conformation all but insignificant as a factor for D_1 agonist activity (Kohli et al., 1982). Further, just when it appeared that two OH groups analogous to the 3,4-hydroxyls of dopamine were essential for D_1 agonist activity (for references see Kohli and Goldberg, 1987), along came a benzergoline molecule with no phenolic or catechol group (CY 208-243) showing marked D_1 agonist activity in this benzergoline molecule (Kohli et al., 1989, see fig. 4). Even more remarkable was the lack of D_2 agonist activity in this compound (Kohli and Horn, 1991). CY 208-243 is an ergoline molecule similar to several D_2 receptor agonists, and which contains a pyrrolethylamine within its structure believed to be the pharmacophore for D_2 activity, and yet it showed little D_2 activity.

Of the octahydrobenzo[f]quinolines, only the trans-fused BC ring isomers are active; the cis-fused isomers are inactive. Both α- and β-rotameric analogs of the trans-fused systems have been synthesized and studied by Cannon and colleagues (for references see Cannon, 1983). N-Alkyl-substituted derivatives of both the rotameric conformers exhibited potent D_2 agonist activity. More interestingly, it was reported that the β-conformers, which had been shown to be the active conformation required for D_1 activity, had no renal vasodilating activity.

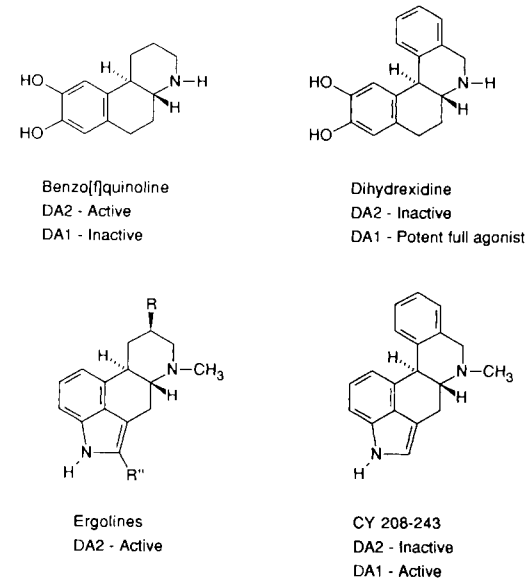

Fig. 4. Structural formulas of some compounds with agonist properties at peripheral dopamine receptors.

It is, therefore, very interesting to note that the addition of a phenyl ring to an octahydrobenze [f]quinoline, a D_1-inactive molecule, resulted in a potent and preferential D_1 agonist. By the same token it is to be noted that the addition of a phenyl ring to the ergoline moiety (a D_2-active and D_1-inactive molecule) resulted in a similar transformation from a D_2-selective to a D_1-selective molecule (vide supra). This finding adds a new dimension to the considerations for molecular determinants of dopamine receptor activities and emphasizes the importance of a phenyl ring accessory binding region on the peripheral dopamine D_1 receptor, not possessed by the peripheral dopamine D_2 receptor, which parallels that of the CNS D_1 and D_2 receptors (Brewster et al., 1990). The addition of this phenyl ring evidently also excludes the molecule from the D_2 receptor.

In summary dihydrexidine appears to be a potentially useful agonist at peripheral dopamine D_1 receptors without α- or β-adrenoceptor activity and only weak, if any, peripheral D_2 activity. Its chemical structure introduces a new factor for consideration in determining structural requirements for dopamine receptor activities.

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