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Deviating central hypotensive activity of urapidil in the cat

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Urapidil, a novel antihypertensive drug, as well as possessing a peripheral α_1-adrenoceptor antagonistic effect, also has a significant degree of central hypotensive activity. When injected into the left vertebral artery of chloralose-anaesthetized cats the dose-dependent hypotensive effect of the drug was much stronger than after its systemic administration. Prior treatment, also via the vertebral artery, with various receptor antagonists (yohimbine, prazosin, diphenhydramine, metiamide, sulpiride, pirenzepine, R 56413, naloxone) did not antagonize the central hypotensive effect of urapidil administered subsequently. Accordingly, the central hypotensive action of urapidil is not mediated by central receptors of the following types: α_2- or α_1-adrenoceptors; H_1- and H_2-histamine; dopaminergic; muscarinic; 5-hydroxytryptamine; opiate. As such the mechanism of the central hypotensive action remains unexplained. It obviously deviates from that of classical centrally acting antihypertensive drugs like clonidine, guanfacine and α-methyldopa, which are agonists of central α_2-adrenoceptors.

Urapidil, a novel antihypertensive agent derived from uracil, is generally recognized to be an antagonist of postsynaptic α_1-adrenoceptors (Eltze 1979; Bousquet et al 1983; Sanders et al 1983; Zimmerman & Largent 1983; van Zwieten et al 1985), which simultaneously displays other effects that contribute to the drug's hypotensive action. Apart from a peripheral vasodilator effect based upon α_1-adrenoceptor blockade, a centrally-mediated reduction of peripheral sympathetic tone has been suggested as an additional, major contribution to the drug's antihypertensive effect (Schoetensack et al 1983; Sanders et al 1983; Sanders & Jurna 1985). Several authors have demonstrated urapidil's central hypotensive activity by different techniques, which all require injection of the drug into different brain areas (Brody et al 1984; Shebuski & Zimmerman 1984; Kellar et al 1984; Zeigler et al 1984; van Zwieten et al 1985). We have shown (van Zwieten et al 1984, 1985) that urapidil displays potent central hypotensive activity after its injection into the left thoracic vertebral artery of cats. This drew our attention to the fact that the central hypotensive action could not be antagonized by the selective α_2-adrenoceptor antagonist yohimbine, which is known to be an effective blocker of the central effects of clonidine, guanfacine and α-methyl-dopa. This finding, which was confirmed in a different model by Kellar et al (1984), strongly suggests that the central hypotensive activity of urapidil is not mediated by central α_2-adrenoceptors, in contrast to that of the classical centrally-acting antihypertensive clonidine and related drugs, which are agonists at the level of central α_2-adrenoceptors (van Zwieten et al 1984).

In the present investigation a series of different receptor antagonists was studied in an attempt to further characterize the mechanism of urapidil's central hypotensive activity.

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Materials and methods

Cats of either sex (2·1–4·0 kg) were anaesthetized with α-glucochloralose (60 mg kg^{-1}, i.p.) and placed on a thermostatically-controlled heated table maintained at 37 °C. After tracheotomy and intubation the animals were artificially ventilated with room air using a Braun-Melsungen positive pressure pump. Following left-side thoracotomy, the left subclavian artery was located and all the side branches, except the vertebral artery, were ligated close to the subclavian artery. After distal ligation of the axillary artery a PE-50 polyethylene catheter was introduced into the subclavian artery and pushed caudally until its tip was situated just distal to the ostium of the vertebral artery. The method has been described in detail by van Zwieten (1975). The femoral artery and vein were cannulated for monitoring intra-arterial pressure and heart rate and for intravenous injection, respectively. Heparin (1000 iu kg^{-1}) was given i.v. to prevent blood coagulation. Drug solutions were infused into the vertebral artery over 1 min in a volume of 140 μl. Blood pressure and heart rate were measured with Statham P23 Db pressure transducers and recorded on a Hellige Polygraph. The initial level of blood pressure before drug treatment of each individual animal was taken as 100% and all subsequent values (±s.e.m.) expressed as percentage. The mean value of initial pressure before drug treatment was 119 ± 5 mmHg (MAP; mean ± s.e.m., n = 35). Only one antagonist was used per cat.

Drugs used: urapidil (Byk, Konstanz, W. Germany); diphenhydramine (Parke Davis, USA); metiamide (Smith Kline & French Laboratories, UK); sulpiride (Pharmexport, Haarlem, The Netherlands); R56413 (3-{2-[4-(bis(4-fluorophenyl)methylene)-1-piperidinyl]-ethyl}-2-methyl-4*H*-pyrido-(1,2-a)pyrimidin-4-one) (Janssen Pharmaceutica, Beerse, Belgium); pirenzepine (Thomae GMbH, Biberach a.d. Riss, W. Germany); prazosin HCl (Pfizer, Sandwich, UK); naloxone HCl (Endo Laboratories, USA).

Results and discussion

As in earlier experiments urapidil caused a dose-dependent (30–300 μg kg^{-1}) fall in blood pressure when injected into the vertebral artery. This effect was significantly stronger for all doses studied than after injection of the drug into a femoral artery. Heart rate did not significantly change, either after central or after systemic administration of the drug. In previous experiments (van Zwieten et al 1985) it had been shown that a dose of 300 μg kg^{-1} urapidil (vertebral artery) was submaximal. This dose was chosen for the present experiments. It had also been shown that pretreatment with yohimbine (30 μg kg^{-1}, 15 min previously via the vertebral artery) did not diminish the hypotensive response after infusion of urapidil via the same route (van Zwieten et al 1985). A series of antagonists of various receptors were studied with respect to their potential infuence on the effect of urapidil according to the same protocol as mentioned for yohimbine. The doses of the antagonists were chosen in such a manner that i.v. injection of the same dose would have caused significant blockade of the receptors involved, that is at least 50% blockade of a dose of agonist producing a maximal effect. Accordingly, blockade of the following types of central receptors was studied by means of the antagonist given in parentheses: histamine H_1 (diphenhydramine) and H_2 (metiamide); dopamine DA_2 (sulpiride); 5-hydroxytryptamine 5-HT_2 (R 56413); muscarine M_1 (pirenzepine); α_1-adrenoceptor (prazosin); opiate (naloxone). None of the receptor antagonists caused any significant persistent change in blood pressure and heart rate. Yohimbine (30 μg kg^{-1}) caused a transient fall in pressure by approximately 10 mmHg which recovered within 5 min. Urapidil was injected only after full recovery of blood pressure.

The results are summarized in Table 1. Obviously, none of the receptor antagonists was able to reduce the drug's central hypotensive activity. A small but significant enhancement of the hypotensive effect of urapidil was induced by prior treatment with the selective 5HT_2-receptor blocker R 56413. It seems very unlikely that central α_1-adrenoceptor blockade is an explanation of the central hypotensive effect as such, since in the present model even high doses of prazosin and related α_1-adrenoceptor antagonists do not show any central hypotensive activity (authors, unpublished results).

The results obtained suggest that the central hypotensive activity of urapidil is not mediated by α_1- or α_2-adrenoceptors, nor by muscarinic (M_1), dopaminergic (DA_2), histaminergic (H_1 and H_2), opiate or 5-hydroxytryptamine (5-HT_2) receptors. In radioligand binding studies urapidil was shown to possess significant affinity for α_1-adrenoceptors and furthermore weak affinity for dopaminergic receptors, whereas no significant binding to any other receptor subtype could be established (Kellar et al 1984; van Zwieten et al 1985). The central hypotensive activity of urapidil so far remains unexplained at the receptor level and it is clearly different from that of classical centrally-acting α_2-adrenoceptor agonists, of which clonidine is the prototype. Urapidil is therefore the second example of this type, recalling the unexplained but potent central activity of the experimental compound R 28935 (erythro-1-{1-[2-(1,4-benzodioxan-2-yl)-2-hydroxyethyl]-4-piperidyl}-2-benzimidazolinone) (van Zwieten et al 1975).

Table 1. Influence of various receptor antagonists on the central hypotensive effect of urapidil. The receptor antagonists were injected into the left thoracic vertebral artery of chloralose-anaesthetized cats, 15 min before the administration of urapidil (300 μg kg^{-1}), injected via the same route. Initial values of mean arterial blood pressure were taken as 100%. The maximal decrease in blood pressure caused by urapidil which invariably occurs 2 min after injection was expressed as percentage of the initial value. Means ± s.e.m. for 3–5 animals.

Pretreatment v.a.	Central receptor blocked	Maximal decrease in blood pressure by urapidil
None (saline)	—	28·4 ± 5·9 (n = 6)
Prazosin (3 μg kg^{-1})	α_1-Adreno-	22·4 ± 6·5 (n = 4) ns
Yohimbine (30 μg kg^{-1})	α_2-Adreno-	28·8 ± 4·2 (n = 3) ns
Diphenhydramine (100 μg kg^{-1})	H_1-Histamine	25·4 ± 7·5 (n = 4) ns
Metiamide (100 μg kg^{-1})	H_2-Histamine	31·2 ± 6·5 (n = 4) ns
Sulpiride (100 μg kg^{-1})	Dopaminergic (DA_2)	20·4 ± 4·8 (n = 3) ns
R 56413 (100 μg kg^{-1})	5-HT_2	40·6 ± 14 (n = 3)*
Pirenzepine (100 μg kg^{-1})	Muscarinergic (M_1)	32·6 ± 3 (n = 3) ns
Naloxone (100 μg kg^{-1})	Opiate	24·7 ± 5·7 (n = 5) ns

* $P < 0.05$.

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