J. Pharm. Pharmacol. 1989, 41: 173–178
Received April 14, 1988

Effects of Urapidil on Catecholamine Turnover and Release in the Central Nervous System of the Rat

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Abstract—The actions of urapidil, prazosin, idazoxan, and haloperidol on the turnover of noradrenaline in the hypothalamus and dopamine in the nucleus accumbens of the rat were investigated using changes in the ratios of 3-methoxy-4-hydroxyphenyl-glycol/noradrenaline (MHPG/NA) and 3,4-dihydroxyphenylacetic acid/dopamine (DOPAC/DA), respectively, as measures for drug-induced effects. Urapidil (2·5–30 mg kg^{-1} i.v.) increased the ratios of MHPG/NA and DOPAC/DA. Its effects on NA turnover were maximal at 60 min (160% of control at 30 mg kg^{-1}), and on DA turnover at 30 min (138% of control at 30 mg kg^{-1}). Prazosin (0·5–2·5 mg kg^{-1} i.v.) had no effect, but the high dose of 5 mg kg^{-1} i.v. significantly increased the ratio of MHPG/NA in the hypothalamus. Idazoxan (2–50 mg kg^{-1} i.v.) and haloperidol (0·02–0·5 mg kg^{-1} i.v.) selectively enhanced turnover of NA and DA, respectively. In experiments on field-stimulated overflow of tritium from slices of hypothalamus and nucleus accumbens labelled with [^{3}H]NA or [^{3}H]DA, respectively, urapidil (1 μmol L^{-1}) facilitated the evoked responses in both regions. Prazosin (0·1 μmol L^{-1}) had no effect in either of the two areas. Idazoxan (0·1 μmol L^{-1}) increased stimulated overflow of [^{3}H]NA from the hypothalamus but not of [^{3}H]DA from the nucleus accumbens. Conversely, haloperidol (0·1 μmol L^{-1}) greatly enhanced evoked overflow of [^{3}H]DA but not of [^{3}H]NA. From the present results it is concluded that urapidil has an antagonistic effect at central α_2-adrenoceptors and also a weak antagonistic action at central dopamine D_2-receptors.

Urapidil (6-[[3-[4-(*o*-methoxyphenyl)-1-piperazinyl]-propyl] amino]-1,3-dimethyluracil) is an antihypertensive drug described as peripheral α_1- and weak α_2-adrenoceptor antagonist (Zimmermann & Largent 1983; Sanders et al 1985; Kellar et al 1984). In addition, there is considerable evidence for a central site of action: In the anaesthetized cat, urapidil attenuates the pressor response to bilateral carotid occlusion at doses which do not lower blood pressure significantly (Schoetensack et al 1977) and causes a dose-dependent fall in blood pressure after injection into the vertebral artery (van Zwieten et al 1985). In the dog, intravenous (i.v.) or intracisternal (i.c.) administration of urapidil leads to a suppression of reflex tachycardia elicited by bradykinin (Shebuski & Zimmerman 1984, 1985). Furthermore, a decrease in sympathetic nerve activity was seen after i.v. administration in rats and cats (Sanders & Jurna 1985).

These properties of urapidil suggest a possible action on catecholamine-containing neurons in the central nervous system. In fact, Pugsley & Myers (1986) observed in the rat an increase by urapidil of central L-dopa accumulation after injection of a dopa-decarboxylase inhibitor. Furthermore, Jackisch et al (1987) investigated the effect of urapidil on the release of [^{3}H] monoamines from rabbit brain slices. The authors described a facilitatory action on impulse evoked overflow of [^{3}H] noradrenaline compatible with an antagonistic effect at central α_2-adrenoceptors. These findings prompted us to perform a detailed study in the rat on the action of urapidil on central noradrenaline and dopamine mechanisms in-vivo and in-vitro.

Catecholamine turnover was estimated using a method which does not disrupt steady state conditions, and the effects of urapidil were compared to those of prazosin, idazoxan, and haloperidol. Furthermore, a possible presynaptic site of action was investigated in-vitro in the same species, using electrical field stimulation of superfused brain slices preincubated with [^{3}H]noradrenaline ([^{3}H]NA) or [^{3}H] dopamine ([^{3}H]DA).

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Materials and Methods

Experiments on turnover of noradrenaline and dopamine

Male Sprague-Dawley rats (150–180 g; Forschungsanstalt für Versuchstierzucht, Himberg, Austria) were used. Groups of 4–6 animals received single i.v. injections of test drugs in a volume of 1·3 mL kg^{-1}. Urapidil was dissolved in 0·9% NaCl containing a few drops of 1 M HCl, and the resulting solution was neutralized with 1 M phosphate buffer (saline). Prazosin was dissolved in hot saline containing dimethyl sulphoxide (20% v/v). Idazoxan and haloperidol were dissolved in saline. Controls received injections of appropriate vehicles. At various times after the injections (indicated in the Figures and Tables) the animals were decapitated, the brains quickly removed and immediately frozen on dry ice. With the atlas of König & Klippel (1963) as a guide: the nucleus accumbens was dissected from a coronal slice between A 10·0 to 8·5, and the corpus striatum from a slice between A 8·5 and 7·0. The hypothalamus was prepared as described by Glowinski & Iversen (1966). All tissues were weighed and kept at −90°C until biochemical analysis (not longer than 4 days). The wet weight of the tissue samples (mg; means ± s.e.) was 8·4 ± 0·3 (n = 32), 11·9 ± 0·39 (n = 21), and 51·6 ± 0·98 (n = 32) for nucleus accumbens, corpus striatum, and hypothalamus, respectively. For the determination of dopamine (DA) and 3,4-dihydroxyphenylacetic acid (DOPAC) samples of nucleus accumbens or corpus striatum were homogenized by sonication in 0·3 mL perchloric acid (0·1 M; Branson Sonifier B 15; Branson Sonic Power, Danbury, Connecticut, USA), centrifuged at 12 000 *g* and aliquots of the resulting supernatants directly applied to high pressure liquid chromatography with electrochemical detection (HPLC-EC) according to the method of Sperk (1982).

For determination of noradrenaline (NA) and 3-methoxy-4-hydroxy-phenylglycol (MHPG), tissues were homogenized in 0·4 mL 0·12 M sodium acetate, pH 5·0. The homogenates were then centrifuged at 12 000 *g* and an aliquot of 0·05 mL was taken for the assay of noradrenaline (HPLC-EC according to Felice et al 1978). To hydrolyse conjugated MHPG, 0·2 mL of the supernatants were incubated with 1 mg sulphatase and 10 pmol internal standard (3-ethoxy-4-hydroxyphenylglycol, EHPG) in a final volume of 0·5 mL for 16 h at 37°C (all reagents in 0·12 M sodium acetate, pH 5·0). Under these conditions hydrolysis was quantitative, which was routinely checked in parallel incubations containing sulphatase and MHPG-sulphate. The samples were subsequently cooled on ice, centrifuged at 12 000 *g*, and the supernatants applied to Sep-Pak C18 cartridges. After a wash with 0·5 mL H_2O the samples were eluted with 1·5 mL 80% acetonitrile, dried in a Speed Vac concentrator (SVC 100H, Savant Instruments Inc., Hicksville, New York, USA) and reconstituted in 0·3 mL H_2O. Aliquots of 0·1 mL were injected into the liquid chromatography system. The overall recovery of this procedure was 80–90% as judged by the recovery of the internal standard, EHPG, or of known amounts of 3-methoxy-4-hydroxyphenylglycol-4-sulphate added to "split" samples.

The HPLC-system consisted of a M510 solvent delivery pump (Waters, Milford, Massachusetts, USA), a model 7125 Rheodyne-injector (Rheodyne, Cotati, California, USA) and a μBondapak C18-reversed phase column (Waters). An LC-4A amperometric detector and a TL-5 glassy carbon electrode from Bioanalytical Systems (West Lafayette, Indiana, USA) were used. The mobile phase for MHPG-determinations was 0·1 M NaH_2PO_4 (pH adjusted to 3·9) containing 0·1 mM EDTA and 5% v/v methanol delivered at 2 mL min^{-1}. The retention time for MHPG was 7 min under these conditions. The sensitivity was 120 pA $pmol^{-1}$ at an oxidation potential of 0·88 V. The standard curve was linear in the range from 0·5 pmol to 10 pmol.

Measurement of systolic blood pressure

Groups of 4 rats received single i.v. injections of urapidil (10 or 30 mg kg^{-1}), prazosin (2·5 mg kg^{-1}), idazoxan (10 mg kg^{-1}), haloperidol (0·1 mg kg^{-1}), or saline in a volume of 1·3 mL kg^{-1}. Systolic blood pressure was recorded immediately before and one hour after the injection of drugs or saline using the tail plethysmographic method (Gerold & Tschirky 1968).

Experiments on stimulation-evoked release of [^{3}H] noradrenaline and [^{3}H] dopamine

Untreated rats (see above) were decapitated, the brains quickly removed, chilled on ice, and slices of nucleus anterior hypothalami (NAH) or nucleus accumbens (coordinates A6360–A5340 and A10050–A9410, respectively, in the atlas of König & Klippel 1963) were prepared from 0·4 mm coronal slices of the whole brain using small scissors or a punch needle (1·5 mm diameter). The tissue samples were then incubated with 0·125 μmol L^{-1} [^{3}H]NA [40 Ci $mmol^{-1}$; NAH] or 0·04 μmol L^{-1} [^{3}H]DA (40 Ci $mmol^{-1}$; nucleus accumbens) for 30 min at 37°C, transferred to superfusion chambers (one slice per chamber), and superfused at 25°C with physiological salt solution (0·6 mL min^{-1}; for details see Cichini et al, 1987) containing 3 μmol L^{-1} desipramine ([^{3}H]NA experiments) or 10 μmol L^{-1} nomifensine ([^{3}HDA] experiments). After a 60 min washout period to stabilize efflux of radioactivity, the experiments were started at zero time with the collection of 5 min fractions. Two min periods of electrical field stimulation were applied at 15 min (S_1) and 85 min (S_2) after start. Stimuli were delivered from a Stimulator T (Hugo Sachs Electronics, Hugstetten, FRG): monophasic rectangular pulses, pulse width 2 ms, frequency 3 Hz with a current strength of 12 mA ([^{3}H]NA experiments) or 0·3 Hz with a current strength of 14 mA ([^{3}H]DA experiments). Test drugs were added 20 min before S_2. Outflow of tritium per fraction was expressed as percentage of radioactivity in the slice at the onset of the respective 5 min collection period. Stimulation-evoked overflow was calculated as the difference between total outflow during and after stimulation, and estimated basal outflow, which was assumed to decline linearly (Reichenbacher et al 1982); it was expressed as the percentage of radioactivity present in the slice at the onset of stimulation ($\%S_1$, $\%S_2$). Drug effects were expressed using the S_2/S_1 ratio ($\%S_2/\%S_1$). Effects of drugs on basal efflux of tritium were estimated by calculating the ratio between the value of fractional outflow during the 5 min period immediately preceding S_2 and the 5 min collection period preceding S_1 (L_2/L_1).

Statistics

All data are given as arithmetic means ± s.e. (n); n = number of observations. Student's two tailed *t*-test was used for comparison of mean values of amines and metabolites. The *t*-test for paired samples was used for comparison of blood pressure values before and after the administration of drugs. The Mann Whitney U-test was employed for calculation of statistical significances regarding S_2/S_1 ratios as well as ratios of MHPG/NA and DOPAC/DA.

Drugs and reagents used

1-[7,8-^{3}H] noradrenaline, [7,8-^{3}H]dopamine (Amersham, UK); sulphatase (from Helix pomatia, type H-5), noradrenaline (NA), dopamine (DA), 3-methoxy-4-hydroxyphenylglycol (MHPG), and 3,4-dihydroxyphenylacetic acid (DOPAC), Sigma (Munich, FRG). The following compounds were kindly donated: 3-ethoxy-4-hydroxy-phenylglycol (EHPG; Dr J. Schipper, Duphar, The Netherlands), 3-methoxy-4-hydroxyphenylglycol-4-sulphate potassium salt (Hoffmann-La Roche, Basel, Switzerland), idazoxan (Reckitt and Colman, Hull, UK), haloperidol (Janssen, Beerse, Belgium), urapidil (Byk Gulden, Konstanze, FRG).

Results

Experiments on the effect of urapidil on catecholamine turnover

Time courses of the effects of urapidil (30 mg kg^{-1} i.v.) on the ratios of MHPG/NA and DOPAC/DA are shown in Fig. 1.

The ratio of MHPG/NA in the hypothalamus increased by about 60% with a maximum at 1 h after the injection, whereas the ratio of DOPAC/DA in the nucleus accumbens increased by about 38% with its maximum at 30 min. These elevations in metabolite/amine ratios were mainly due to an increase in metabolite levels. They diminished in the course

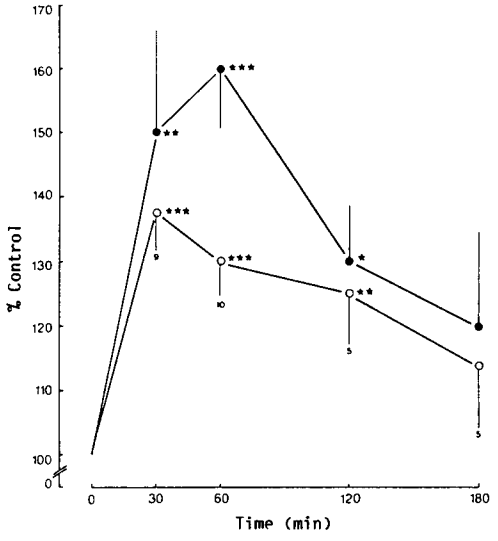

FIG. 1. Time courses of the effects of urapidil (30 mg kg^{-1} i.v.) on the ratios of MHPG/NA and of DOPAC/DA in rat hypothalamus and nucleus accumbens, respectively. Values are presented as percentages of control ratios at the respective time points. Means ± s.e. are indicated. Numbers next to symbols refer to numbers of observations. For absolute values of monoamines, metabolites and corresponding ratios of vehicle-treated control animals see Table 1. ●——● MHPG/NA; ○——○ DOPAC/DA; *$P<0.05$, **$P<0.01$, ***$P<0.001$ vs corresponding control.

of the following 2 h, and 3 h after the injection of urapidil no significant differences were observed between treated animals and controls.

Levels of MHPG and NA in the hypothalamus, and DOPAC and DA in the nucleus accumbens and corpus striatum of control animals (treated with vehicle for urapidil) as well as the corresponding metabolite/amine ratios are presented in Table 1.

When dose-response curves for the effects of urapidil, idazoxan, prazosin, and haloperidol on the ratio of MHPG/NA in the hypothalamus were generated (Fig. 2), dose-dependent increases were observed with urapidil and idazoxan. In contrast, haloperidol had no effect, and prazosin did not change the ratio up to a dose of 2·5 mg kg^{-1} i.v. At a dose of 5 mg kg^{-1} prazosin caused a significant elevation in the ratio of MHPG/NA. The ratio of DOPAC/DA in the nucleus accumbens was augmented by urapidil and, to a much higher degree, by haloperidol. Idazoxan and prazosin were without effect in this respect (Fig. 2). In addition, a dose-dependent increase by urapidil of the ratio of DOPAC/DA was observed in the corpus striatum (Fig. 2).

Table 1. Control values for NA, MHPG, MHPG/NA in hypothalamus, and DA, DOPAC, DOPAC/DA in nucleus accumbens and corpus striatum of vehicle-treated rats. Animals were injected with 1·3 mL kg^{-1} urapidil-vehicle and killed 60 min later. Levels of amines and metabolites are given as pmol kg^{-1} wet weight (means ± s.e.).

	NA	MHPG	MHPG/NA	n
Hypothalamus	7·2 ± 0·34	1·4 ± 0·07	0·20 ± 0·01	24
	DA	Dopac	Dopac/DA	n
Nucleus accumbens	54·4 ± 2·40	8·3 ± 0·47	0·15 ± 0·01	22
Corpus striatum	58·9 ± 2·29	10·1 ± 0·56	0·17 ± 0·01	14

Effects of drugs on systolic blood pressure

Mean systolic blood pressure before the administration of drugs was 107 ± 2·3 mm Hg (n = 24). The injection of saline (1·3 mL kg^{-1} i.v.) did not affect systolic blood pressure. Urapidil at doses of 10 and 30 mg kg^{-1} lowered systolic blood pressure by 22 and 39%, respectively ($P<0.01$ vs respective controls, n = 4 per dose). Prazosin (2·5 mg kg^{-1}) led to a decrease of 36%, idazoxan to a decrease of 14%, and haloperidol to a decrease of 21% (all values significantly different from respective controls, $P<0.01$, n = 4 per group).

Experiments of stimulus-evoked release of tritium from brain slices

The results are summarized in Table 2. Urapidil (1 μmol L^{-1}) increased stimulus-evoked overflow of radioactivity from slices of NAH preincubated with [^{3}H]NA, whereas the α_1-adrenoceptor blocker prazosin (0·1 μmol L^{-1}) and the dopamine D_2-receptor blocker haloperidol (0·1 μmol L^{-1}) had no effects. The α_2-adrenoceptor blocker idazoxan (0·1 μmol L^{-1}) strongly increased the electrically induced release of tritium from NAH-slices.

Urapidil (1 μmol L^{-1}) also facilitated the stimulated overflow of tritium from nucleus accumbens slices labelled with [^{3}H]DA. Prazosin and idazoxan had no effect in these experiments, whereas haloperidol exerted a pronounced facilitatory action.

At a concentration of 10 μmol L^{-1}, urapidil markedly increased the basal efflux of radioactivity from brain slices incubated with [^{3}H]NA or [^{3}H]DA. The effects of this concentration of the drug on electrically stimulated overflow of tritium were therefore not evaluated.

Discussion

In the present experiments the effects of the antihypertensive drug urapidil on central NA and DA containing neurons were examined by assessing metabolite/monoamine ratios in different areas of the brain. MHPG (in the rat, predominantly in its conjugated form) is the major metabolite of central NA metabolism (Schanberg et al 1968). It has been suggested as good correlate of noradrenergic activity (Meek & Neff 1973), although the interpretation of a drug-induced change in the molar ratio of MHPG to NA as change in noradrenergic activity is based on the assumption that the metabolic pathways and metabolite elimination are not changed by the experimental condition (Weiner 1974). With these limitations in mind, the dose-dependent increase in the ratio of MHPG/NA in the hypothalamus after i.v. administration of urapidil may be regarded as consequence of a blockade of central α-adrenoceptors (for binding data see Kellar et al 1984). Both α_2- and α_1-adrenoceptor antagonists have been shown to accelerate NA turnover in the brain (Andén et al 1978). A dose-dependent effect of the selective α_2-adrenoceptor antagonist idazoxan was demonstrated in the present experiments. In contrast, the selective α_1-adrenoceptor antagonist prazosin did not increase the ratio of MHPG/NA up to a dose of 2·5 mg kg^{-1}. Since this dose of prazosin caused a similar decrease in systolic blood pressure as 30 mg kg^{-1} urapidil, it can be concluded that the increased NA utilization after urapidil did not merely occur as a consequence of a fall in blood pressure. The high dose of 5 mg kg^{-1} prazosin

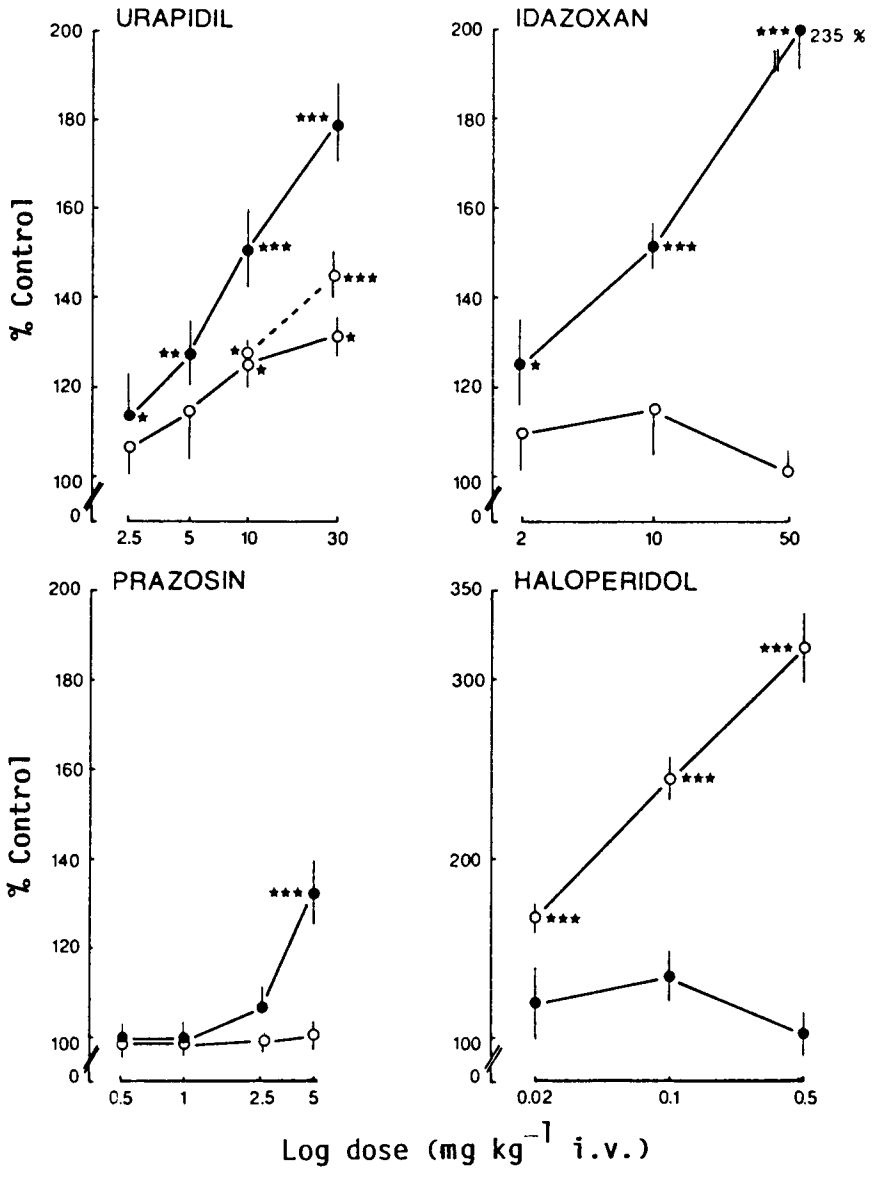

FIG. 2. Dose-response curves for the effects of urapidil, prazosin, idazoxan, and haloperidol on the ratios of MHPG/NA and DOPAC/DA in rat hypothalamus and nucleus accumbens, respectively. In addition, the effect of urapidil on the ratio of DOPAC/DA in the corpus striatum is shown. The animals were killed 60 min after i.v. administration of test drugs. Values are presented as percentages of corresponding control ratios. Means ± s.e. of 4–8 observations are indicated. For absolute values of monoamines, metabolites and corresponding ratios of vehicle-treated control animals see Table 1. ●——● MHPG/NA; ○——○ DOPAC/DA nucleus accumbens; ○ - - - ○ DOPAC/DA corpus striatum; * $P<0.05$, ** $P<0.01$, *** $P<0.001$ vs corresponding control.

Table 2. Effects of drugs on the evoked overflow of tritium from slices of nucleus anterior hypothalami (NAH) preincubated with [^{3}H]noradrenaline or nucleus accumbens preincubated with [^{3}H]dopamine. After incubation, the slices were superfused at 25°C and stimulated for 2 min after 15 (S_1) and 85 min (S_2) of superfusion; desipramine 3 μmol L^{-1} ([^{3}H]noradrenaline experiments) or nomifensine 10 μmol L^{-1} ([^{3}H]dopamine experiments) were present throughout superfusion. Test drugs were added 20 min before S_2. Effects on evoked overflow of tritium are expressed as S_2/S_1 ratio and effects on basal efflux as L_2/L_1 ratio (see methods). Means ± s.e. are given. The percentages of tritium released by S_1 were: [^{3}H]noradrenaline experiments: 1·54 ± 0·08 (n = 40); [^{3}H]dopamine experiments: 0·97 ± 0·06 (n = 37). n.e. = not evaluated, because drug had marked effect on basal efflux (see corresponding L_2/L_1 ratios). *$P<0.05$, ***$P<0.001$ vs drug-free control.

	[^{3}H]Noradrenaline release			[^{3}H]Dopamine release		
Drug added 20 min before S_2	S_2/S_1	L_2/L_1	n	S_2/S_1	L_2/L_1	n
None	0·91 ± 0·03	0·87 ± 0·03	14	1·07 ± 0·05	0·87 ± 0·04	16
Urapidil (1 μmol L^{-1})	1·20 ± 0·04***	0·89 ± 0·03	5	1·30 ± 0·10*	1·00 ± 0·05	6
Urapidil (10 μmol L^{-1})	n.e.	1·37 ± 0·05***	10	n.e.	1·40 ± 0·05***	3
Prazosin (0·1 μmol L^{-1})	0·99 ± 0·02	0·94 ± 0·01	4	1·04 ± 0·10	0·90 ± 0·03	4
Idazoxan (0·1 μmol L^{-1})	2·55 ± 0·14***	0·85 ± 0·04	3	1·17 ± 0·06	0·81 ± 0·02	4
Haloperidol (0·1 μmol L^{-1})	0·91 ± 0·06	0·89 ± 0·01	4	2·22 ± 0·22***	0·91 ± 0·04	4

significantly increased the MHPG/NA ratio, which confirms findings of Andén et al (1978) and Fuller et al (1978) who report an acceleration of NA turnover after similar doses of prazosin.

The results of the in-vitro experiments on stimulus-evoked [^{3}H]NA release point to a blockade by urapidil of prejunctional α_2-adrenoceptors. The results are in accordance with a recent report (Jackisch et al 1987), in which a dose-dependent facilitation by urapidil of electrically evoked [^{3}H]NA release from rabbit cortex slices and an antagonism to the effect of clonidine was observed. Thus, it is conceivable to assume that urapidil exerts its effect on NA-turnover, at least in part, via prejunctional α_2-adrenoceptors.

Dopaminergic neurotransmission in the brain is also affected by urapidil. An increase in the ratio of DOPAC/DA was evident after administration of doses above 5 mg kg^{-1}. Although the use of the ratio of DOPAC/DA as a measure for in-vivo turnover of DA meets similar limitations in interpretation as already discussed with regard to the ratio of MHPG/NA (Westerink 1985), the observed increase points to a modest blocking activity of urapidil at DA receptors (Kellar et al 1984; Pugsley & Myers 1986). Furthermore, the facilitation by urapidil of electrically evoked release of tritium from nucleus accumbens slices incubated with [^{3}H]DA support the assumption that urapidil blocks presynaptic dopamine D_2-receptors. The finding is in line with results of Jackisch et al (1987) on [^{3}H]DA release from caudate slices of the rabbit. The effect of urapidil on DA turnover was most likely not brought about by the α-adrenoceptor blocking properties of the drug, since both idazoxan and prazosin did not exert a significant effect on levels of DOPAC or DA or on stimulus-induced release of [^{3}H]DA. There have been reports of enhanced DOPAC- or homovanillic acid levels in the central nervous system after injection of α-adrenoceptor antagonists, but these increases were observed in NA-rich regions (Andén & Grabowska-Andén 1983) or cerebrospinal fluid (Scheinin 1986) and are interpreted as consequence of increased noradrenergic activity (Scatton et al 1984). It is also important to note that the dopamine D_2-receptor antagonist haloperidol strongly increased the ratio of DOPAC/DA and electrically stimulated release of [^{3}H]DA but did not change the ratio of MHPG/NA or release of [^{3}H]NA. Taken together, the results indicate that the tested α-adrenoceptor- or dopamine D_2-receptor antagonists selectively influenced noradrenergic or dopaminergic systems in the respective brain areas, and that the dual action of urapidil is most likely due to separate effects on each system. Furthermore, the present data on catecholamine turnover are in marked agreement with the results of Pugsley & Myers (1986) who measured the effect of urapidil on DOPA accumulation in the striatum and the brain stem of rats after administration of a DOPA-decarboxylase inhibitor. The observed percentages of increase in DOPA accumulation were virtually identical with the percentages of changes of molar metabolite/amine ratios obtained in the present study.

Although α- and dopamine D_2-receptor blocking qualities of urapidil can be demonstrated in-vivo and in-vitro, it is not clear whether or to which extent they are responsible for the hypotensive action of this compound. For instance, van Zwieten et al (1985) have shown in anaesthetized cats that the hypotensive action of urapidil following an injection into the vertebral artery is not compromised by yohimbine or sulpiride given via the same route. On the other hand, Shebuski & Zimmerman (1984) suggest that the inhibitory effect of urapidil on reflex tachycardia may be dissociated from its blood pressure-lowering action. The doses that caused significant elevations of metabolite/monoamine ratios in the present study are in the upper range of those producing a decrease in sympathetic nervous activity (Sanders & Jurna 1985) or a suppression of reflex tachycardia elicited by bradykinin (Shebuski & Zimmerman 1984).

In conclusion, the present data describe a profile of action of urapidil as α_2- and weak dopamine D_2-receptor antagonist in the brain. However, it is not likely that the central hypotensive effect of urapidil can be fully explained on the basis of these properties.

Recent studies reporting a high affinity of urapidil for 5-HT1A binding sites (Fozard & Mir 1987; Groß et al 1987), and evidence that central 5-HTIA-receptors are involved in blood pressure regulation (Fozard et al 1987), may point to a blood pressure-lowering action of this compound through central 5-HT mechanisms.

Acknowledgements

The expert technical assistance of E. Dorn and H. Drobny is gratefully acknowledged. We thank Dr N. Kolassa (Byk Gulden, Konstanz, FRG) for his valuable discussion of the manuscript. We are indebted to E. Kotai for preparing the graphs and to L. Pirker for secreterial help. This work was supported by the "Anton-Dreher Gedächtnisschenkung für Medizinische Forschung" (project 97/87).

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