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Pyridazine Derivatives. XI: Antihypertensive Activity of 3-Hydrazinocycloheptyl[1,2-c]pyridazine and Its Hydrazone Derivatives

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Received August 7, 1991, from the *Department of Pharmacology and the [‡]Department of Organic Chemistry, Laboratory of Pharmaceutical Chemistry, University of Santiago de Compostela, 15706 Santiago de Compostela, Spain. Accepted for publication July 27, 1992.

Abstract □ 3-Hydrazinocycloheptyl[1,2-c]pyridazine (4) and its hydrazone derivatives 3-[N¹-(isopropylidene)]hydrazinocycloheptyl[1,2-c]pyridazine (5) and 3-[N¹-(isobutylidene)]hydrazinocycloheptyl[1,2-c]pyridazine (6) were prepared, and their activity against genetic, neurogenically-induced, and deoxycorticosterone acetate -NaCl-induced hypertension was found to be at least as great as that of hydralazine. The results of studying vasorelaxation of rat aorta by 4 and hydralazine suggest that both these compounds owe their antihypertensive activity to direct relaxation of vascular smooth muscle.

Hydrazinophthalazines were first synthesized by Gross et al.¹ in 1950 and are used clinically as antihypertensives, the most important being hydralazine and dihydralazine. Structure-activity studies have shown significant antihypertensive activity to be exhibited by a number of related hydrazine pyridazines, and this group of compounds continues to be the object of prospect for new drugs with greater activity and fewer side effects. For several years we have been working on the synthesis of modified hydrazino pyridazines, most of which have proved to have considerable antihypertensive activity.²

We now report the results of a detailed study of the antihypertensive activity of 3-hydrazinocycloheptyl[1,2-c]pyridazine (4) and its hydrazone derivatives, 3-[N¹-(isopropylidene)]hydrazinocycloheptyl[1,2-c]pyridazine (5) and 3-[N¹-(isobutylidene)]hydrazinocycloheptyl[1,2-c]pyridazine (6), together with a modified synthetic procedure.

Experimental Section

Chemistry—Melting points were determined with a Gallenkamp melting point apparatus and were uncorrected. IR spectra were recorded with a Perkin-Elmer 2640 FT (Fourier transform) spectrophotometer. ¹H NMR spectra were recorded with a Bruker WM 250 spectrophotometer using tetramethylsilane as internal standard. Microanalysis was performed with a Perkin-Elmer 240 B instrument in the Microanalysis Service of the University of Santiago de Compostela; results were within ±0.4% of the theoretical values.

3-Chlorocycloheptyl[1,2-c]pyridazine (3)—Cycloheptyl[1,2-c]3(2H)pyridazinone (2; 2 g, 0.0066 mol) was dissolved in tetrachloroethane (50 mL) by heating. Chlorosulphonyl isocyanate (0.16 g, 0.0066 mol) in tetrachloroethane (15 mL) was added, and the resulting solution was warmed at 60 °C with stirring for 6 h. The reaction mixture was then left to stand overnight at room temperature, the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel, with chloroform-methanol as eluant, to afford 0.44 g (40%) of a yellow liquid that was used in the next stage without further purification; IR (NaCl): 3100–2850 (NH); 1600 (C = C arom); 750–640 cm⁻¹; no carbonyl bands were present.

3-Hydrazinocycloheptyl[1,2-c]pyridazine (4)—A suspension of 2 g (0.012 mol) of 3 in 20 mL (0.41 mol) of 98% hydrazine hydrate was refluxed for 2 h and then cooled to obtain a solid that on recrystall-

ization from ethanol afforded 1.32 g of 4 in a yield of 89% with a mp of 137–139 °C; IR (KBr): 3200 (NH), 1640–1600 (C = N, C = C aromatic) cm⁻¹; ¹H NMR (CDCl₃): δ (ppm) 6.71 (s, 1H, pyridazine); 3.14 (br s, 3H, NH-NH₂); 2.99 (m, 2H, -CH₂-CH₂-CH₂-).

Anal.—Calcd for C₈H₁₂N₄ (164.2): C, 58.5; H, 7.3; N, 34.1. Found: C, 58.6; H, 7.16; N, 34.0.

Pharmacology—Antihypertensive Activity—Antihypertensive activity was determined indirectly (tail-cuff methods) by measuring systolic arterial pressure (SAP) in the caudal artery of unanesthetized rats³ that were previously accustomed to the procedures (restraint in containers, heating to 39 °C) necessary for the measurement of SAP to avoid false values due to stress.

Activity against genetically inherent hypertension was evaluated with spontaneously hypertensive rats (SHR)⁴ weighing 275 ± 25 g (from Ifa-Credo), which had basal SAP values of 180 mmHg or more. Activity against neurogenically-induced hypertension was determined in male Sprague-Dawley rats (NHR), weighing 325 ± 25 g and manipulated as per Krieger.⁵ Activity against deoxycorticosterone acetate NaCl (DOCA-NaCl)-induced hypertension was evaluated as per Stanton and White⁶ with female Sprague-Dawley rats (DOCA-NaCl rats) weighing 95 ± 15 g at the beginning of the experiment.

Lots of six (SHR) or five (NHR and DOCA-NaCl) rats were starved for 24 h. Basal SAP and heart rates were determined prior to oral administration (in 1 mL/100 g body weight) of hydralazine (5, 7.5, or 10 mg/kg), new compounds under test (5, 7.5, or 10 for SHR; or 1, 2.5, or 5 mg/kg for NHR and DOCA-NaCl rats), or deionized water for control rats. Effects on pressure and heart rate were recorded 1 h after administration. SAP was measured with a Narco Bio-Systems PE300 programmed electrophysiomonometer connected to a Narco Bio-Systems pneumatic pulse transducer and a Scientific Instrument Centre model 2125 physiopolygraph. Heart rate was obtained from the recorded SAP wave. The rats were warmed for 15 min at 39 ± 1 °C prior to measurements.

Isolated Rat Thoracic Aorta—Male Sprague-Dawley rats weighing 250–350 g were killed by a blow on the head. The thoracic aorta was rapidly removed and stripped of endothelium by rubbing the intimal surface with a cotton bud. A simple hematoxylin-eosin technique was used to verify the absence of endothelial cells and the integrity of underlying smooth muscle. The aorta was cut in cylindrical segments (4 mm in length) that were immediately transferred to an organ bath with a Krebs solution containing (mM) NaCl (119), KCl (4.7), MgSO₄ · 7H₂O (1.2), CaCl₂ · 2H₂O (2.5), KH₂PO₄ (1.2), NaHCO₃ (25), glucose (11), ascorbic acid (0.567), and EDTA (0.03) thermoregulated at 37 °C and bubbled with 95% O₂ + 5% CO₂. Calcium-free solution was prepared in the same way but omitting CaCl₂.

The aorta segments were set up in the bath by inserting two stainless steel pins through the lumen, one pin being fixed to the organ bath and the other to a force-displacement transducer for recording of isometric tension with a computerized Celaster IOS1 system.

After an equilibration period of at least 1 h under 2 g of resting tension, isometric contractions induced by 10 μM noradrenaline (NA) or 60 mM K⁺ (without keeping osmolality constant) were recorded for 15 min. Cumulative doses of hydralazine or 4 were then added, and the effect of each was observed for 10 min.

To measure contractions in a calcium-free medium, artery preparations were equilibrated for 60 min in normal Krebs solution and then washed three times over a 20-min period with a calcium-free

solution containing 0.5 mM ethylene glycol-bis(β -aminoethyl ether)- N,N,N',N' -tetraacetic acid (EGTA) before addition of NA. To study the effects of hydralazine and 4, the preparations were further washed in normal Krebs solution for 60 min (to fill the Ca^{2+} stores depleted by the first contraction), and preincubated for a further 20 min in calcium-free solution before a suitable concentration of hydralazine or 4 was added, followed 10 min later by NA. Other aorta rings were simultaneously subjected to the same procedure, but omitting 4 and hydralazine.

^{45}Ca Influx—Aortic rings weighing 5–9 mg were equilibrated for at least 60 min in physiological solution (composition (mM): NaCl (139), KCl (5), MgCl_2 (1), CaCl_2 (1.5), N -2-hydroxyethylpiperazine- N' -2-ethanesulfonic acid (HEPES) (5) glucose (10)) maintained at 37°C and aerated with 100% O_2 . The rings were then incubated for 5 min in a medium containing $0.6 \mu\text{Ci} \cdot \text{mL}^{-1}$ ^{45}Ca (New England Nuclear, Madrid, Spain; specific activity $35 \text{ mCi} \cdot \text{mg}^{-1}$) with or without $10 \mu\text{M}$ NA or 60 mM K^+ . To investigate the effects of hydralazine and 4 on the uptake, these agents were added to the equilibration medium 20 min before incubation and also to the incubation medium. After incubation, the rings were washed for 45 min in 500 mL of an ice-cold calcium-free physiological solution of pH 7.4 containing 2 mM EGTA, which was bubbled with 100% O_2 to remove extracellular Ca^{2+} from the tissue. The rings were then blotted, weighed, and digested in 1 mL H_2O_2 (110 volumes) at 115°C for 90 min. After cooling, 5 mL of Ready-Safe Beckman were added and the radioactivity of the samples was measured in a liquid scintillation counter (Beckman LS 3801).

Expression and Statistical Analysis of Results—Unless otherwise specified, results shown in the text and figures are means \pm standard errors of the mean (SEM). The statistical significance of differences between means was estimated by the Student's two-tailed t test for paired or unpaired data.

Antihypertensive activity and effects on heart rate were quantified as percentage change with respect to basal values.² The ED_{50} (the dosage necessary to produce a 30% fall in SAP or a 30% rise in heart rate) was calculated from the equations of straight lines fitted to the response-log dosage data.

The ^{45}Ca uptake was calculated as follows: ^{45}Ca uptake (nmol $^{45}\text{Ca}/\text{kg}$ wet tissue) = [counts per min in tissue/wet tissue weight (kg)] \times [nmol ^{45}Ca in 1 L solution/counts per min in 1 L of solution]. To avoid inaccuracy in the calculation of ^{45}Ca uptake, the 1.5 mM Ca^{2+} present in physiological solution was not included in the "nmol ^{45}Ca in 1 L of solution" factor of this expression.

The 50% inhibition concentrations (IC_{50}) of hydralazine and 4 were calculated from their cumulative dose-response curves.

Drugs and Chemicals—The following drugs were used: (-)-noradrenaline bitartrate, atropine sulfate, and DOCA (Sigma, Madrid, Spain), hydralazine hydrochloride (Ciba Geigy, Barcelona, Spain), and compounds 4, 5, and 6. Hydralazine, 4, 5, 6, and atropine solutions were dissolved in deionized water immediately before use. Microsuspension of DOCA (1%) was prepared in a 0.25% polysorbate 80 (Tween 80), 0.125% carboxymethyl cellulose, and 0.9% of NaCl. NA was prepared daily with deionized water from a 100 mM stock solution kept at -20°C ; 0.2% sodium bisulfite was added to prevent oxidation.

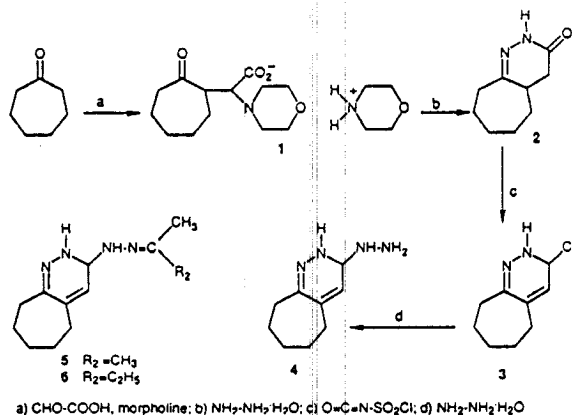
The chemicals used in the preparation of the physiological solutions were of analytical grade.

Results and Discussion

Chemistry—Compound 4 was previously prepared⁷ by a general four-step procedure: (1) synthesis of the morpholinium salt of cycloheptanone, 1; (2) reaction with hydrazine hydrate to give cycloheptyl[1,2- c]3(2H) pyridazinone, 2; (3) chlorination with phosphorous oxychloride; and (4) introduction of the hydrazino group. The limiting step of this procedure is step 3, which has yields of 20% or less. We have now found that these yields can be increased to 40–50% with the recently described chlorinating agent⁸ chlorosulphonyl isocyanate (Scheme 1).

The hydrazones 3-[N^1 -(isopropylidene)]hydrazinocyclohexyl[1,2- c]pyridazine 5 and 3-[N^1 -(isobutylidene)]hydrazinocycloheptyl[1,2- c]pyridazine 6 were prepared from 4 as described by Ravina and Estevez.⁹

Pharmacology—Antihypertensive Effects—Antihypertensive activity was evaluated for hypertension of three different origins. The new compounds tested clearly reduced SAP



Scheme 1

(Table I) and increased heart rate (Table II) in SHR 1 h after administration. At a dosage level of 5 mg/kg, the percentage reductions in SAP induced by 4 ($40.24 \pm 1.14\%$) and 6 ($38.29 \pm 1.52\%$) were significantly greater ($p < 0.05$) than that induced by hydralazine ($33.33 \pm 1.14\%$); at other dosage levels, the differences were not statistically significant and neither were the differences in percentage increase in heart rate (at any dosage level). As shown in Tables I and II, the new compounds were clearly more effective than hydralazine in reducing both neurogenically- and DOCA-NaCl-induced hypertension 1 h after administration. There were no significant variations in either SAP or heart rate following control administration of deionized water.

Vasorelaxation in Normal Krebs Solution—NA ($10 \mu\text{M}$) and high potassium concentration (60 mM) produced sustained contractions of 4137 ± 402 and $3239 \pm 304 \text{ mg}$ ($n = 10$), respectively, in isolated rat aorta arterial rings. These contractions were considered the maximum response (100%).

Hydralazine (0.1 – 5 mM) and 4 dose dependently and non-specifically inhibited the contractions induced by NA ($\text{IC}_{50} = 0.68 \pm 0.019$ and $2.1 \pm 0.16 \text{ mM}$, respectively) and by K^+ ($\text{IC}_{50} = 0.6 \pm 0.064$ and $4.2 \pm 0.28 \text{ mM}$, respectively; Figure 1). For neither hydralazine nor 4 was there any significant difference between the IC_{50} values obtained with K^+ and NA ($n = 5$, $p > 0.05$; Figure 2).

Vasorelaxation in Calcium-Free Krebs Solution—NA ($10 \mu\text{M}$) produced its characteristic two-component contraction; that is, an initial transient (fast component) tension of $1125 \pm 51 \text{ mg}$ ($n = 10$) relaxing to a sustained (slow component) tension of $270 \pm 24 \text{ mg}$. Both phases were strongly inhibited by 1 mM hydralazine, which reduced the transient tension to $95.6 \pm 8 \text{ mg}$ and the sustained tension to $40 \pm 5 \text{ mg}$ ($n = 5$, $p < 0.01$), and by 4, which reduced the transient tension to $227 \pm 16 \text{ mg}$ and the sustained tension to $91 \pm 9 \text{ mg}$ ($n = 5$, $p < 0.01$).

^{45}Ca Uptake—Calcium uptake by the rat aorta segments in the absence of other agents (basal uptake) was $9.01 \pm 0.21 \text{ nmol} \cdot \text{kg}^{-1}$ ($n = 10$). The addition of 4 or hydralazine (1 mM) did not affect the uptake significantly (tissue ^{45}Ca contents

Table I—Effects on SAP

Compound	ED_{50} (mg/kg) in:		
	SHR	NHR	DOCA-NaCl Rats
Hydralazine	4.34	4.34	>5
4	2.50	1.58	1.29
5	3.17	1.63	1.87
6	3.18	1.76	1.67

8.9 ± 0.23 and 8.7 ± 0.32 nmol \cdot kg $^{-1}$, respectively; $n = 5$, $p > 0.05$).

NA and high K^+ concentration considerably increased basal ^{45}Ca uptake (tissue ^{45}Ca content = 13.12 ± 0.74 nmol \cdot kg $^{-1}$ with NA and 15.28 ± 0.68 nmol \cdot kg $^{-1}$ with 60 mM K^+ ; $n = 10$, $p < 0.01$). Neither 4 nor hydralazine (1 mM)

Table II—Effects on Heart Rate

Compound	ED ₅₀ (mg/kg) in:		
	SHR	NHR	DOCA-NaCl Rats
Hydralazine	>5	— ^a	>10
4	>5	—	>5
5	4.87	—	3.58
6	4.53	—	>5

^a —, Not determined.

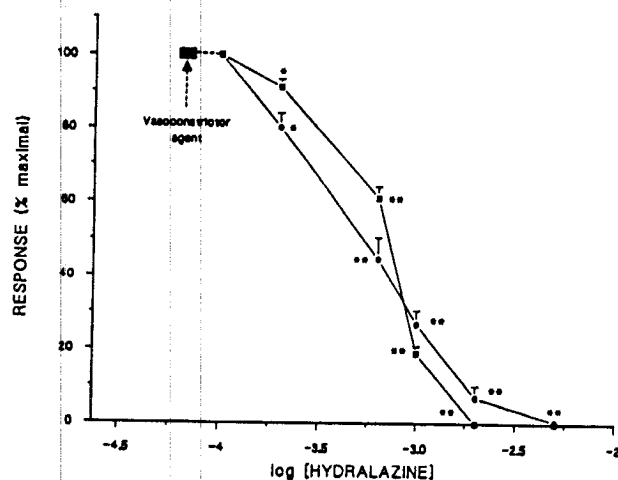


Figure 1—Effect of hydralazine (0.1–5 mM) on contractions of rat aorta rings without endothelium induced by K^+ (60 mM, ■) and NA (10 μM , ●). Each point represents the mean \pm standard error of the mean (SEM) of five experiments. Key: (*) $p < 0.05$; (**) $p < 0.01$ with respect to the maximum tension (100%). The IC_{50} values are 0.6 ± 0.064 and 0.68 ± 0.019 mM for NA and K^+ , respectively.

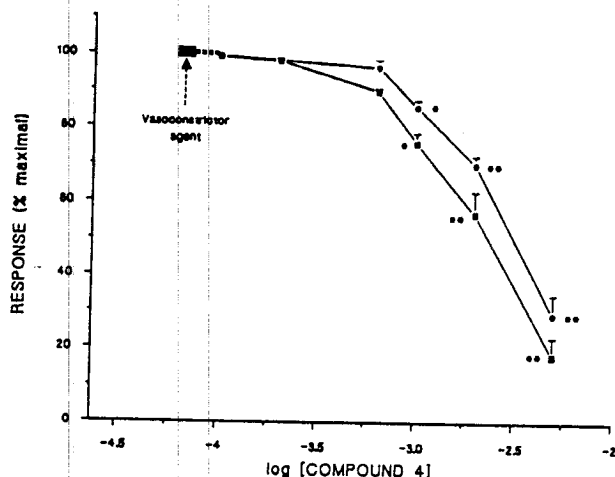


Figure 2—Effect of 4 (0.1–5 mM) on contractions of rubbed rat aorta rings induced by K^+ (60 mM, ■) and NA (10 μM , ●). Data are plotted as mean \pm SEM ($n = 5$). Key: (*) $p < 0.05$; (**) $p < 0.01$ with respect to the maximum tension (100%). The IC_{50} values are 4.2 ± 0.28 and 2.1 ± 0.16 mM for NA and K^+ , respectively.

significantly inhibited NA- and K^+ -induced ^{45}Ca uptake [tissue ^{45}Ca contents for 4, 12.32 ± 0.64 nmol \cdot kg $^{-1}$ with NA and 14.1 ± 0.59 nmol \cdot kg $^{-1}$ with 60 mM K^+ ($n = 5$, $p > 0.05$); for hydralazine, 11.31 ± 0.82 nmol \cdot kg $^{-1}$ with NA and 13.4 ± 0.72 nmol \cdot kg $^{-1}$ with 60 mM K^+ ($n = 5$, $p > 0.05$); Figure 3].

The above results show that the hypotensive activities of both hydralazine and the new compounds against all three types of hypertension considered are greater than those in normotensive rats.⁷ In general, the new compounds were at least as active as hydralazine.

The type of hypertension least affected by the new compounds was that of genetic origin, which is characterized, after onset, by normal cardiac output and increased peripheral resistance.¹⁰ It is the type that is most similar to human essential hypertension¹¹; its development and maintenance involve a number of mechanisms that are still not fully understood and that may make it more refractory to pharmacological treatment than the others. The new compounds were more active than hydralazine against both hypertension induced by manipulation of the sympathetic system (by denervation),⁵ and against hypertension induced by DOCA-NaCl, which may involve hyperactivity of the sympathetic system and/or retention of sodium and water due to electrolyte imbalance.¹²

The tachycardia that accompanies the fall in blood pressure induced by hydralazine in conscious normotensive rats has been reported as being a sympathetic reflex initiated by the detection of the drop in pressure by arterial baroreceptors,^{13,14} though the poor correlation between arterial pressure changes and heart rate in some studies has led to suggestions that a central mechanism^{15,16} or hemodynamic factors¹⁷ may be involved. The antihypertensive effects of the new compounds were accompanied by increased heart rate in both SHR and DOCA-NaCl rats, suggesting that the tachycardia was of reflex origin. However, in NHR, which lack the afferent pathways from arterial baroreceptors, a very wide range of heart rates was observed, with a less evident increase than for the other types of hypertension. This may have been because the cardiac stimulus was not totally reflex in nature, having a central contribution also, or because denervation was not complete, or because the fibers of vagus nerve baroreceptors took over control of the bulbar cardiovascular neurons.¹⁸

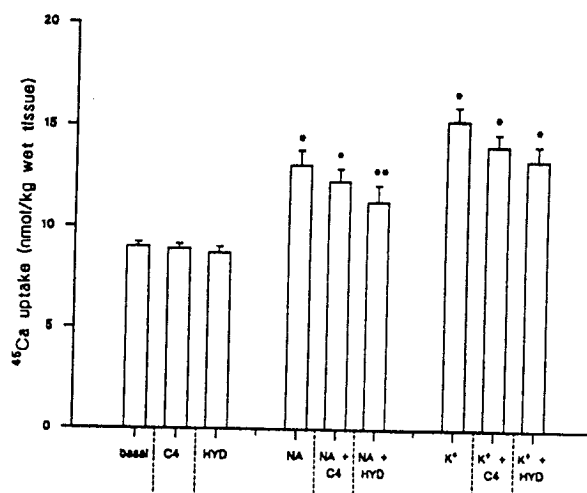


Figure 3—Effects of 4 (C4, 1 mM) and hydralazine (HYD, 1 mM) on ^{45}Ca uptake induced by K^+ (60 mM) and NA (10 μM) in rubbed rat aorta rings. Each bar shows the mean \pm SEM of five experiments. Key: (*) $p < 0.05$; (**) $p < 0.01$ with respect to the basal uptake.

The hydrazones of hydralazine are generally unstable, liberating parent drug into the blood. However, it is not yet clear whether the hypotensive effect of hydrazones of hydralazine should be attributed to their intrinsic activity or to back-conversion to the parent drug, hydralazine.^{19,20} The stability of hydrazones in vitro, even at pH 7.4, is not well understood (the literature contains conflicting results^{21,22}) and in the present study we present in vitro data for 4 (the most active) but not for 5 and 6.

Both hydralazine and the new compound, 4, relaxed NA- and K⁺-induced contractions of rat aorta dose dependently and nonspecifically. These in vitro results correlate well with the in vivo findings and, although the active dose of hydralazine in aorta is considerably greater than the concentration reached in plasma²³ (possibly because of biotransformation to active metabolites),²² they suggest that the hypotensive and antihypertensive action of this drug may be due basically to its effects on vascular smooth muscle cells.

High K⁺ concentrations cause strong contraction of rat aorta tissue by depolarizing smooth muscle cells and so increasing the influx of calcium through L voltage-dependent channels.²⁴ Also, activation of α_1 -adrenergic receptors in rat aorta by NA induces a two-phase process in which an initial, fast, transient contraction caused by the inositol 1,4,5-trisphosphate-mediated release of calcium from intracellular stores is followed by a slow, sustained contraction caused by Ca²⁺ influx through receptor-operated Ca²⁺ channels.²⁵ The results presented here show that hydralazine and 4 relax both K⁺- and NA-induced contractions with equal effectiveness. These results suggest that their primary action occurs within the cell (as has been reported for the action of hydralazine in human arteries²⁶), though there may also be a secondary, nonselective action on the cell membrane that would consist of blocking calcium influx through voltage-dependent and receptor-operated channels (in agreement with previous studies of the action of hydralazine in rat tail artery²⁷).

Hydralazine and 4 reduced neither basal uptake of ⁴⁵Ca nor uptake induced by NA and K⁺, contrary to the results obtained by McLean et al.²² and by Weiss et al.²⁸ for hydralazine using rabbit aorta. These results suggest that hydralazine and 4 do not, after all, block transmembrane calcium movements through leak, voltage-dependent, and receptor-operated calcium channels in rat aorta.

In the absence of external Ca²⁺, addition of NA is known to induce a fast, transient contraction attributed to release of stored Ca²⁺, followed by a smaller, slow, sustained contraction whose mechanism is not clear²⁹ (although it has been shown that diacylglycerol derived from phosphoinositide breakdown activates protein kinase C and that activation of protein kinase C induces a sustained contraction in the presence of a low concentration of Ca²⁺).³⁰ In this work, hydralazine and 4 inhibited both phases of the contraction elicited by NA in calcium-free solution, showing that they act intracellularly (as reported by Lipe and Moulds²⁶ for the action of hydralazine in human arteries and veins). This action may consist of inhibition of inositol 1,4,5-trisphosphate-induced release of intracellular calcium, of direct action on the contractile apparatus (as reported by Jacobs³¹ for the action of hydralazine in bovine carotid arteries), or of activation of intracellular storage of Ca²⁺. It is unlikely that this intracellular action is due to an increased rate of calcium loss (directly or indirectly via an increase in cyclic nucleotides), as hydralazine does not stimulate calcium-dependent ATPase in rat aorta.³²

Cromakalim and other potassium channel openers relax contractions induced in various vascular preparations by low (<25 mM) but not high (>30 mM) KCl concentrations. This is the behavior expected of agents that only open K⁺ channels.³³ However, hydralazine and 4 relax contractions in-

duced by high potassium concentrations (60 mM). Thus, hydralazine and 4 do not exert their vasorelaxant effects in rat aorta by opening membrane K⁺ channels.

In this study we have looked at the mechanism of the vasodilatory action of hydralazine in aorta without endothelium of normotensive rat. The effects described do not, therefore, involve the action of drugs on the vascular endothelium with consequent effects on the release of endothelial factors. Likewise, previous studies in our laboratory have indicated that hydralazine has identical effects on rat aorta with or without endothelium. These results, ruling out any effect of hydralazine on the release of endothelial factors, are in agreement with those of Bullock et al.³⁴ in rat aorta, but contradict those of Spokas et al.³⁵ in rabbit aorta. It is also of interest that some of the mechanisms susceptible to modulation by hydralazine and 4 are, however, altered in SHR smooth muscle.³⁶⁻³⁸ For this reason, and considering that our preliminary results indicate that SHR aorta rings have higher sensitivity to the vasodilatory effects of hydralazine, it may be of interest to study the vasodilatory action of hydralazine in aorta of genetically hypertensive rats.

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