J. Pharm. Pharmacol. 1993, 45: 292–297
Received March 25, 1992

Differential Vasorelaxant Effects of K^+-Channel Openers and Ca^{2+}-Channel Blockers on Canine Isolated Arteries

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Abstract—The vasorelaxant effects of the K^+-channel openers, pinacidil and cromakalim, were compared with those of the Ca^{2+}-channel blockers, verapamil and KB-2796 (1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride), in canine isolated coronary, renal, basilar and mesenteric arteries precontracted with U46619, a thromboxane A_2 mimetic. The relaxation induced by pinacidil and cromakalim was greater in coronary than in other arteries, the magnitude of relaxation being in the order of coronary > renal > basilar > mesenteric arteries. The relaxant responses to both drugs were inhibited by glibenclamide, a blocker of ATP-sensitive K^+ channels. The relaxation induced by verapamil and KB-2796, in contrast, was greater in basilar than in other arteries, the magnitude of relaxation being in the order of basilar > coronary > renal and mesenteric arteries. In fura-2-loaded, U46619-stimulated arteries, pinacidil and cromakalim produced a greater reduction in intracellular Ca^{2+} concentration and muscle tension in coronary than in mesenteric arteries, while verapamil and KB-2796 reduced these values more potently in basilar than in mesenteric arteries. These results suggest that K^+-channel openers exhibit a vasorelaxant selectivity for coronary arteries, whereas Ca^{2+}-channel blockers exhibit such selectivity for cerebral arteries. The selective vasorelaxant action induced by these drugs appears to correspond, in part, to their effects on the concentration of intracellular Ca^{2+}.

Pinacidil (Arrigoni-Martelli et al 1980; Bray et al 1987; Videbaek et al 1988) and cromakalim (Hamilton et al 1986; Weir & Weston 1986) belong to a new class of vasodilators which are thought to act by opening K^+ channels in smooth muscle membrane. Both drugs have been demonstrated to increase $^{86}Rb^+$ and $^{42}K^+$ efflux from vascular smooth muscle preparations and to induce membrane hyperpolarization (Hamilton et al 1986; Weir & Weston 1986; Cook et al 1988a; Quast & Baumlin 1988). These effects were competitively inhibited by glibenclamide, a selective blocker of ATP-sensitive K^+ channels in the pancreas (Schmid-Antomarchi et al 1987; Zunkler et al 1988; Buckingham et al 1989; Quast & Cook 1989; Standen et al 1989; Winquist et al 1989). Recently, it has been reported that pinacidil and cromakalim reduce intracellular Ca^{2+} concentration ([Ca]i) in vascular tissues (Anabuki et al 1990; Yanagisawa et al 1990). These findings suggest that both of these drugs relax vascular smooth muscle through the indirect closure of Ca^{2+} channels produced by the hyperpolarization they induce.

In contrast, verapamil (Glossmann et al 1985; Lazdunski et al 1987; Karaki et al 1991) and KB-2796 (1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride) (Kanazawa & Toda 1987; Iwamoto et al 1991), a Ca^{2+}-channel blocker, relaxes vascular smooth muscle by directly inhibiting voltage-dependent Ca^{2+} channels. Ca^{2+}-channel blockers produce a greater relaxation in canine isolated cerebral arteries than in coronary and mesenteric arteries (Hayashi & Toda 1977; Shimizu et al 1980; Gerthoffer et al 1987; Kanazawa & Toda 1987), and prominently increase cerebral blood flow in anaesthetized dogs (Takenaka & Handa 1979; Hof 1983; Kanazawa et al 1990). In contrast to Ca^{2+}-channel blockers, however, relatively little is known about the vasorelaxant selectivity of K^+-channel openers for different vascular beds.

The present study was designed to investigate whether K^+-channel openers have selective vasorelaxant activity in different arteries, as has been observed for Ca^{2+}-channel blockers.

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Materials and Methods

Drugs

Pinacidil, cromakalim and KB-2796 were synthesized by the New Drug Research Laboratories, Kanebo Ltd, Osaka, Japan. Other drugs were obtained from the following sources: verapamil (Eisai Co., Tokyo, Japan), U46619 (9,11-dideoxy-11α, 9α-epoxymethano-prostaglandin $F_{2\alpha}$; Sigma Chemical Co., St Louis, MO, USA), glibenclamide (Yamanouchi Pharmaceutical Co., Tokyo, Japan), substance P (Peptide Institute, Osaka, Japan), papaverine (Wako Pure Chemicals, Tokyo, Japan), fura-2/AM (fura-2 acetoxymethyl ester; Dojindo Laboratories, Kumamoto, Japan) and cremophor EL (Nacalai Tesque, Kyoto, Japan).

Verapamil, substance P and papaverine were dissolved in distilled water, and the other drugs were dissolved in 99% (v/v) dimethyl sulphoxide (DMSO). These stock solutions were diluted with distilled water to the desired concentrations. The final concentration of DMSO in the bath was 0·5% at maximum. At this concentration, DMSO itself had negligible effects on contractile and fluorescent responses.

Preparation of arterial strips

Mongrel dogs of both sexes, 8–16 kg, were anaesthetized with sodium pentobarbitone (30 mg kg^{-1}, i.v.), and killed by bleeding from the common carotid arteries. The heart, brain and kidneys were rapidly removed. Ventral interventricular

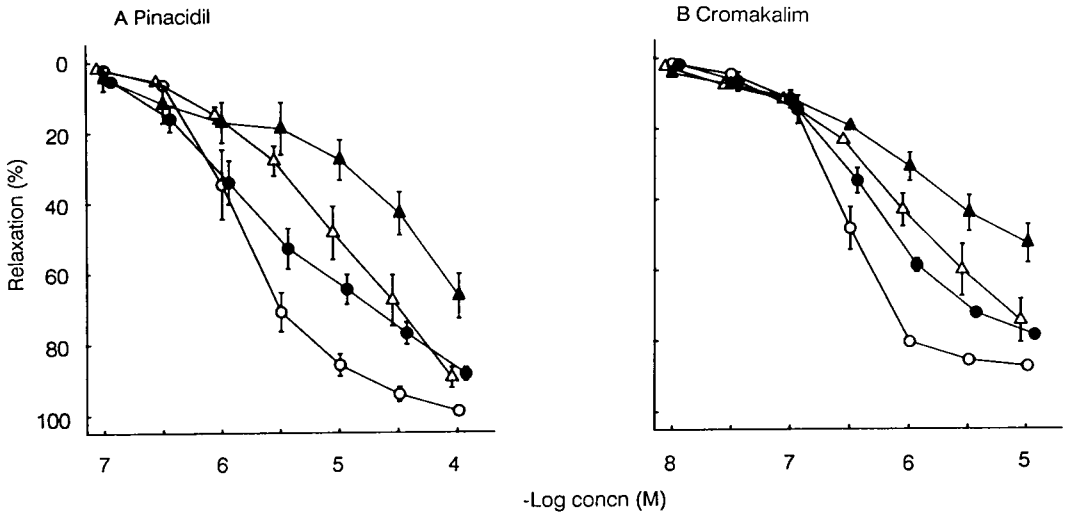

FIG. 1. Dose-relaxation curves for pinacidil (A) and cromakalim (B) in canine coronary (○), renal (●), basilar (△) and mesenteric (▲) arteries precontracted with U46619. Pinacidil (0·1–100 μM) and cromakalim (0·01–10 μM) were added cumulatively during the sustained contraction induced by 0·1 μM U46619. Relaxation induced by 100 μM papaverine was taken as 100% in each preparation. Vertical bars represent s.e.m. In A, n = 6. In B, for coronary arteries n = 8, for renal and basilar arteries n = 6, and for mesenteric arteries n = 9.

branches of the left coronary artery (0·7–1·0 mm outside diam.), basilar artery (0·5–1·0 mm) and interlobar branches of the renal artery (0·6–0·8 mm) were dissected under a binocular microscope. Distal portions of the superior mesenteric artery (0·5–0·8 mm) were also removed. These arteries were cut into spiral strips (20 mm long). The specimens were vertically fixed, between stainless-steel holders, in organ baths containing a physiological salt solution of the following composition (mM): NaCl 120, KCl 5·4, $NaHCO_3$ 25, $CaCl_2$ 2·2, $MgCl_2$ 1·0 and glucose 5·6 (pH 7·3–7·4). This solution was aerated continuously with 95% O_2–5% CO_2 and kept at 37±0·5°C. For the measurement of tension, a stainless-steel holder anchoring the upper end of the strip was connected to the lever of a force-displacement transducer (TB-611T, Nihon Kohden, Tokyo, Japan) at a resting tension of 1·5 g, which is optimal for inducing maximum contraction (Toda et al 1978). Before the experiments began, each strip was allowed to equilibrate in the normal physiological salt solution for 60–90 min.

Measurement of relaxation response

Isometric contraction and relaxation were displayed on a recorder. The contractile response to 43 mM KCl was obtained first, and then 0·1 μM substance P-induced relaxa-

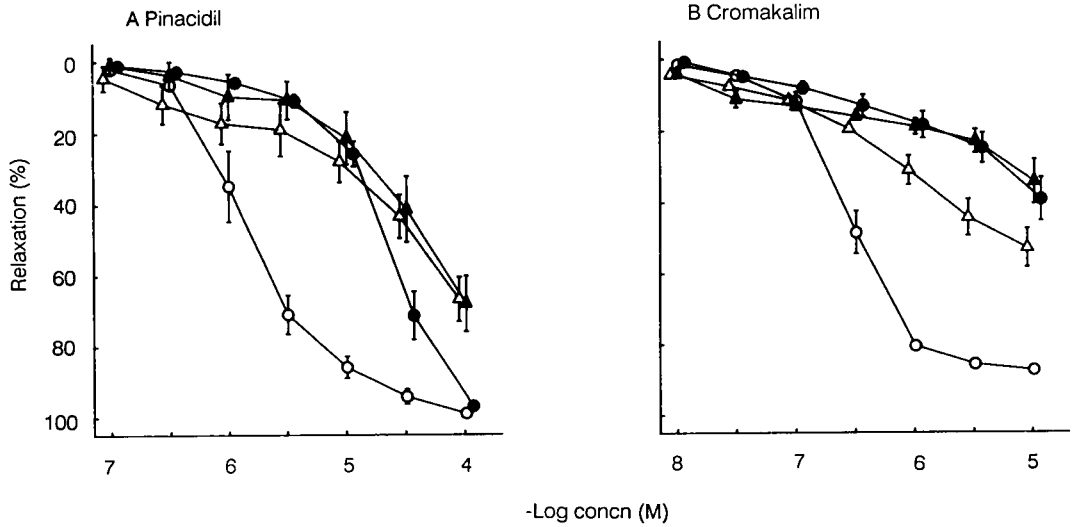

FIG. 2. Effects of glibenclamide on the dose-relaxation curves for pinacidil (A) and cromakalim (B) in canine coronary (○, ●) and mesenteric (△, ▲) arteries contracted with U46619. Glibenclamide treatment (1 μM) (●, ▲) began 20 min before relaxants were added and continued throughout the relaxant treatment period. Relaxation induced by 100 μM papaverine was taken as 100% in each preparation. Vertical bars represent s.e.m. Control ○, △. In A, n = 6. In B, for treated coronary and mesenteric arteries n = 5, for control coronary arteries n = 8, and for control mesenteric arteries n = 9.

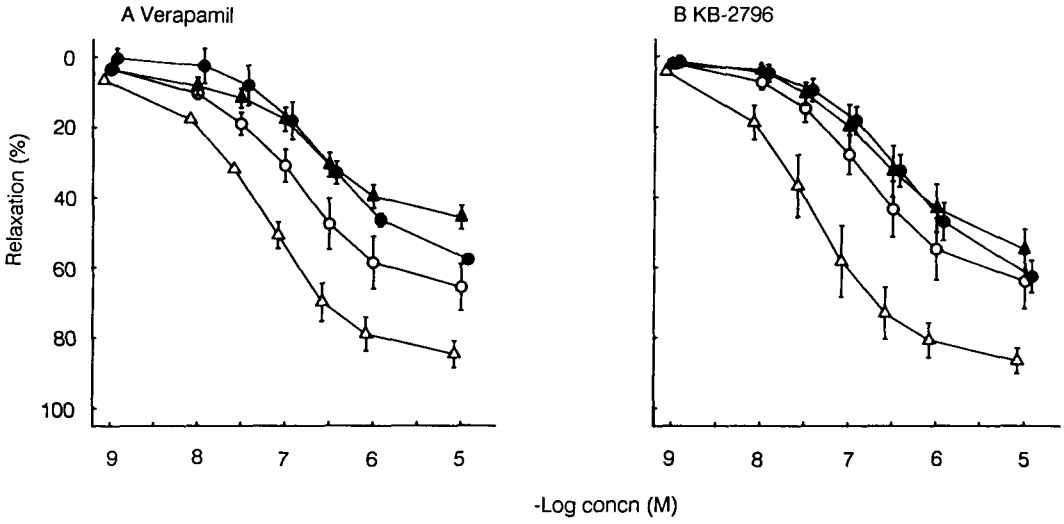

FIG. 3. Dose-relaxation curves for verapamil (A) and KB-2796 (B) in canine coronary (○), renal (●), basilar (△) and mesenteric (▲) arteries contracted with U46619. Verapamil (0·001–10 μM) and KB-2796 (0·001–10 μM) were added cumulatively during the sustained contraction induced by 0·1 μM U46619. Relaxation induced by 100 μM papaverine was taken as 100% in each preparation. Vertical bars represent s.e.m. In A, n = 4. In B, n = 5.

tion was tested to determine endothelial cell function. The strips were washed three times with physiological salt solution and equilibrated for 45–60 min. They were then contracted with 0·1 μM U46619, a thromboxane A_2 mimetic. The contractile tensions developed by 0·1 μM U46619 were 1·68 ± 0·15 g (n = 23) for coronary arteries, 1·96 ± 0·17 g (n = 21) for renal arteries, 1·33 ± 0·13 g (n = 21) for basilar arteries and 2·20 ± 0·16 g (n = 24) for mesenteric arteries. Relaxants were added to the bath cumulatively at 15–30 min intervals during the sustained contraction. In the experiments in which responses to relaxants were obtained in the presence of glibenclamide, glibenclamide was added 20 min before the addition of the relaxants. At the end of each series of experiments, 100 μM papaverine was added to the bath to obtain the maximum relaxation. The papaverine-induced relaxation was taken as 100% for determining relaxation responses to test drugs.

Measurement of intracellular Ca^{2+} concentration ([Ca]i)

Arterial strips (10 mm long) were prepared as described above. Endothelium was removed by rubbing the endothelial surface gently with a cotton pellet. [Ca]i in a strip was measured with fura-2 by a modification of the method of Ozaki et al (1987) and Sato et al (1988). Strips were exposed to physiological salt solution containing 5 μM fura-2/AM, 0·25% (v/v) cremophor EL, a non-cytotoxic detergent, and 0·5% (w/v) bovine serum albumin for 6–12 h at room temperature (21°C). They were then held horizontally in a temperature-controlled 7 mL tissue bath (37 ± 0·5°C) attached to a fluorimeter (CAF-100, Japan Spectroscopic, Tokyo, Japan). One end of the muscle strip was connected to the lever of a force-displacement transducer (TB-611T, Nihon Kohden) for the measurement of muscle tension. The strip was illuminated (48 Hz) alternately with excitation wave lengths of 340 and 380 nm and the fluorescence emission at 500 nm was collected by the photomultiplier. The fluorescence induced by 340 nm excitation (F340) and 380 nm excitation (F380) was measured and the ratio (R340/380) was calculated automatically. The R340/380 ratio was used as an indicator of relative [Ca]i.

Statistical analysis

The concentration of drug producing 50% inhibition (IC50) of U46619-induced contraction was determined using linear regression analysis. All values represent the mean ± s.e.m. The significance of differences between two means was assessed by using Student's *t*-test. *P* values less than 0·05 were considered to be significant.

Results

Relaxation induced by pinacidil and cromakalim in canine arteries

In coronary, renal, basilar and mesenteric arteries precontracted with U46619, pinacidil (0·3–100 μM) and cromakalim (0·1–10 μM) produced a concentration-dependent relaxation (Fig. 1). Pinacidil and cromakalim were more potent relaxants in coronary than in other arteries, the rank order of potency being coronary > renal > basilar > mesenteric arteries. The order for maximum responses to pinacidil (100 μM) and cromakalim (10 μM) was coronary > renal = basilar > mesenteric arteries. In the coronary arteries, cromakalim (IC50 = 0·37 ± 0·06 μM, n = 8) was about 5 times more potent than pinacidil (IC50 = 1·8 ± 0·5 μM, n = 6).

Fig. 2 shows the effects of glibenclamide, a blocker of ATP-sensitive K^+ channels, on the concentration-response curves for pinacidil and cromakalim in coronary and mesenteric arteries. Glibenclamide at the concentration used (1 μM) had no significant effects on the resting tension or U46619-induced contraction of coronary and mesenteric arteries. In the coronary arteries, 1 μM glibenclamide caused a parallel shift to the right of the relaxant response to pinacidil, with no attenuation of maximum response. In contrast, the effect of glibenclamide on the relaxant response

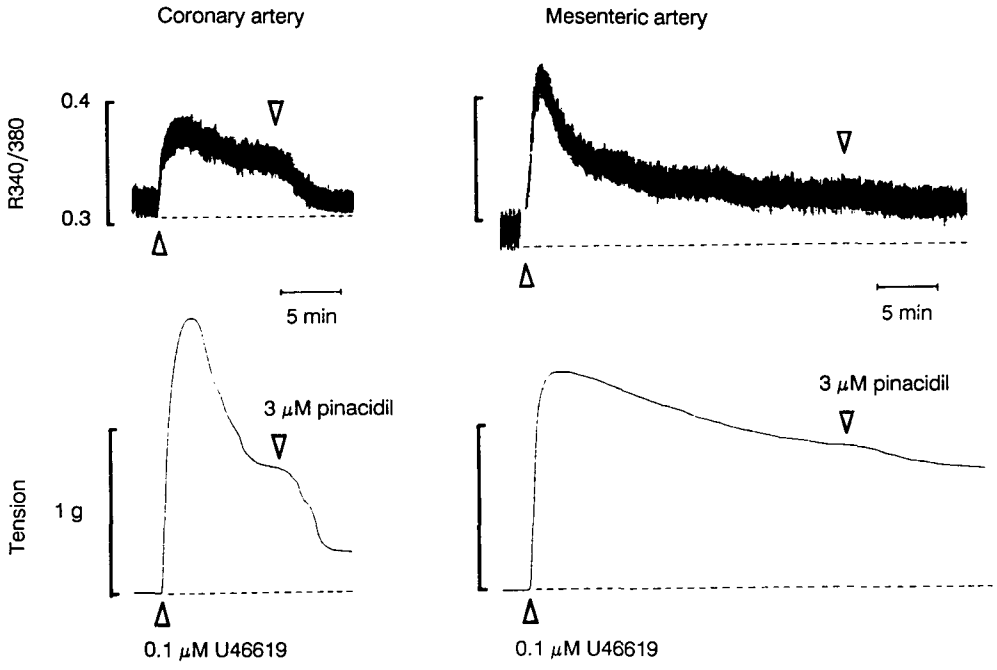

FIG. 4. Effects of 0·1 μM U46619 on [Ca]i (upper trace) and tension (lower trace) in canine coronary and mesenteric arteries, and inhibition induced by 3 μM pinacidil. [Ca]i is shown by the fura-2-fluoroescence ratio (R340/380).

to cromakalim was to produce a marked attenuation, both in terms of absolute potency and in terms of maximum response. In the mesenteric arteries, glibenclamide also inhibited the relaxant response to cromakalim, but not that to pinacidil. In the presence of glibenclamide, the moderate relaxation responses to pinacidil (< 10 μM) and cromakalim in coronary arteries were similar to those in mesenteric arteries.

Relaxation induced by verapamil and KB-2796 in canine arteries

Verapamil (0·01–10 μM) and KB-2796 (0·01–10 μM) relaxed coronary, renal, basilar and mesenteric arteries precontracted with U46619 in a concentration-dependent manner (Fig. 3). Verapamil and KB-2796 were more potent relaxants in basilar than in other arteries, the rank order of potency being basilar > coronary > renal = mesenteric arteries. The order for maximum responses to verapamil was basilar > coronary > renal > mesenteric arteries, and for KB-2796 was basilar > coronary = renal > mesenteric arteries. In the basilar arteries, the relaxant potency of verapamil (IC50 = 0·11 ± 0·03 μM, n = 4) and KB-2796 (IC50 = 0·15 ± 0·05 μM, n = 5) was similar.

Table 1. Effects of pinacidil and cromakalim on [Ca]i and muscle tension in U46619-stimulated canine coronary and mesenteric arteries.

	Inhibition (%)	
	Coronary (n)	Mesenteric (n)
Pinacidil 3 μM		
[Ca]i	75 ± 9	29 ± 6**
Tension	71 ± 3 (4)	23 ± 8** (4)
Cromakalim 0·3 μM		
[Ca]i	82 ± 11	40 ± 7*
Tension	68 ± 11 (5)	9 ± 3** (4)

The strips were treated with 0·1 μM U46619; 3 μM pinacidil or 0·3 μM cromakalim was added after the increases induced by U46619 in [Ca]i and contraction reached a plateau. Changes in [Ca]i and tension were expressed by taking the differences between basal and plateau values of U46619 as 100% (see Fig. 4). Each value represents the mean ± s.e.m. *$P < 0.05$, **$P < 0.01$, compared with the corresponding values in coronary arteries (Student's t-test).

Effects of pinacidil, cromakalim, verapamil and KB-2796 on [Ca]i in canine U46619-stimulated arteries

In coronary, basilar and mesenteric arteries preloaded with fura-2, 0·1 μM U46619 induced a sustained increase in [Ca]i, which was followed by a sustained increase in muscle tension (Fig. 4).

The addition of 3 μM pinacidil or 0·3 μM cromakalim reduced both [Ca]i and muscle tension in U46619-stimulated coronary and mesenteric arteries, as shown in Fig. 4 and Table 1. The reduction induced by either drug in [Ca]i and muscle tension was significantly greater in coronary than in mesenteric arteries. Cromakalim tended to produce a greater reduction in [Ca]i than in muscle tension in both coronary and mesenteric arteries, but pinacidil reduced these values to a similar extent.

Verapamil (0·3 μM) and KB-2796 (0·3 μM) also reduced both [Ca]i and muscle tension in U46619-stimulated basilar and mesenteric arteries (Table 2). The reduction induced by either drug in [Ca]i and muscle tension was significantly greater in basilar than in mesenteric arteries, the reductions in [Ca]i being greater than that in muscle tension.

Table 2. Effects of verapamil and KB-2796 on [Ca]i and muscle tension in U46619-stimulated canine basilar and mesenteric arteries.

	Inhibition (%)	
	Basilar (n)	Mesenteric (n)
Verapamil 0·3 μM		
[Ca]i	126±15	80±7**
Tension	47±6	16±8**
	(4)	(4)
KB-2796 0·3 μM		
[Ca]i	112±10	55±3*
Tension	54±7	9±1**
	(4)	(4)

The strips were treated with 0·1 μM U46619; 0·3 μM verapamil or 0·3 μM KB-2796 was added after the increases induced by U46619 in [Ca]i and contraction reached a plateau. Changes in [Ca]i and tension were expressed by taking the differences between basal and plateau values of U46619 as 100%. Each value represents the mean ± s.e.m. $*P < 0.05$, $**P < 0.01$, compared with the corresponding values in basilar arteries (Student's *t*-test).

Discussion

In the present experiments, K^+-channel openers showed selective vasorelaxant activity in canine coronary, renal, basilar and mesenteric arteries precontracted with U46619. Relaxation induced by cromakalim and pinacidil was significantly greater in coronary than in other arteries, the magnitude of relaxation being in the following order: coronary > renal > basilar > mesenteric arteries. Recently, Masuzawa et al (1991) also showed that the relaxant responses to cromakalim, determined in 20·9 mM K^+-contracted canine arteries, were greater in coronary than in mesenteric and middle cerebral arteries. These findings show that K^+-channel openers are selective coronary vasorelaxants in canine arteries contracted either with receptor agonist or by low K^+-depolarization. In contrast, verapamil and KB-2796 inhibited U46619-induced contraction more potently in basilar than in other arteries. Thus, the vasorelaxant selectivity of K^+-channel openers seems to be distinctly different from that of Ca^{2+}-channel blockers.

The mechanism of the fundamental action of K^+-channel openers in vascular smooth muscle is to open K^+ channels and then to cause hyperpolarization (Hamilton et al 1986; Weir & Weston 1986; Videbaek et al 1988). When the vascular smooth muscle membrane is hyperpolarized, receptor agonist-induced Ca^{2+} influx via Ca^{2+} channels is thought to decrease (Cook 1988; Cook et al 1988b; Weston 1989). In U46619-stimulated canine arteries, we confirmed that pinacidil and cromakalim produced a reduction in [Ca]i, and we found that the reduction in [Ca]i, as well as that in muscle tension, induced by both drugs was greater in coronary than in mesenteric arteries (Table 1). This result indicates that vasorelaxation induced by K^+-channel openers is associated with a reduction in [Ca]i. Furthermore, we found that pinacidil- and cromakalim-induced relaxation was more potently attenuated by a high concentration (1 μM) of glibenclamide, a blocker of ATP-sensitive K^+ channels, in coronary than in mesenteric arteries, and that the vasorelaxant selectivity of pinacidil (< 10 μM) and cromakalim for coronary arteries was masked by glibenclamide (Fig. 2). Therefore, K^+-channel opening induced by pinacidil and cromakalim seems likely to be greater in coronary than in mesenteric arteries. This suggestion is consistent with the results of a previous report which showed that the ability of cromakalim to increase $^{86}Rb^+$ efflux from 20·9 mM K^+-contracted canine arteries was greater in coronary than in mesenteric arteries (Masuzawa et al 1991). Thus, from these findings it appears that the vasorelaxant selectivity of K^+-channel openers for coronary arteries is associated with greater K^+-channel opening and a greater reduction in [Ca]i, in coronary, than in other arteries.

In contrast to K^+-channel openers, verapamil and KB-2796, which directly inhibit voltage-dependent Ca^{2+} channels, exhibited a vasorelaxant selectivity for cerebral arteries, as previously observed with several Ca^{2+}-channel antagonists (Hayashi & Toda 1977; Shimizu et al 1980; Gerthoffer et al 1987; Kanazawa & Toda 1987). In addition, we also found that verapamil and KB-2796 produced a greater decrease in [Ca]i, as well as in muscle tension, in basilar than in mesenteric arteries (Table 2). Previously, we reported that KB-2796 inhibited high K^+-induced $^{45}Ca^{2+}$ influx more potently in cerebral than in mesenteric canine arteries (Iwamoto et al 1991). These findings suggest that the vasorelaxant selectivity of Ca^{2+}-channel blockers for cerebral arteries may be, at least in part, attributed to a greater inhibition of Ca^{2+} influx via Ca^{2+} channels in cerebral than in other arteries.

Karaki et al (1991) have reported that verapamil produced a greater reduction in [Ca]i than in muscle tension in noradrenaline-stimulated vascular strips. In the present study, verapamil and KB-2796 produced a greater reduction in [Ca]i than in muscle tension in U46619-stimulated basilar and mesenteric arteries (Table 2). These results suggest that the agonist-induced sustained contraction may be attributable not only to the increase in [Ca]i but also to Ca^{2+} sensitization and to a Ca^{2+}-independent mechanism. Similarly, cromakalim tended to produce a greater reduction in [Ca]i than in muscle tension in U46619-stimulated coronary and mesenteric arteries. In contrast, pinacidil produced a reduction of similar extent in [Ca]i and muscle tension in both coronary and mesenteric arteries (Table 1). Furthermore, antagonism by glibenclamide of the relaxant response to pinacidil was different from that of the response to cromakalim. The relaxant response to pinacidil at a higher concentration (over 30 μM) was only partly attenuated by glibenclamide (Fig. 2). These findings suggest that pinacidil exerts some of its relaxing effects by a mechanism independent of K^+-channel opening, as previously suggested (Anabuki et al 1990; Yanagisawa et al 1990).

The present study indicated that K^+-channel openers exhibit a vasorelaxant selectivity for coronary arteries. We used U46619 as a stimulant for vasocontraction in this study, as thromboxane A_2 is one of the putative mediators of coronary vasospasm (Ellis et al 1976; Wang et al 1980). Thus, the beneficial effects of K^+-channel openers are thought to be through vasodilating action for coronary arteries. In fact, pinacidil and cromakalim have recently been reported to improve myocardial blood flow and reduce infarct size in experimental models of ischaemic heart disease (Bache et al 1990; Grover et al 1990).

References

Anabuki, J., Hori, M., Ozaki, H., Kato, I., Karaki, H. (1990) Mechanisms of pinacidil-induced vasodilation. Eur. J. Pharmacol. 190: 373–379

Arrigoni-Martelli, E., Nielsen, C. K., Olsen, U. B., Petersen, H. J. (1980) *N''*-Cyano-*N*-4-pyridyl-*N'*-1,2,2-trimethylpropylguanidine, monohydrate (P 1134): a new, potent vasodilator. Experientia 36: 445–447

Bache, R. J., Dai, X., Baran, K. W. (1990) Effect of pinacidil on myocardial blood flow in the chronically pressure overloaded hypertrophied left ventricle. J. Cardiovasc. Pharmacol. 16: 890–895

Bray, K. M., Newgreen, D. T., Small, R. C., Southerton, J. S., Taylor, S. G., Weir, S. W., Weston, A. H. (1987) Evidence that the mechanism of the inhibitory action of pinacidil in rat and guinea-pig smooth muscle differs from that of glyceryl trinitrate. Br. J. Pharmacol. 91: 421–429

Buckingham, R. E., Hamilton, T. C., Howlett, D. R., Mootoo, S., Wilson, C. (1989) Inhibition by glibenclamide of the vasorelaxant action of cromakalim in the rat. Br. J. Pharmacol. 97: 57–64

Cook, N. S. (1988) The pharmacology of potassium channels and their therapeutic potential. Trends Pharmacol. Sci. 9: 21–28

Cook, N. S., Quast, U., Hof, R. P., Baumlin, Y., Pally, C. (1988a) Similarities in the mechanism of action of two new vasodilator drugs: pinacidil and BRL34915. J. Cardiovasc. Pharmacol. 11: 90–99

Cook, N. S., Weir, S. W., Danzeisen, M. C. (1988b) Anti-vasoconstrictor effects of the K^+ channel opener cromakalim on the rabbit aorta—comparison with the calcium antagonist isradipine. Br. J. Pharmacol. 95: 741–752

Ellis, E. F., Oelz, O., Roberts, L. J., Payne, N. A., Sweetman, B. J., Nies, A. S., Oates, J. A. (1976) Coronary arterial smooth muscle contraction by a substance released from platelets: evidence that it is thromboxane A_2. Science 193: 1135–1137

Gerthoffer, W. T., Shafer, P. G., Taylor, S. (1987) Selectivity of phenytoin and dihydropyridine calcium channel blockers for relaxation of the basilar artery. J. Cardiovasc. Pharmacol. 10: 9–15

Glossmann, H., Ferry, D. R., Goll, A., Striessnig, J., Zernig, G. (1985) Calcium channels and calcium channel drugs: recent biochemical and biophysical findings. Arzneim. Forsch. 35: 1917–1935

Grover, G. J., Sleph, P. G., Dzwonczyk, S. (1990) Pharmacologic profile of cromakalim in the treatment of myocardial ischaemia in isolated rat hearts and anaesthetized dogs. J. Cardiovasc. Pharmacol. 16: 853–864

Hamilton, T. C., Weir, S. W., Weston, A. H. (1986) Comparison of the effects of BRL34915 and verapamil on electrical and mechanical activity in rat portal vein. Br. J. Pharmacol. 88: 103–111

Hayashi, S., Toda, N. (1977) Inhibition by Cd^{2+}, verapamil and papaverine of Ca^{2+}-induced contractions in isolated cerebral and peripheral arteries of the dog. Br. J. Pharmacol. 60: 35–43

Hof, R. P. (1983) Calcium antagonist and the peripheral circulation: differences and similarities between PY 108–068, nicardipine, verapamil and diltiazem. Br. J. Pharmacol. 78: 375–394

Iwamoto, T., Morita, T., Sukamoto, T. (1991) Calcium antagonism by KB-2796, a new diphenylpiperazine analogue, in dog vascular smooth muscle. J. Pharm. Pharmacol. 43: 535–539

Kanazawa, T., Toda, N. (1987) Inhibition by KB-2796, a new Ca^{2+} entry blocker, of the contractile response of isolated dog cerebral and peripheral arteries. Folia Pharmacol. Japon. 89: 365–373 (Abstract in English)

Kanazawa, T., Morita, T., Harada, K., Iwamoto, T., Ohtaka, H., Sukamoto, T., Ito, K., Nurimoto, S. (1990) Selective effect of KB-2796, a new calcium entry blocker, on cerebral circulation: a comparative study of the effects of calcium entry blockers on cerebral and peripheral arterial blood flows. J. Cardiovasc. Pharmacol. 16: 430–437

Karaki, H., Sato, K., Ozaki, H. (1991) Different effects of verapamil on cytosolic Ca^{2+} and contraction in norepinephrine-stimulated vascular smooth muscle. Jpn. J. Pharmacol. 55: 35–42

Lazdunski, M., Schmid, A., Romey, G., Renaud, J. F., Galizzi, J. P., Fosset, M., Borsotto, M., Barhanin, J. (1987) Molecular properties of the voltage-sensitive calcium channel. J. Cardiovasc. Pharmacol. 9 (Suppl. 4): S10–S16

Masuzawa, K., Matsuda, T., Asano, M. (1991) The diverse effects of cromakalim on tension and ^{86}Rb efflux in canine arterial smooth muscle. Br. J. Pharmacol. 103: 1033–1040

Ozaki, H., Sato, K., Satoh, T., Karaki, H. (1987) Simultaneous recordings of calcium signals and mechanical activity using fluorescent dye fura 2 in isolated strips of vascular smooth muscle. Jpn. J. Pharmacol. 45: 429–433

Quast, U., Baumlin, Y. (1988) Comparison of the effluxes of $^{42}K^+$ and $^{86}Rb^+$ elicited by cromakalim (BRL34915) in tonic and phasic vascular tissue. Naunyn Schmiedebergs Arch. Pharmacol. 338: 319–326

Quast, U., Cook, N. S. (1989) In vitro and in vivo comparison of two K^+ channel openers, diazoxide and cromakalim, and their inhibition by glibenclamide. J. Pharmacol. Exp. Ther. 250: 261–271

Sato, K., Ozaki, H., Karaki, H. (1988) Changes in cytosolic calcium level in vascular smooth muscle strips measured simultaneously with contraction using fluorescent calcium indicator fura 2. J. Pharmacol. Exp. Ther. 246: 294–300

Schmid-Antomarchi, H., Weille, J. D., Fosset, M., Lazdunski, M. (1987) The receptor for antidiabetic sulfonylureas controls the activity of the ATP-modulated K^+ channel in insulin-secreting cells. J. Biol. Chem. 262: 15840–15844

Shimizu, K., Ohta, T., Toda, N. (1980) Evidence for greater susceptibility of isolated dog cerebral arteries to Ca antagonists than peripheral arteries. Stroke 11: 261–266

Standen, N. B., Quayle, J. M., Davies, N. W., Brayden, J. E., Huang, Y., Nelson, M. T. (1989) Hyperpolarizing vasodilators activate ATP-sensitive K^+ channels in arterial smooth muscle. Science 245: 177–180

Takenaka, T., Handa, J. (1979) Cerebrovascular effects of YC-93, a new vasodilator, in dogs, monkeys and human patients. Int. J. Clin. Pharmacol. Biopharmacy 17: 1–11

Toda, N., Hatano, Y., Hayashi, S. (1978) Modifications by stretches of the mechanical responses of isolated cerebral and extracerebral arteries to vasoactive agents. Pflugers Arch. 374: 73–77

Videbaek, L. M., Aalkajaer, C., Mulvany, M. J. (1988) Pinacidil opens K^+-selective channels causing hyperpolarization and relaxation of noradrenaline contractions in rat mesenteric resistance vessels. Br. J. Pharmacol. 95: 103–108

Wang, H. H., Kulkarni, P. S., Eakins, K. E. (1980) Effects of prostaglandins and thromboxane A_2 on the coronary circulation of adult dogs and puppies. Eur. J. Pharmacol. 66: 31–41

Weir, S. W., Weston, A. H. (1986) The effects of BRL34915 and nicorandil on electrical and mechanical activity and on ^{86}Rb efflux in rat blood vessels. Br. J. Pharmacol. 88: 121–128

Weston, A. H. (1989) Smooth muscle K^+ channel openers; their pharmacology and clinical potential. Pflugers Arch. 414 (Suppl. 1): S99–S105

Winquist, R. J., Heaney, L. A., Wallace, A. A., Baskin, E. P., Stein, R. B., Garcia, M. L., Kaczorowski, G. J. (1989) Glyburide blocks the relaxation response to BRL34915 (cromakalim), minoxidil sulfate and diazoxide in vascular smooth muscle. J. Pharmacol. Exp. Ther. 248: 149–156

Yanagisawa, T., Teshigawara, T., Taira, N. (1990) Cytoplasmic calcium and the relaxation of canine coronary arterial smooth muscle produced by cromakalim, pinacidil and nicorandil. Br. J. Pharmacol. 101: 157–165

Zunkler, B. J., Lenzen, S., Manner, K., Panten, U., Trube, G. (1988) Concentration-dependent effects of tolubutamide, meglitinide, glipizide, glibenclamide and diazoxide on ATP-regulated K^+ currents in pancreatic B-cells. Naunyn Schmiedebergs Arch. Pharmacol. 337: 225–230