Mechanism of Action of KRN2391, a Novel Vasodilator, in Canine Mesenteric Artery

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Received August 26, 1992 Accepted December 26, 1992

ABSTRACT—The present study was performed to clarify the mechanism of vasodilation of KRN2391 in canine mesenteric artery compared with those of nicorandil and cromakalim. We used the responses of isolated cranial mesenteric artery in vitro and changes in mesenteric blood flow in vivo as indicators reflecting the responses of a conductive artery and resistive arterioles, respectively. In isolated cranial mesenteric artery, KRN2391 (10^{-8} - 10^{-5} M), nicorandil (10^{-7} - 10^{-4} M) and cromakalim (10^{-7} - 10^{-5} M) relaxed contractions caused by 25 mM KCl in a concentration-dependent manner. The concentration-relaxation curve for KRN2391 was shifted to the right by either methylene blue (10^{-5}M) or glibenclamide (10^{-6}M), but the inhibitory effect of methylene blue was more potent than that of glibenclamide. The concentration-relaxation curve for nicorandil was shifted to the right by methylene blue, but not by glibenclamide. In addition, the curve for cromakalim was shifted to the right by glibenclamide, but not by methylene blue. In in vivo experiments, the injections of KRN2391 (0.3 - 3 μg/kg), nicorandil (10 - 100 μg/kg) or cromakalim (1 - 10 μg/kg) into the mesenteric artery increased mesenteric blood flow in a dose-dependent manner. Glibenclamide (5 mg/kg, i.v.) attenuated the increase in mesenteric blood flow caused by KRN2391, nicorandil and cromakalim, but had no effect on that caused by nifedipine (1 μg/kg). The ED_{20} value increased about 4.7-fold for KRN2391, 3.7-fold for nicorandil and 11.5-fold for cromakalim after administration of glibenclamide, as estimated from the % change to the absolute increase in mesenteric blood flow induced by nifedipine (1 μg/kg). These results suggest that KRN2391 shows nitrate and K channel opening actions in canine mesenteric artery, but the ratio of both actions appears to depend on the segment of mesenteric artery.

Keywords: KRN2391, Nicorandil, Cromakalim, Nifedipine, Mesenteric artery

KRN2391, N-cyano-N'-(2-nitroxyethyl)-3-pyridinecarboximidamide monomethanesulfonate (Fig. 1), is a novel agent possessing a vasodilating effect and antihypertensive properties (1 - 3). The effects of KRN2391 in vascular smooth muscles are variable and at least two mechanisms have been proposed. The first mechanism is a K channel opening action. KRN2391 produces an increase in the efflux of ^{86}Rb which is used as a marker for K in isolated rat aortae (2). Glibenclamide, a pharmacological antagonist of K channel openers (4, 5), also antagonizes the relaxation caused by KRN2391 in isolated rat aortae (2). The second mechanism is its action as a nitrate. In isolated canine large coronary artery, the relaxation caused by KRN2391 is antagonized by methylene blue, an inhibitor of soluble guanylate cyclase (6), but not by glibenclamide (7). Recently, Jinno et al. (8) have observed that KRN2391 increased the cyclic GMP level in porcine coronary artery. Nicorandil as well as KRN2391 is also reported to show such a dual mechanism of action as a K channel opener and a nitrate (9, 10).

In in vivo experiments using anesthetized dogs, the intravenous administration of KRN2391 markedly increases coronary and mesenteric blood flows in comparison with other peripheral blood flows (11). In coronary

Fig. 1. Chemical structure of KRN2391.
arteries, it has been demonstrated that the behaviors of KRN2391 and nicorandil depend on the segment of coronary artery; i.e., they act as a nitrate in large coronary artery (7, 12) and as a K channel opener in resistive coronary arterioles (13, 14). Both K channel opening and nitrate-like actions can be demonstrated in canine small coronary artery (15). However, the mechanisms of action of KRN2391 and nicorandil in mesenteric artery remain unclear despite showing relatively potent effects on mesenteric blood flow and coronary blood flow. In the present study, we analyzed the mechanisms of action of KRN2391 and nicorandil in canine mesenteric artery compared with that of cromakalim, a K channel opener (16, 17), in vitro and in vivo. The responses of isolated cranial mesenteric artery and mesenteric blood flow were used as the indices reflecting those of a conductive artery and resistive arterioles, respectively.

MATERIALS AND METHODS

In vitro

Beagle dogs of either sex weighing 8.3–11.5 kg were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and exsanguinated. Cranial mesenteric arteries, which were large arteries near the aorta, were removed and dissected from adhering connective tissue. The arteries were cut into 2- to 3-mm-long ring segments, and the endothelium was removed by gentle rubbing. Ring segments of arteries were mounted on stainless steel wires in an organ bath filled with 10 ml Krebs-Henseleit solution of the following composition: 118 mM NaCl, 4.7 mM KCl, 1.2 mM MgSO4, 2.5 mM CaCl2, 1.2 mM KH2PO4, 25 mM NaHCO3 and 10 mM glucose, at 37°C aerated with a gas mixture of 95% O2 and 5% CO2. The artery rings were stretched by an initial resting tension of 1 g. After an initial equilibration period of 120 min, the artery rings were contracted by changing the solution in the bath to one containing 25 mM KCl. This potassium depolarizing solution was prepared by replacing 20.3 mM NaCl with 20.3 mM KCl in the control solution. After the arteries reached a stable tension, vasodilators were added in a cumulative manner. Methylene blue and glibenclamide were added 20 min before the arteries were contracted by 25 mM KCl. Isometric tension was measured with a mechanical transducer (TB-611T, Nihon Kohden, Tokyo).

In vivo

Twelve beagle dogs of either sex, ranging in weight from 9.1 to 11.8 kg, were anesthetized with sodium pentobarbital (30 mg/kg, i.v.) and artificially ventilated with room air. Systemic blood pressure in the right femoral artery was measured with a pressure transducer (TP-200T, Nihon Kohden) through a carrier amplifier (AP-601G, Nihon Kohden). Heart rate was measured by a heart rate counter (AT-601G, Nihon Kohden) triggered by the arterial pressure pulse. The cephalic vein was cannulated for intravenous administration of glibenclamide. A left flank incision was made to expose the cranial mesenteric artery. Mesenteric blood flow was measured with a flow probe placed around cranial mesenteric artery and linked to an electromagnetic flowmeter (MFV2100, Nihon Kohden). For administrations of KRN2391, nicorandil, cromakalim and nifedipine, a 23-gauge curved needle connected to polyethylene tubing was inserted into the cranial mesenteric artery proximal to the flow probe.

The experimental protocol consisted of 2 periods. The first period was the control phase in which intra-arterial injections of KRN2391, nicorandil and cromakalim were made to estimate their vasodilatory effects. In the second phase, the effects of KRN2391, nicorandil and cromakalim were observed again starting 10 min after intravenous administration of glibenclamide (5 mg/kg). The effect of nifedipine (1 µg/kg) was also examined in all groups. Group I consisted of 4 dogs; they received 3 doses of KRN2391 (0.3–3 µg/kg) injected in random dose order at more than 5-min intervals. Group II also consisted of 4 dogs; they received 3 doses of nicorandil (10–100 µg/kg) injected in random dose order at more than 5-min intervals. Group III consisted of 4 dogs; they received 3 doses of cromakalim (1–10 µg/kg) injected in random dose order at more than 5-min intervals. Furthermore, the effects of 10 µg/kg of KRN2391 and 30 µg/kg of cromakalim were examined after administration of glibenclamide in groups I and III, respectively. The injection rate was 10 sec and the volume was 0.1 ml.

Drugs

KRN2391, nicorandil and cromakalim were synthesized in our laboratory. Methylene blue was purchased from Wako (Osaka), and nifedipine and glibenclamide were from Sigma (St. Louis, MO, USA).

For the in vitro experiments, drugs were prepared as follows: KRN2391 was dissolved in Krebs-Henseleit solution at 10⁻² M; nicorandil, in 0.1 N HCl at 15 x 10⁻² M; and cromakalim, in dimethylsulfoxide at 10⁻² M. Glibenclamide and methylene blue were dissolved at 10⁻³ M in dimethylsulfoxide and at 10⁻² M in double-distilled water. These solutions were diluted to the appropriate concentration in Krebs-Henseleit solution.

For the in vivo experiments, drugs were prepared as follows: KRN2391 and nicorandil were dissolved in 0.9% saline. Nifedipine and cromakalim were dissolved in 0.9% saline / polyethylene glycol 400 / ethanol (70:15:15, vol. / vol.) and in 0.9% saline / polyethylene glycol 200 (50:50, vol./vol.), respectively. Glibenclamide was dissolved in...
dimethylformamide at the appropriate concentration in 0.5 ml.

Data analyses

In the in vitro experiments, relaxation caused by the test drugs was expressed as the percentage of maximum relaxation obtained by the addition of 10^{-4} M papaverine at the end of each experiment. In each preparation, the concentration-relaxation curve for each drug was fitted to a logistic equation:

\[ E = \frac{M \times A^p}{(A^p + K^p)} \]

where \( E \) is the normalized effect, \( M \) is the maximum effect, \( A \) is the drug concentration, \( K \) is the EC50 value of each drug and \( p \) is the slope parameter. To estimate the potency of cromakalim under various conditions, we calculated the EC20 values instead of EC50 values.

In the in vivo experiments, part of the results with KRN2391, nicorandil and cromakalim was expressed as percent changes to the absolute increase in mesenteric blood flow induced by nifedipine (1 \( \mu \)g/kg). The inhibitory effect of glibenclamide on the increase in mesenteric blood flow caused by KRN2391, nicorandil and cromakalim was also estimated by ED20 because a high dose of nicorandil can not be administered. The ED20 were determined by the dose-response curves which were fitted by linear regression.

Data are presented as the mean±S.E.M. Differences were considered significant at \( P < 0.05 \), using Student’s \( t \)-test for paired data for single comparison and analysis of variance for multiple comparisons. When multiple comparisons were made with a single control, Dunnett’s test was used to determine levels of significance.

RESULTS

Effect on isolated cranial mesenteric artery

KRN2391 (10^{-8}–10^{-5} M), nicorandil (10^{-7}–10^{-4} M) and cromakalim (10^{-7}–10^{-5} M) produced a concentration-dependent relaxation in coronary arteries contracted by 25 mM KCl (Fig. 2). With KRN2391 and nicorandil, relaxation was nearly complete at their maximum effects. However, with cromakalim, relaxation was about 51% even at its maximum effect. Therefore, the effects of methylene blue and glibenclamide on cromakalim-induced relaxation were evaluated with the EC20 values.

The concentration-relaxation curves for KRN2391 were shifted to the right by either 10^{-5} M methylene blue or 10^{-6} M glibenclamide, but the inhibitory effect of methylene blue was more potent than that of glibenclamide (Fig. 2). The EC50 value for KRN2391 in the presence of methylene blue was significantly higher than that for the control (Table 1). The concentration ratio of KRN2391 calculated on the basis of its EC50 values were 4.3 in the presence of methylene blue. Glibenclamide showed a tendency to increase the EC50 value for KRN2391 but the change was not significant (Table 1). The slope of the line for KRN2391 in the presence of methylene blue was less steep than that of the control (Table 1).

The concentration-relaxation curve for nicorandil was shifted by methylene blue but not by glibenclamide (Fig. 2). The EC50 value for nicorandil in the presence of methylene blue was significantly higher than that for the control (Table 1). The concentration ratio of nicorandil calculated based on its EC50 values was 8.5 in the presence of methylene blue. This ratio of nicorandil was also greater

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**Fig. 2.** Concentration-relaxation curves for KRN2391, nicorandil and cromakalim in canine cranial mesenteric artery contracted by 25 mM KCl in the absence (○) and the presence of methylene blue (10^{-5} M, ●) or glibenclamide (10^{-6} M, □). Each point is the mean±S.E.M. of 5–7 experiments. *: \( P < 0.05 \), **: \( P < 0.01 \), compared with the corresponding control values.
than that of KRN2391. However, there were no differences between the EC50 value in the control and that in the presence of glibenclamide (Table 1). The slope of the line for nicorandil in the presence of methylene blue was less steep than that of the control (Table 1).

The concentration-relaxation curve for cromakalim shifted to the right by glibenclamide (Fig. 2). Methylene blue had no effect on the concentration-relaxation curve for cromakalim (Fig. 2). The EC20 value for cromakalim in the presence of glibenclamide was significantly higher than that for the control (Table 1). The concentration ratio calculated based on its EC20 values were 8.2 in the presence of glibenclamide. This ratio of cromakalim was also greater than that of KRN2391. However, there were no differences between the EC20 values in the absence or the presence of methylene blue (Table 1).

Effect on mesenteric blood flow

A decrease in basal mesenteric blood flow was observed after intravenous administration of glibenclamide (5 mg/kg) as shown in Figs. 3–5. The mean blood pressure increased slightly from 148 ± 6 to 152 ± 6 mmHg (N = 12, P < 0.01), and the heart rate decreased from 183 ± 7 to 174 ± 8 beats/min (N = 12, P < 0.01) 10 min after administration of glibenclamide.

Intra-arterial injections of KRN2391 (0.3 to 3 μg/kg), nicorandil (10 to 100 μg/kg) or cromakalim (1 to 10 μg/kg) produced dose-dependent increases in mesenteric blood flow. KRN2391, nicorandil- or cromakalim-induced increases in mesenteric blood flow were significantly reduced after administration of glibenclamide (Figs. 3–5). However, glibenclamide had no effect on the increase in mesenteric blood flow induced by nifedipine (1 μg/kg) in each group (Figs. 3–5).

The inhibitory effect of glibenclamide on the increase in mesenteric blood flow induced by KRN2391, nicorandil and cromakalim, estimated as the % change to the absolute increase in blood flow induced by nifedipine (1 μg/kg), is shown in Fig. 6. In this expression, the effects of KRN2391, nicorandil and cromakalim were also inhibited by glibenclamide. In addition, the ED20 values for these drugs, which were obtained from Fig. 6, increased after administration of glibenclamide (Table 2). How-

| Table 1. EC50 (for KRN2391 and nicorandil), EC20 (for cromakalim) and the slopes of the concentration-relaxation curve |
|---------------------------------------------------------------|
| **log EC50** or **log EC20** | **Slope** |
|-----------------------------|-----------|
| **KRN2391**                 |           |
| Control                     | -6.57±0.08| 1.23±0.07 |
| Methylene blue, 10⁻⁵ M      | -5.95±0.09**| 0.67±0.06**|
| Glibenclamide, 10⁻⁶ M       | -6.24±0.11| 1.16±0.09 |
| **Nicorandil**              |           |
| Control                     | -5.49±0.06| 0.86±0.08 |
| Methylene blue, 10⁻³ M      | -4.62±0.12**| 0.63±0.07*|
| Glibenclamide, 10⁻⁶ M       | -5.32±0.08| 0.92±0.03 |
| **Cromakalim**              |           |
| Control                     | -6.29±0.13| 1.69±0.28 |
| Methylene blue, 10⁻⁵ M      | -6.16±0.11| 1.48±0.28 |
| Glibenclamide, 10⁻⁶ M       | -5.29±0.08**| 1.72±0.18|

Each value is a mean±S.E.M. of 5–7 experiments. *P<0.05, **P<0.01, significant difference from the corresponding control value.

Fig. 3. Effect of glibenclamide (5 mg/kg, i.v.) on the increase in mesenteric blood flow (MBF) induced by intra-arterial administrations of KRN2391 and nifedipine. Values under the columns indicate the blood flow immediately before administration of each dose of KRN2391 and nifedipine. Each value is a mean±S.E.M. (n=4). *: P<0.05, **: P<0.01, compared with control values. □: control, ◼: after administration of glibenclamide.

Fig. 4. Effect of glibenclamide (5 mg/kg, i.v.) on the increase in mesenteric blood flow (MBF) induced by intra-arterial administration of nicorandil and nifedipine. Values under the columns indicate the blood flow immediately before administration of each dose of nicorandil and nifedipine. Each value is a mean±S.E.M. (n=4). *: P<0.05, **: P<0.01, compared with control values. □: control, ◼: after administration of glibenclamide.
ever, the increase in the ED_{20} value for cromakalim was greater than those for KRN2391 and nicorandil.

DISCUSSION

In this study, the mechanism of vasodilation of

Table 2. Inhibitory effects of glibenclamide (5 mg/kg, i.v.) on the increase in mesenteric blood flow induced by KRN2391, nicorandil and cromakalim in anesthetized dogs

|                | ED_{20} (μg/kg) before glibenclamide | ED_{20} (μg/kg) after glibenclamide | Ratio   |
|----------------|--------------------------------------|--------------------------------------|---------|
| KRN2391        | 0.47±0.05                            | 2.16±0.21*                           | 4.69±0.30* |
| Nicorandil     | 12.84±0.53                           | 46.81±5.51*                          | 3.74±0.61 |
| Cromakalim     | 1.47±0.10                            | 17.77±7.64*                          | 11.49±4.39 |

The dose (ED_{20}) that produced an increase in mesenteric blood flow by 20% in Fig. 6 was determined from the respective dose-response curves which was fitted by linear regression. Ratio=(Value after glibenclamide)/(Value before glibenclamide). Each value is a mean±S.E.M. (n=4). *P<0.05, compared with the corresponding control value.

KRN2391 was different from those of nicorandil and cromakalim in isolated cranial mesenteric artery. KRN2391-induced relaxation was antagonized by methylene blue, an inhibitor of soluble guanylate cyclase (6), and glibenclamide, a pharmacological antagonist of K channel openers (4, 5). Nicorandil-induced relaxation was antagonized by methylene blue alone, while cromakalim-induced relaxation was antagonized by glibenclamide alone. However, the increases in concentration ratios of nicorandil and cromakalim were greater than those of KRN2391 in the presences of methylene blue and glibenclamide, respectively. In control observations, the

Fig. 5. Effect of glibenclamide (5 mg/kg, i.v.) on the increase in mesenteric blood flow (MBF) induced by intra-arterial administration of cromakalim and nifedipine. Values under the columns indicate the blood flow immediately before administration of each dose of cromakalim and nifedipine. Each value is a mean±S.E.M. (n=4). *: P<0.05, **: P<0.01, compared with control values. □: control, ■: after administration of glibenclamide.

Fig. 6. Dose-response curves of mesenteric blood flow (MBF) for KRN2391, nicorandil and cromakalim before and after administration of glibenclamide (5 mg/kg, i.v.). The change of MBF is expressed as the 010 change to the absolute increase in MBF induced by nifedipine (1 μg/kg) in each experiment. Before (□) and after (●) the administration of glibenclamide. Each point is a mean±S.E.M. of 4 experiments.
vasodilating action of KRN2391 was also more potent than those of nicorandil and cromakalim. These results suggest that K channel opening and nitrate-like actions of KRN2391 are less potent than those of nicorandil and cromakalim, respectively, but the potent vasodilating effect of KRN2391 is operated by these two mechanisms. The stimulation of guanylate cyclase induced by nicorandil is supported by the finding of Endoh and Taira (18) that nicorandil increases cyclic GMP formation in isolated canine mesenteric artery. It is also reported that cromakalim has no appreciable effect on cyclic GMP level in rabbit mesenteric artery (17). Although it remains unclear whether KRN2391 produces an increase in cyclic GMP level in canine cranial mesenteric artery, we have recently observed that KRN2391 increased the cyclic GMP level in porcine large coronary artery (8).

Furthermore, in the in vivo study, we examined the effect of glibenclamide on the responses of mesenteric blood flow induced by KRN2391, nicorandil and cromakalim to clarify their mechanisms of action in resistive mesenteric arterioles. Glibenclamide attenuated the increase in mesenteric blood flow caused by KRN2391, nicorandil and cromakalim. Since glibenclamide had no effect on the response to nifedipine, a Ca channel blocker (19), glibenclamide was thought to act as a K channel blocker in the present study. It is also reported that the decrease in blood pressure and the increase in coronary blood flow induced by nitroglycerin were not affected by glibenclamide in anesthetized dogs (14, 20). Therefore, it is considered that K channel opening action is involved in the effects of KRN2391 and nicorandil as well as cromakalim in increasing mesenteric blood flow, i.e., KRN2391 and nicorandil show a K channel opening action in resistive mesenteric arterioles. However, the inhibitory effect of glibenclamide was greater in the cromakalim-induced response than in the KRN2391- or nicorandil-induced responses. Although the reason for the differential inhibition by glibenclamide remains unelucidated in the present study, a nitrate action may contribute, at least partly, to the increase in mesenteric blood flow caused by KRN2391 and nicorandil.

As mentioned above, in cranial mesenteric artery, KRN2391 acted as both a K channel opener and a nitrate, whereas nicorandil behaved only as a nitrate. Although it is indicated in the present study that KRN2391 and nicorandil show the action of a nitrate in resistive mesenteric arterioles, it seems at least that they behave mainly as K channel openers in mesenteric arterioles. The profiles in which the mechanisms of action of KRN2391 and nicorandil depend on the segment of blood vessel have also been observed in coronary artery. KRN2391 and nicorandil act as a nitrate alone in canine large coronary artery because KRN2391- and nicorandil-induced relaxations were inhibited by methylene blue but not by glibenclamide in isolated canine large coronary artery (7, 12). Both K channel opening and nitrate-like actions can be demonstrated in canine small coronary artery (15). In contrast, KRN2391 and nicorandil act predominantly as a K channel opener in resistive coronary arterioles because the increase in coronary blood flow induced by KRN2391 and nicorandil was inhibited by pretreatment with glibenclamide in anesthetized dog (14, 21). Therefore, whether KRN2391 and nicorandil act as a nitrate and/or a K channel opener appears to depend on the type and the segment of blood vessel.

The different profiles of KRN2391 and nicorandil are thought to be associated with the physiological characteristics of each blood vessel. Imagawa et al. (22) report that glibenclamide (i.v.) produces a decrease in coronary blood flow but does not change the diameter of the left circumflex coronary artery in anesthetized dogs. In the present study, the decrease in mesenteric blood flow was also induced by glibenclamide (i.v.), suggesting that glibenclamide-sensitive K channels contribute to the maintenance of basal tone in resistive arterioles more potently than in a conductive artery. Although, to our knowledge, there have been no comparative study between large and small segments of mesenteric artery in nitrate- and K channel opener-induced relaxations, it is reported that nitroglycerin and sodium nitroprusside dilate large coronary artery to a greater extent than small coronary artery (23, 24). On the other hand, Struijker Boudier et al. (25) showed that BRL 38227, a K channel opener, dilated the smallest arterioles (diameter: 10–35 μm) at doses lower than those needed to dilate arterioles of 70–120 μm in conscious spontaneously hypertensive rats, suggesting a preferential sensitivity of small precapillary arterioles. These results suggest that conductive artery and resistive arterioles are more sensitive to nitrates and K channel openers, respectively. Therefore, it is considered that KRN2391 and nicorandil show nitrate actions rather than K channel opening actions in large (conductive) artery and K channel opening actions in addition to nitrate actions in resistive arterioles. However, further studies are needed to define the basic mechanism and the clinical implication of such profiles of KRN2391 and nicorandil.

In conclusion, KRN2391 behaved as a nitrate and a K channel opener and nicorandil as a nitrate in cranial mesenteric artery, a conductive artery. In contrast, KRN2391 and nicorandil mainly showed K channel opening actions in resistive mesenteric arterioles, though their nitrate actions were partly indicated. These results suggest that the mechanism of action of KRN2391 and nicorandil depends on the segment of mesenteric artery.
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