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The Mechanism of K⁺-Induced Vasodilation of the Coronary Vascular Bed of the Dog

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SUMMARY We tested a number of hypotheses concerning the mechanism of K⁺-induced vasodilation of the coronary vascular bed. Blood flow in the circumflex artery was measured in pentobarbital-anesthetized, open-chest dogs. Intracoronary artery bolus injections of 40 μmol of isosmotic KCl produced decreases in coronary vascular resistance ranging from 34% to 48%, depending on the initial resistance of the vascular bed. K⁺ administration had no effect on heart rate and produced a 4 mm Hg decrease in mean arterial pressure. K⁺ injection caused a 0.2 vol% increase in coronary sinus O₂ content in a preparation in which left common coronary flow was held constant. The magnitude of K⁺-induced vasodilation was not significantly affected by the administration of propranolol, atropine, acetylcholine, or phentolamine, or lidocaine. K⁺-induced vasodilation was attenuated (50%) by ouabain plus lidocaine. Acetylcholine-induced vasodilation was not significantly diminished by ouabain plus lidocaine. We conclude that the mechanism of K⁺-induced vasodilation does not involve an increase in the metabolic activity of the heart or an interaction between K⁺ and tissue neural elements. Our data do support the hypothesis that K⁺-induced vasodilation is at least partly the result of an activation of the electrogenic Na⁺-K⁺ transport system of coronary smooth muscle.

K⁺ IS RELEASED from myocardial cells under a variety of circumstances that are associated with decreased coronary vascular resistance. Moreover, K⁺ is a vasodilator of both the intact and isolated coronary vascular bed. For these reasons it has been proposed that K⁺ may be one mediator of the coronary vasodilation associated with increases in the metabolic activity of the heart. The mechanism of K⁺-induced vasodilation of the coronary vascular bed has not been fully investigated. Evidence gained from isolated vessel and heart preparations has largely supported the hypothesis that changes in vascular reactivity produced by small increases in extracellular K⁺ concentration are the result of a K⁺-stimulated increase in the activity of the electrogenic Na⁺-K⁺ transport system of coronary smooth muscle. However, other possible mechanisms of K⁺-induced vasodilation have not been excluded. It is possible that in intact systems, in which the level of coronary blood flow is determined by a number of factors, small increases in extracellular K⁺ concentration may produce increases in coronary blood flow not only through a direct effect of K⁺ on coronary vascular smooth muscle, but also indirectly by affecting other determinants of coronary blood flow. In this study we have investigated these possibilities. More specifically, we have attempted to determine whether the mechanism of K⁺-induced coronary vasodilation involves: (1) a primary increase in the metabolic activity of the heart, (2) an increased release of norepinephrine from sympathetic nerve terminals in the heart, (3) an increased release of acetylcholine from parasympathetic nerve terminals in the heart, (4) a withdrawal of α-adrenergic-mediated coronary vascular smooth muscle tone, or (5) an activation of the electrogenic Na⁺-K⁺ transport system of coronary vascular smooth muscle.

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Methods

Experimental Preparation

Male mongrel dogs, ranging in weight from 20 to 30 kg, were anesthetized with morphine sulfate (4 mg/kg by subcutaneous injection) and sodium pentobarbital (25 mg/kg or to effect by intravenous injection). Supplemental doses of sodium pentobarbital were administered throughout the course of the experiment to maintain adequate surgical anesthesia. A cuffed endotracheal tube was positioned, and positive pressure ventilation was provided by a Harvard large animal respirator. A polyethylene cannula was inserted into the thoracic aorta via the femoral artery to measure intra-aortic blood pressure. A femoral vein was isolated and cannulated for the return of extracorporeal blood (in experiments in which coronary sinus O₂ saturation was measured) and for the administration of a variety of pharmacological agents (described below). After a priming dose of sodium heparin (500 U/kg), a solution containing sodium bicarbonate (15 mg/ml), sodium heparin (50 U/ml), and dextran (9 mg/ml) was infused intravenously at a constant rate (60–120 ml/hr) throughout the course of the experiment to counteract anesthesia-induced acidosis, to prevent coagulation, and to correct for estimated blood loss during surgery, respectively.

The heart was exposed by opening the chest between the 4th and 5th ribs. The pericardium was incised and fashioned into a cradle. A short segment (1.0–2.0 cm) of the circumflex artery was isolated just distal to the bifurcation of the left common coronary artery. A polyvinyl catheter with an outside diameter of 0.6 mm was placed (using the method of Herd and Barger) in the distal portion of that segment. The catheter was used for K⁺ and intra-arterial drug administration. An electromagnetic flow probe (Zepedas model SWF-3RD) was positioned just proximal to this catheter to measure of circumflex blood flow. A snare, positioned between the flow probe and catheter, permitted occlusion of the artery during the course of the experiment to check for electronic baseline drift of the flow probe. The flow probe was calibrated in situ at the end of each experiment by making timed collections of blood pumped through the circumflex artery into a graduated cylinder. The outputs of the pressure transducer and flow meter were recorded on an ink-writing oscillograph. Heart rate was measured and recorded on the oscillograph with a tachograph channel using either the systemic pressure measurement signal or the flow probe signal as input. The heart was excised and weighed at the end of each experiment.

Drugs

Bolus injections (0.4 ml) of the following agents were made directly into the circumflex artery via the Herd-Barger catheter: (1) 40 μmol of isosmotic KCl, (2) 0.9% NaCl, (3) 0.1 ml of isoproterenol (Isuprel; Winthrop Labs), (4) 0.1 μg of acetylcholine (Sigma).

Propranolol hydrochloride (Inderal; Ayerst Labs) and atropine sulfate (Merck) were diluted in isotonic saline and infused intravenously at a rate of 1.0–2.0 ml/min over a 15-minute period to achieve a total dose of 1.0–2.0 and 0.5–1.0 mg/kg, respectively. Lidocaine (Elkins-Sinn) and ouabain (Lilly) were infused intravenously at 1.0–2.0 ml/min over a 45-minute period to achieve total doses of 2–3 mg/kg and 50–70 μg/kg, respectively. Lidocaine was used to delay the onset of ouabain-induced arrhythmias.

Phentolamine (Regitine; Ciba Pharmaceuticals) was infused directly into the circumflex artery (0.5 ml/min) via the Herd-Barger catheter to achieve a total dose of 1.0–2.0 mg/kg.

Protocol

After the circumflex artery cannulation was completed, the preparation was allowed to stabilize. When circumflex blood flow reached a steady level, a series of bolus injections directly into the circumflex artery was begun. Alternate injections of KCl, NaCl, and either acetylcholine or isoproterenol were made at 5-minute intervals during the first hour of the experiment. During this control period, the effects of K⁺ administration on heart rate (HR) and mean aortic pressure (MAP) were determined. This was followed by an infusion of one of the blocking agents (atropine, propranolol, phentolamine, lidocaine, ouabain-lidocaine). A 2- to 3-hour experimental period followed, during which the alternate injection sequence of the agents listed was repeated. These experiments were designed to examine the effect of the various blocking agents on the magnitude of K⁺-induced vasodilation.

At the termination of each experiment, the dog was killed by the rapid intravenous injection of a saturated potassium chloride solution. After the in situ calibration of the flow probe, the heart was excised and weighed.

Data Analysis and Presentation

The calculated changes in resistance (i.e., mean aortic pressure-circumflex blood flow) produced by KCl, isoproterenol, and acetylcholine injections represent the difference between the peak change in resistance and the average resistance over the 30-second period that immediately preceded administration of the vasodilator. All responses have been corrected for the small, nonspecific vascular effect produced by the intracircumflex artery bolus injection, as determined by isotonic NaCl injections of equal volume (0.4 ml).

The data have been divided into three separate categories for grouping and statistical analyses.

1. Effect of initial resistance on the magnitude of K⁺-induced vasodilation. In this series, 153 vascular responses to K⁺ were collected from dogs during the first hour of each experiment. The individual responses then were grouped within different ranges of initial resistance [intervals of 0.5 PRU (peripheral resistance units: mm Hg/ml·min⁻¹) starting with initial resistance of 1.0 PRU] and expressed as the mean ± 1 SEM for that range of initial resistance.

2. Effect of K⁺ on HR and MAP was examined simultaneously in seven dogs (119 observations). HR during the minute immediately preceding the administration of
K⁺ was compared to the HR during the minute immediately following K⁺ administration. At the same time, the MAP associated with the peak increase in circumflex blood flow produced by K⁺ was compared to the average MAP during the 30-second period immediately preceding K⁺ administration. These data were statistically analyzed by Student’s t-test modified for paired replicates.

3. Effect of propranolol (n = 10 dogs), atropine (n = 8 dogs), phentolamine (n = 5 dogs), lidocaine (n = 4 dogs), and ouabain-lidocaine (n = 8 dogs) on the magnitude of K⁺-induced vasodilation. In this series we tested the effect of the various blocking agents on the magnitude of K⁺-induced vasodilation. In all cases a number of control vascular responses to K⁺ were obtained during the first hour of each experiment and then were compared to those vascular responses obtained during the succeeding 2–3 hours of each experiment. These data were grouped and analyzed in the following manner.

(a) Each series of experiments was treated separately.

(b) “Control” responses (i.e., vascular responses obtained during the first hour of the experiment) and “experimental” responses (i.e., vascular responses obtained during the succeeding 2–3 hours of the experiment) were treated separately.

(c) A given set of responses for each dog was separated into several intervals of initial resistance (intervals of 1.0 PRU, starting with initial resistance of 1.0 PRU). There were two exceptions to this convention: (1) the effects of ouabain-lidocaine on acetylcholine-induced vasodilation, where the responses were grouped in initial resistance intervals of 1.0–2.0, 2.0–2.5, and 2.5–3.5 PRU; and (2) the effects of atropine on acetylcholine-induced vasodilation, where the experimental responses were grouped in initial resistance intervals of 1.0–1.5, 1.5–2.0, and 2.0–4.0 PRU.

(d) Responses within each interval of initial resistance for each dog were averaged and the mean value used in all subsequent analyses. In this way the response of each dog was weighted equally.

(e) The average responses within each interval of initial resistance from all dogs within a series were averaged, and the variance among dogs was determined.

(f) Within each interval of initial resistance, a statistical analysis of the difference in the mean values between “control” and “experimental” vascular responses was performed using Student’s t-test [where sample size (n) equals the number of dogs in the control and experimental groups for that particular interval of initial resistance].

This method of grouping permitted a direct comparison of the effects of the various blocking agents on the magnitude of K⁺-induced vasodilation, independent of the effects of initial resistance.

![Figure 1](image-url)
**Measurement of Myocardial Oxygen Consumption**

To measure transient changes in myocardial oxygen consumption produced by K⁺ administration, we placed a modified Gregg cannula in the left common coronary artery and perfused the left coronary system at constant flow. We sampled venous blood draining this bed by means of a catheter placed in the coronary sinus. We drew coronary sinus blood through a cuvette densitometer (Waters model 0-600) calibrated to give blood oxygen content as described in a previous study. We examined the effects of intracoronary artery bolus injections of 40 μmol of isometric KCl on coronary sinus O₂ content, which at constant flow and constant arterial O₂ content reflects changes in myocardial O₂ consumption. Three individual responses were observed in each of four dogs. The peak in coronary sinus O₂ content produced by K⁺ administration was compared with the average coronary sinus O₂ content during the 30-second period immediately preceding K⁺ administrations. These data were statistically analyzed using Student's t-test modified for paired replicates.

**Results**

Representative responses of the circumflex coronary artery preparation to intracircumflex artery bolus injec-

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**TABLE 1 Effects of Injection of 40 μmol of Isosmotic KCl on Mean Arterial Pressure (MAP), Heart Rate (HR), and Coronary Sinus Oxygen Content (Cso₂)**

<table>
<thead>
<tr>
<th>Dog</th>
<th>n</th>
<th>MAP (mm Hg)</th>
<th>HR (beats/min)</th>
<th>Cso₂ content (vol%)</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
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<td>104.3</td>
<td>119</td>
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<td>79.8</td>
<td>101</td>
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<td>Mean</td>
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<td>97.5</td>
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<td>&lt;0.005</td>
<td>&gt;0.50</td>
<td>&lt;0.01</td>
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</tbody>
</table>

n = number of dogs observed. Dogs 12-5-74 through 1-19-75 were circumflex artery (free flow) preparations; dogs 2-3-76 through 5-28-76 were common coronary artery constant flow preparations. P values are for paired t-tests.
tions of 40 μmol of isosmotic KCl are shown in Figure 1. The administration of this amount of K⁺ caused a clear increase in mean, systolic, and diastolic circumflex blood flow. The magnitude of K⁺-induced decreases in resistance is a function of the initial resistance of the vascular bed (Fig. 2). The data displayed in this figure were obtained during a 1-hour control period from 17 dogs. The standard error of the mean for initial resistance was always <±10% for an individual dog. The decrease in resistance produced by K⁺ is linearly related to the initial resistance of the bed (y = 0.51x - 0.57), with a correlation coefficient of 0.87. Depending on the initial resistance of the bed, this amount of K⁺ produced decreases in coronary vascular resistance ranging from 34% to 48%.

Metabolic Action of K⁺

As is shown in Table 1, K⁺ administration had no effect on heart rate, and produced a small (4 mm Hg) but significant decrease in MAP. The constant flow left common coronary artery preparation enabled us to measure transients in myocardial O₂ consumption. As shown in Table 1, K⁺ administration produced a small (0.2 ± 0.04 vol%) but significant increase in coronary sinus oxygen content, which at constant flow indicates a decrease in myocardial O₂ consumption. These data indicate that the mechanism of K⁺-induced vasodilation is not directly related to an increase in myocardial metabolic activity.

Neural Action of K⁺

The magnitude of K⁺-induced vasodilation was not significantly attenuated by propranolol (Fig. 3A), atropine (Fig. 4A), or phentolamine (Fig. 5). The doses of pro-
pranolol and atropine were sufficient, however, to abolish almost completely isoproterenol-induced vasodilation (Fig. 3B) and acetylcholine-induced vasodilation (Fig. 4B), respectively. We were unable to check the efficacy of the a-blockade because a-agonists did not cause reproducible coronary vasoconstriction in our preparation. The data indicate that K+-induced vasodilation is not the result of an interaction between K+ and the neural influences on coronary blood flow investigated.

**Effect of Ouabain**

K+-induced vasodilation was, however, significantly attenuated (approximately 50%) by the administration of ouabain-lidocaine (Fig. 6). The diminished vascular response to K+ appears to be caused primarily by ouabain, since the magnitude of K+-induced vasodilation was only insignificantly depressed by the administration of lidocaine alone (Fig. 7). The decrease in the magnitude of K+-induced vasodilation does not appear to be the result of a nonspecific inhibition of vascular smooth muscle reactivity, because the administration of ouabain-lidocaine failed to have a significant effect on acetylcholine-induced vasodilation (Fig. 8). These data support the hypothesis that the mechanism of K+-induced vasodilation involves an activation of the electrogenic Na+-K+ transport system of coronary smooth muscle.

**Discussion**

The multiplicity of possible mechanisms by which increased interstitial K+ concentration might cause coronary vasodilation predicated this study. In situ coronary vasodilation produced by K+ could be the result of an alteration in one or more of the major determinants of coronary blood flow. For the sake of discussion we have divided these determinants into four categories: (1) myocardial metabolism, (2) myocardial systolic compression, (3) neural control of coronary vessels, and (4) direct effects on coronary smooth muscle.

**Myocardial Metabolism**

Increased myocardial metabolism is the most powerful stimulus for increased coronary blood flow. If elevated interstitial K+ concentration produced increased myocardial oxygen consumption, then a metabolically induced increase in coronary blood flow could result. On the basis of our data we can reject this hypothesis (Table 1). K+ administration had no effect on heart rate, and produced a 4 mm Hg decrease in mean arterial pressure. Changes in these variables are usually good predictors of changes in myocardial oxygen consumption (e.g., Feigl18). Even more conclusively, K+ administration resulted in a 0.2 vol% increase in coronary sinus O2 content, whereas coronary blood flow was constant (Table 1), reflecting an actual decrease in myocardial oxygen consumption. This is direct evidence against the hypothesis that K+-induced vasodilation is the result of an increase in myocardial metabolic activity.

**Myocardial Systolic Compression**

Contraction of the heart during systole impedes coronary blood flow by compressing the coronary vascular bed.19 K+-induced vasodilation could, therefore, be the result of a decrease in the myocardial systolic compressive effect on coronary blood flow. The possible effects of systolic compression can be avoided by observing K+-induced changes in flow during diastole. We observed K+-induced increases in both systolic and diastolic flow (Fig. 1). Similarly, Bünjer et al.20 observed increases of 40% in diastolic coronary inflow in the isolated perfused guinea pig heart. Thus it appears that K+-induced vasodil-
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Neural Control of Coronary Vessels

Sympathetic α-receptor coronary vasoconstriction and parasympathetic cholinergic coronary vasodilation have been observed. Several investigators have demonstrated the existence of sympathetic β-receptors in isolated strips of coronary vascular smooth muscle. Moreover, release and/or re-uptake of neurotransmitters from nerve endings can be influenced by the extracellular K+ concentration. Also, small increases in extracellular K+ concentration have been shown to inhibit the vasoconstrictor effects of exogenously administered norepinephrine and sympathetic stimulation in isolated vascular smooth muscle. Small increases in interstitial K+ concentration causes vasodilation via a response to an adequate stimulus.

Direct Effect on Coronary Smooth Muscle

Having essentially excluded the above-mentioned mechanisms as being responsible for K+-induced vasodilation, we examined the possibility that K+-induced vasodilation was the result of a direct action on coronary vascular smooth muscle. Specifically, we tested the hypothesis that K+-induced vasodilation should be attenuated or abolished following the administration of pharmacological antagonists specific to the agonists in question. However, our data show (Figs. 3-5) that the magnitude of K+-induced vasodilation was not significantly affected by the administration of either propranolol, atropine, or phentolamine. This is direct evidence against the hypotheses that the mechanism of K+-vasodilation is the result of (1) an increased release of norepinephrine from sympathetic nerve terminals in the heart, (2) an increased release of acetylcholine from parasympathetic nerve terminals in the heart, or (3) a withdrawal of sympathetic α-adrenergic-mediated vascular smooth muscle tone.

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References


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