Reflex Parasympathetic Coronary Vasodilation Elicited from Cardiac Receptors in the Dog

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ABSTRACT

Veratrum alkaloids injected into the coronary circulation stimulate myocardial receptors to produce reflex bradycardia and arterial hypotension (the Bezold-Jarisch reflex). This study investigated the hypothesis that parasympathetic coronary vasodilation occurs as part of the Bezold-Jarisch reflex. Blood flow in the circumflex coronary artery was measured in chloralose-anesthetized, closed-chest dogs with a newly developed cannula-tip flow transducer. Alpha-receptor blockade with Dibozane (2 mg/kg) was used to prevent peripheral vasodilation, and beta-receptor blockade with propranolol (1 mg/kg) was used to prevent adrenergic cardiac effects. Electrical pacing was used to maintain a constant heart rate. Under these conditions, veratridine injected into the anterior descending coronary artery but not into the circumflex coronary artery produced a 63% increase in circumflex coronary blood flow and an 88% increase in diastolic coronary conductance. The effect was abolished when the reflex arc was interrupted by either vagotomy or atropine administration. It is concluded that a cardio-coronary reflex parasympathetic coronary vasodilation can be elicited by stimulating cardiac receptors with veratridine.

In 1867 Bezold and Hirt (1) described bradycardia and arterial hypotension following intravenous injections of veratum alkaloids. Jarisch and co-workers (2-4) established that the sensory receptors for this response are in the heart and the afferent path is the vagus nerve. Krayer (5) reviewed the history of the reflex and proposed that it be called the Bezold-Jarisch effect.

A previous study in this laboratory demonstrated that stimulation of the efferent vagus nerve results in parasympathetic coronary vasodilation which is independent of the inotropic and chronotropic effects of vagal stimulation (6). The present study was designed to test whether reflex parasympathetic coronary vasodilation is part of the Bezold-Jarisch reflex. The plan of the experiment was to observe circumflex coronary artery blood flow during injection of veratridine into the anterior descending and septal coronary arteries before and after interruption of the postulated reflex arc.

Methods

GENERAL PREPARATION

Adult male dogs (23-27 kg) were medicated with morphine sulfate (2.5 mg/kg, sc) and anesthetized with alpha-chloralose (50 mg/kg, iv), with supplements given as needed. The dogs were mechanically ventilated via a cuffed endotracheal tube. The ventilation pump (Harvard 607) was adjusted to give an end-expiratory carbon dioxide content between 4.5% and 5.0% as monitored by an infrared analyzer (Beckman LB-2). Rectal temperature was regulated to 38°C with a heating pad. The metabolic acidosis which accompanies chloralose anesthesia (7) was combated with an intravenous drip of 1.5% sodium bicarbonate at the rate of 5 ml/kg hour^-1. Blood pressure in the ascending aorta was measured with a strain-gauge manometer (Statham P23Dd) via a 75-cm polyethylene (PE 260) catheter passed from the femoral artery.

Two pacing electrodes (U. S. Catheter Instrument no. 5651) were inserted via the right external jugular vein. One pacing electrode was placed in the right atrium and the other in the right ventricle using a fluoroscope.

The right common carotid artery was separated from the vagosympathetic trunk so as not to damage the nerve. The dog was anticoagulated with heparin (an initial dose of 750 µg/kg plus 250 µg/kg hour^-1 via the intravenous drip), and a cannula-tip coronary flow transducer was inserted into the circumflex coronary artery via the right carotid artery, the aorta, and the coronary ostium. The flow transducer was a stainless steel tube with a special tip that was wedged inside the circumflex coronary artery. Blood flowed from the ascending aorta via a pair of inlets through the tube to the circumflex coronary artery at the outlet. Flow in the rigid tube was measured by the ultrasound Doppler shift technique. The instrument had a side injection tube with a port inside the coronary ostium but above the wedge-shaped tip that formed a seal in the circumflex coronary artery. Material injected via this side injection port was delivered to the anterior descending and septal branches of the left coronary artery but not to the circumflex branch, which was sealed off by the wedged tip. The flow transducer has been described in detail elsewhere (8).

The flow transducer was calibrated in situ post-mortem at the end of the experiment. The left chest was...
opened, the circumflex coronary artery was tied off proximal and distal to the flow transducer tip, and the artery was incised so that a Silastic tube could be fitted over the outlet. The Silastic tube was connected to a syringe pump (Harvard 941), and the flowmeter was calibrated by pumping blood in and out of the aorta through the transducer.

**EXPERIMENTAL DESIGN**

After the preparation had been completed, a test dose of 2 µg (0.2 ml) of veratridine was injected into the anterior descending coronary artery via the side injection port of the flow transducer. If this injection produced a Bezold-Jarisch reflex (bradycardia and hypotension), the experiment would proceed. If a Bezold-Jarisch reflex could not be elicited after the placement of the flow transducer had been checked, the preparation was discarded.

Dibozane (1,4-[bis-1,4-benzodioxan-2-y1 methyl]pipera- zine, McNeil Laboratories), an alpha-receptor blocking agent, was given (2.0 mg/kg, iv) to blunt the hypotension from peripheral sympathetic inhibition which is part of the Bezold-Jarisch reflex. Propranolol (1.0 mg/kg, iv.), a beta-receptor blocking agent, was administered to prevent secondary reflex cardiac effects. A supplemental dose of 0.25 mg/kg of propranolol was given after 1 hour in two dogs.

The heart was paced with 1.8-msec rectangular pulses of 4-6 v. Heart rate, adjusted to just exceed the sinus rate, varied from 60 to 136 beats/min among the dogs and averaged 92 beats/min. The atrial-ventricular delay, adjusted for the most consistent pacing, varied from 40 to 60 msec.

Ten minutes after the drugs had been given and when steady pacing could be established, 5 µg (0.5 ml) of veratridine was injected into the anterior descending coronary artery, and the flow response in the circumflex artery, and the flow response in the circumflex branch was recorded. If cardiac pacing was perfect (no missed beats and no extrasystoles), the experiment would proceed; if not, the procedure was repeated after an interval of 10 minutes.

The reflex path of the coronary response to veratridine was tested by cutting the cervical vagosympathetic trunk in four dogs and administering atropine sulfate (1.0 mg/kg in two dogs, 0.5 mg/kg in one dog, and 0.25 mg/kg in one dog) to four other dogs. Veratridine was injected into the anterior descending coronary artery as described previously, except that cardiac pacing was no longer needed to maintain a constant heart rate.

**DRUGS**

A solution was prepared from a few milligrams of veratridine base (K & K Biochemicals) by adding slightly more than an equivalent amount of 0.1N hydrochloric acid and diluted with distilled water to give a concentration of 1 mg/ml. This solution was diluted tenfold, two times with a 3% solution of sodium citrate, to give a final concentration of 10 µg veratridine/ml in citrate for intracoronary administration. Sodium citrate was used, since Dawes (9) has observed that citrate potentiates the action of veratrum alkaloids. Veratridine was chosen among the veratrum alkaloids because it has the least tendency to produce tachyphylaxis (9). An additional precaution against tachyphylaxis was to always wait 10 minutes between veratridine injections.

**Pilot experiments using this procedure, eight or more injections could be made without tachyphylaxis. The experiments reported in the present paper used from three to six veratridine injections.**

**VERIFICATION**

A critical part of this experiment was the secure wedging of the flow transducer tip in the circumflex branch so that veratridine was injected only into the anterior descending and septal branches. Separation of the two distributions was verified in two ways. First, a comparison of the effect of nitroglycerin injected into the anterior descending branch via the side injection port vs. the same dose injected into the circumflex coronary artery via the center injection tube was made as described previously (8). Second, after completion of the experiment, 0.5 ml of a saturated solution of crystal violet was injected into the anterior descending branch of the beating heart in the same manner as the veratridine.

The criteria for a valid experiment were the absence of crystal violet staining in the circumflex branch past the flow transducer tip and the location of the side injection port at least 2 mm within the coronary ostium.

After initial pilot studies in which the methodology and the experimental design were worked out, the experiment was conducted with 15 dogs. Eight dogs passed these validation criteria and had the uninterrupted pacing mentioned earlier. Most of the rejections were due to inadequate pacing.

**DATA ANALYSIS**

Analog records were read every 5 seconds for a 15-second period preceding veratridine injection, every 2 seconds for a 20-second period immediately following the injection, and then every 5 seconds for the 20-50-second interval following the injection. A straight line was drawn through the diastolic portion of the pulsatile flow record for one beat on each side of the time point; this line was used as the basis for simultaneous diastolic flow and pressure measurements for each of the two beats. Diastolic coronary conductance (flow/pressure) was calculated for each of the two beats, and the average of the two beats was used as a single value for that time point.

The experiment was designed to have each dog serve as its own control, with the values preceding veratridine injection being the control data. The control value for an individual dog was taken to be the average of the values 15 seconds, 10 seconds, and 5 seconds before veratridine injection. The percent of preinjection control was calculated for each time point (−15 seconds through +50 seconds) for each experimental condition and each dog. The averages of these values for all eight dogs are shown in the figures. The standard errors given in the figures are a measure of the variability among dogs and are based on the statistically independent responses of the eight dogs (degrees of freedom = 7).

Two-tailed paired t-tests were used to compare the response of an individual dog before interruption of the reflex arc with the same dog’s response after either vagotomy or atropine administration. Since the responses of the four dogs given atropine were very similar to those of the four dogs subjected to vagotomy, these two treatments were analyzed together. The t-test was performed for each time point in a paired manner for each dog, always based on eight responses expressed as...
percents of the preinjection control values. The statistical results are given in Figure 6.

Results

Injection of veratridine into the anterior descending and septal branches of the left coronary artery in closed-chest, anesthetized dogs resulted in bradycardia and arterial hypotension, the Bezold-Jarisch reflex. Interpretation of the coronary vascular response is difficult with such great changes in heart rate and aortic blood pressure.

The peripheral vasodilation was lessened by administering an alpha-receptor blocking agent (Dibozane), adrenergic cardiac effects were prevented with a beta-receptor blocking agent (propranolol), and a constant heart rate was maintained by electrical pacing. Under these circumstances, injection of 5 μg of veratridine in the anterior descending and septal branches (but not in the circumflex branch) resulted in a clear vasodilation and an increase in flow in the circumflex coronary artery (Fig. 1). The average response for all eight experiments is given in Figure 2. Mean circumflex coronary artery blood flow increased 63% from preinjection values, whereas mean arterial blood pressure fell 8 mm Hg. Diastolic coronary conductance in the circumflex branch increased 88% from preinjection values.

It was postulated that the mechanism causing the vasodilation in the circumflex coronary artery from injection of veratridine into the anterior descending coronary artery is a reflex with its efferent path in the vagus. The role of the vagus was tested by repeating the experiment after bilateral cervical vagotomy (Fig. 3). The average response from four dogs subjected to vagotomy is shown in Figure 4. Coronary vasodilation secondary to veratridine administration was greatly reduced by vagotomy.

The efferent path was tested in the remaining four dogs by atropine administration without vagotomy. The average response from the dogs given atropine is shown in Figure 5. Atropine without vagotomy also greatly reduced the reflex coronary vasodilation.

Figure 6 shows that the diastolic conductance was significantly less in the period 6–14 seconds following veratridine injection after either vagotomy or atropine administration than it had been before interruption of the reflex arc. The difference indicates a reflex with its efferent path in the vagus.

Discussion

The determinants of coronary blood flow may be conveniently discussed under four headings: (1) perfusion pressure, (2) myocardial systolic compression of coronary vessels, (3) myocardial metabolism, and (4) direct neural control of the coronary vessels.

Perfusion Pressure.—Coronary blood flow is dependent on an adequate perfusion pressure, and increases in coronary blood flow could result from an increase in aortic blood pressure. In the present experiment, a 60% increase in coronary blood flow was observed with an 8-mm Hg fall in aortic blood pressure. This result is clear evidence of coronary vasodilation rather than a passive increase in blood flow secondary to an increase in pressure.
Myocardial Systolic Compression.—With each heart beat, the ventricles compress the coronary vessels and hinder blood flow during systole, as can be observed from the pulsatile flow records shown in Figures 1 and 3. The effects of systolic compression can be avoided when coronary blood flow records are interpreted by determining a resistance...
REFLEX CORONARY VASODILATION

Effects of veratridine administration in the anterior descending coronary artery after atropine administration. Diastolic coronary conductance is expressed as a percent of the preinjection value calculated as the average of the values 15, 10, and 5 seconds before injection. Each point represents the average of four observations in four dogs. The bars indicate ±1 SE.

Diastolic conductance in the circumflex coronary artery following veratridine injection in the anterior descending coronary artery. The control curve is the same as that given in Figure 2, and the vagotomy or atropine curve is the average of the two curves given in Figures 4 and 5. Conductance is expressed as a percent of the preinjection value calculated as the average of the values 15, 10, and 5 seconds before injection. Each point represents the average of eight observations in eight dogs. The statistical significance between the responses with and without the reflex arc intact was calculated separately for each time point by the paired t-test.

Myocardial Metabolism.—Cardiac metabolism is a determinant of coronary blood flow through a local regulatory mechanism. The rate of myocardial oxygen consumption is related to heart rate and tension development (17-19). In the present experiments, the heart was paced at a constant rate, and a decrease was observed in aortic blood pressure, indicating that myocardial oxygen consumption probably did not increase. Thus, the coronary vasodilation observed in this study is probably not due to augmented cardiac metabolism. Beta-receptor blockade with propranolol would prevent increases in contractility that might increase cardiac oxygen metabolism.

Neural Control.—Sympathetic alpha-receptor coronary vasoconstriction has been observed (11, 20-22), but it is unlikely that the vasodilation observed in the present investigation was due to inhibition of sympathetic tone, because sympathetic alpha-receptor activity was blocked by Dibozane, and the vasodilation elicited by veratridine was prevented by atropine. Direct parasympathetic cholinergic coronary vasodilation has been demonstrated previously (6, 20, 23). The most probable interpretation of our results is that veratridine injected into the anterior descending and septal branches of the left coronary artery elicited a reflex parasympathetic vasodilation in the circumflex branch.

Vagal afferent traffic from cardiac receptors stimulated by veratrum alkaloids has been extensively studied by numerous investigators and has been reviewed by Paintal (24, 25). Intracoronary administration of veratridine stimulates a variety of receptors with different afferent fiber size. The
functional role of these receptors is not well understood, although it is clear that some of them are mechanoreceptors sensitive to ventricular distortion. Although veratrum alkaloids are capable of stimulating receptors in the great vessels and the nodose ganglion, it is most likely that the effects observed in the present study were due to the known action of veratridine on cardiac receptors. The veratridine was injected directly into the coronary circulation, as verified by dye injection. Intravenous (inferior vena cava) or intra-arterial (ascending aorta) injection of the same dose (5 μg) of veratridine used in the coronary artery failed to produce detectable responses.

Jarisch and co-workers (2-4) demonstrated that the vagus is the afferent path for reflex parasympathetic bradycardia secondary to intracoronary veratrum alkaloid injection. This finding indicates that the probable afferent path for the reflex parasympathetic coronary vasodilation observed in these experiments is the vagus. However, it is possible that sympathetic afferent fibers participate in the reflex. Cardiac sympathetic afferent fibers are also stimulated by veratridine (26, 27).

The existence of intercoronary reflexes (a response initiated by a receptor in one coronary vascular bed resulting in reflex vasomotion in a different coronary vessel) has been proposed previously. Manning and co-workers (28-30) have observed that death due to myocardial infarction secondary to coronary artery ligation in dogs is less frequent in dogs protected by cardiac sympathetic nerves. One postulated mechanism for this effect was the stimulation of an intercoronary reflex spasm occurring in the unligated coronary vessels. Guzman et al. (31) selectively catheterized the anterior descending or circumflex branch of the coronary artery for the injection of lycopodium spores in closed-chest dogs. Embolization of one coronary branch produced vasoconstriction of the other branch demonstrated in coronary angiograms. Curiously, pretreatment with atropine (0.1 mg/kg, iv) prevented the vasoconstriction. Coronary blood flow was not measured and heart rate was uncontrolled.

In contrast to these studies in which intercoronary reflex vasoconstriction has been suggested without measurement of coronary blood flow, there have been a number of investigations employing coronary blood flow measurements which have failed to find an intercoronary reflex vasoconstriction from occluding a coronary vessel (32-37). Increased blood flow was observed in the nonoccluded branch in response to coronary artery occlusion in all of these studies. There are several factors which probably contributed to the augmented flow in the unoccluded branch: (1) increased collateral flow to the compromised area because of the new pressure gradient across the collateral vessels due to the coronary artery occlusion, (2) increased blood flow to the unaffected myocardium which beats more forcefully in compensation for the function lost in the compromised area, (3) decreased myocardial tissue pressure secondary to the occlusion which increased flow, a mechanism stressed by Herzberg et al. (35). Although these mechanisms provide an adequate explanation for the increased flow in the unoccluded branch following coronary artery occlusion, it is possible that an intercoronary reflex vasodilation may also play a role. Grayson and co-workers (37) evaluated the effect of atropine on augmented coronary blood flow in an unoccluded branch following coronary artery ligation, estimating coronary blood flow by the thermal conductivity method. Animals pretreated with atropine showed less vasodilation in the unoccluded coronary artery branch than did an untreated group, but the variability was large and the difference was not judged to be significant. Heart rate was uncontrolled.

The postulated reflex vasomotion in one coronary vessel resulting from occlusion of another coronary artery has been called an “intercoronary reflex” in the past. However, the present findings are more accurately described as a “cardiocoronary reflex,” since veratrum-sensitive receptors have been identified in the myocardium in electrophysiological studies.

Some 30% of patients experiencing a myocardial infarction have an early bradycardia (38). Since the bradycardia is relieved by atropine in such cases, clinicians have postulated that myocardial changes associated with infarction stimulate cardiac receptors to initiate reflex bradycardia (39, 40). Bradycardia secondary to coronary artery occlusion has been observed in cats (41, 42), and Thorén has recently demonstrated that cardiac receptors activated by veratrum alkaloids are also activated by coronary artery occlusion (43). Mark et al. (44) have found that veratrum-sensitive receptors are insensitive to hypoxia and hypercapnia, evidence suggesting that myocardial distortion in an infarcted area may be the mechanical stimulus to these receptors. If patients undergoing a myocardial infarction have a reflex bradycardia triggered from receptors in the myocardium, it is
quite possible that they may also have a reflex coronary vasodilation, as demonstrated in the present experiments. The implications of such a reflex vasodilation regarding the marginal zone at the border of the ischemic area remain to be determined.

In summary, a new parasympathetic cardiocoronary reflex has been demonstrated. Veratridine stimulation of receptors in the area of the ventricular myocardium perfused by the anterior descending and septal coronary arteries resulted in reflex parasympathetic coronary vasodilation in the circumflex coronary artery independent of vagal chronotropic and inotropic effects.

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