Stimulation by Bradykinin of Afferent Vagal C-Fibers with Chemosensitive Endings in the Heart and Aorta of the Dog

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SUMMARY Bradykinin applied directly to the epicardium evokes a reflex increase in blood pressure by stimulating sympathetic afferent nerve endings in the heart, but injected into the coronary artery it evokes vagally mediated reflex decreases in heart rate and blood pressure. The afferents initiating these latter depressor effects have not been identified. We have attempted to determine which vagal sensory nerve endings in the heart are stimulated by bradykinin. In anesthetized dogs, we recorded impulses from afferent vagal fibers with endings in the heart and aorta and injected bradykinin (0.3-1.0 μg/kg) into the left atrium. Neither A- nor C-fiber mechanoreceptors nor aortic body chemoreceptors were stimulated directly by bradykinin, any changes in firing of atrial or ventricular mechanoreceptors, or of aortic baroreceptors or chemoreceptors, being secondary to the cardiovascular effects of bradykinin. However, 16 of 20 irregularly discharging vagal C-fibers with chemoceptive endings in the left atrium, left atrium, and aorta were stimulated by bradykinin; firing increased from 0.2 ± 0.1 to 7.8 ± 1.4 (mean ± SE) impulses/sec and usually remained above control for about 30 seconds. These chemosensitive endings were not stimulated by ventilating the lungs with 5% O₂ in N₂, but they were stimulated by injecting capsaicin or phenyl diguanide into the left atrium. Four chemosensitive endings in the ventricular epicardium were also stimulated by dripping bradykinin (1 μg/ml) onto the heart.

We suggest that these chemosensitive vagal C-fibers are responsible for the reflex decreases in heart rate and blood pressure elicited by bradykinin. Circ Res 46: 476-484, 1980

BRADYKININ, a polypeptide with potent vasodilator and algiesic properties, is released by the ischemic myocardium (Kimura et al., 1973). Acting together with prostaglandins, bradykinin is believed to be the natural stimulus for excitation of the sympathetic afferent nerve endings signalling the pain of myocardial ischemia (Staszewska-Barczak et al., 1976). The cardiovascular effects of bradykinin produced experimentally in anesthetized dogs and cats vary with the route of administration. Injected intravenously, bradykinin decreases peripheral resistance by a direct vasodilator action, heart rate increasing reflexly as a result of systemic hypotension (Nakano, 1965). Applied directly to the exposed epicardium, bradykinin stimulates sympathetic afferent nerve endings (Uchida and Murao, 1974; Nishi et al., 1977; Baker et al., in press) and causes reflex increases in blood pressure and heart rate (Staszewska-Barczak et al., 1976). Injected into the left coronary artery in dogs, bradykinin causes vagally mediated decreases in heart rate and blood pressure (and occasionally also in breathing) by a reflex mechanism believed to be identical with that responsible for the coronary chemoreflex, or Bezold-Jarisch effect (Neto et al., 1974). The afferent vagal fibers responsible for the reflex evoked by bradykinin have not yet been identified in action potential studies.

We have examined in dogs the effect of bradykinin on afferent vagal impulse traffic from the heart. Although unmyelinated vagal fibers appear to carry most if not all of the afferent input when the coronary chemoreflex is evoked by chemicals other than veratridine (Coleridge and Coleridge, 1979), we have not confined our study to the examination of unmyelinated fibers. Bradykinin stimulates both myelinated (Nishi et al., 1977; Baker et al., in press) and unmyelinated sympathetic afferents (Baker et al., in press) in the heart; it also stimulates certain cutaneous myelinated afferents, as well as unmyelinated ones (Beck and Handwerker, 1974). We therefore examined the full range of vagal afferents known to be situated within the vascular territory supplied by the left coronary artery (Coleridge et al., 1973). They included mechanoreceptors (aortic baroreceptors, left atrial receptors, and left ventricular receptors), both those with A-fibers and those with C-fibers, and aortic body chemoreceptors (A-fibers and C-fibers). We also recorded impulses from vagal C-fibers with an irregular and sparse discharge whose endings were in the ventricle, atrium, or aorta (Coleridge et al., 1964a, 1973, 1979). Although not chemoreceptors in the conventional sense, for they are not stimulated by hypoxia or cyanide, these irregularly firing endings are stimulated by a number of chemicals, including capsaicin,
phenyl diguanide, veratridine, and prostaglandin E₂ (Coleridge et al., 1964a, 1973, 1979; Baker et al., 1979). In this paper we refer to these particular vagal afferents as "chemosensitive endings" to distinguish them from the chemoreceptors of the aortic bodies.

**Methods**

**General**

Dogs (12–25 kg) were given promazine hydrochloride (Sparine, Wyeth Laboratories, 50 mg, im); 1 hour later they were anesthetized with 0.25 ml/kg, iv, of a 1:1 mixture of solutions of Dial Compound (allobarbarial 100 mg/ml, urethane 400 mg/ml, Ciba) and sodium pentobarbital (50 mg/ml). The trachea was cannulated, and the chest was opened in the midline. The pericardium was opened widely. The lungs were ventilated by a Harvard pump whose expiratory outlet was placed under 3–5 cm of water.

End-tidal P\text{CO}_2 was monitored by a Beckman LB-1 gas analyzer and was kept at about 35 mm Hg by adjusting ventilation. Pressure in the tracheal cannula was recorded. Blood pressure in the aortic arch was recorded through a catheter inserted via a femoral artery; pressure in the left atrium or left ventricle was recorded through a catheter inserted via a pulmonary vein. Pressures were recorded with Statham P23Gb strain gauges. Vagal impulses were recorded (see below) and were counted by ratemeters (Rate/Interval Analyzer, Frederick Haer & Co.) whose window discriminators were set to accept potentials of a particular amplitude. An electrocardiogram was also recorded. After amplification, action potentials, pressures, and other variables were recorded by an ultraviolet light recorder (SE Laboratories), and all but the action potentials were stored in ice for 5–10 minutes until their P\text{O}_2, P\text{CO}_2, and pH were measured (see below). Arterial blood samples were withdrawn aerobically before and during hypoxia, and were stored in ice for 5–10 minutes until their P\text{O}_2, P\text{CO}_2,
Three methods of stimulation used in the preliminary identification of vagal C-fibers with chemosensitive endings in the heart. 

A: Chemical stimulation. Injection of phenyl diguanide (20 μg/kg) into the left atrium at the signal stimulated a chemosensitive ending in the left ventricular wall (fiber conduction velocity, 1.1 m/sec). 

B: Punctate stimulation. Probing the root of the left atrial appendage stimulated a chemosensitive ending (larger spikes; fiber conduction velocity, 1.3 m/sec); the smaller spikes with a cardiac rhythm arose from a C-fiber mechanoreceptor in the dorsal wall of the left atrium (conduction velocity, 1.0 m/sec). 

C: Stimulation by cardiac distension. Occluding the descending aorta for about 8 seconds increased left ventricular and aortic pressures and stimulated a chemosensitive ending in the dorsal wall of the left ventricle (fiber conduction velocity, 1.3 m/sec). Note that the evoked discharge was devoid of a cardiac rhythm. 

ECG, electrocardiogram; AP, action potentials; ABP, arterial blood pressure recorded in the aortic arch; LVP, left ventricular pressure; Pt, tracheal pressure (upstroke representing inflation).

and pH were determined with an automatic blood gas/pH analyzer (Corning 175).

Chemicals

We injected chemicals into the right atrium through a catheter in an external jugular vein, or into the left atrium through a catheter in a pulmonary vein. Bradykinin triacetate, phenyl diguanide, and sodium cyanide were dissolved in 0.9% NaCl solution. Capsaicin was dissolved as previously described (Coleridge et al., 1964b). Bradykinin (0.3-1.0 μg/kg), phenyl diguanide (10-20 μg/kg), sodium cyanide (200 μg/kg), and capsaicin (10-20 μg/kg) were injected in 0.5-1.0 ml saline and were washed in with 1.0 ml of saline; injection was completed in 1-2 seconds. Injection response times were measured from the beginning of injection. When a chemosensitive ending appeared to be near the surface of the heart or aorta, we applied bradykinin topically. In the case of an ending in the ventral epicardium of the left ventricle, for example, we retracted the cut edges of the pericardial sac and dripped 0.5-1.0 ml of bradykinin solution (1 μg/ml) onto the receptor. Control injections or applications of the solvents in which the various chemicals were administered had no effect on any of the fibers examined.

We did not systematically examine the phenomenon of tachyphylaxis. In early observations on the chemosensitive C-fibers stimulated by bradykinin, we found that tachyphylaxis occurred if injections were given at intervals of 5-10 minutes, but that it usually could be avoided by increasing the interval between injections to at least 20 minutes. Because
of the limited active life of the chemosensitive C-fibers on the recording electrodes, we did not systematically examine their dose-response characteristics. Our injection of 4-20 μg of bradykinin (0.3-1.0 μg/kg) into the left atrium was likely to produce a concentration in coronary arterial blood less than that produced by Neto et al. (1974), who injected 1 μg of bradykinin directly into the left coronary artery.

Control firing rates are averaged over 20 seconds before the injection of bradykinin; maximum firing rates evoked by bradykinin are averaged over 5 seconds at the peak of the response; both are expressed as impulses per second. All values are expressed as the mean ± standard error of the mean. We used paired “t-tests” to determine statistical significance.

Results

C-Fibers with Chemosensitive Endings

We recorded impulses from 20 C-fibers (conduction velocities, 0.6-1.9 m/sec) with chemosensitive endings. Eleven of the endings were in the left ventricle, five were in the left atrium, and four were in the aorta. Eighteen of the 20 endings were stimulated by capsaicin or phenyl diguanide, or by both. The remaining two endings responded to neither of these chemicals, but because they were stimulated by bradykinin (see below) and because they resembled chemosensitive endings in all other respects, we have included them in the category of chemosensitive endings. Chemosensitive endings never fired with a cardiac rhythm of discharge, even when, as was the case with seven of them, they were stimulated by distension of the heart (Fig. 1C) or aorta. They were not stimulated by ventilating the lungs with 5% O2 in N2 (arterial Po2 decreasing to less than 30 mm Hg) or by injecting sodium cyanide (200 μg/kg) into the left atrium.

Injection of bradykinin (0.3-1.0 μg/kg) into the left atrium stimulated 16 of the 20 chemosensitive endings (Figs. 2-4), firing increasing from 0.2 ± 0.1 to 7.8 ± 1.4 impulses/sec at the peak of the response. Firing began 3-15 seconds (8.8 ± 1.0 seconds) after injection (three of the endings being stimulated by guest on July 14, 2017 http://circres.ahajournals.org/ Downloaded from
within 3–5 seconds of the beginning of the injection), and in most cases it had largely reverted to the original frequency 20–50 seconds later. Several fibers continued to fire slightly above the control frequency for several minutes, however (Fig. 4A), and two endings that were very strongly stimulated continued to fire at a frequency of 4–9 impulses/sec for 6–7 minutes. Of the 16 chemosensitive endings stimulated by bradykinin, 10 responded with intermittent bursts of impulses having no obvious relationship to the cardiac or ventilatory cycles (Fig. 3, A and B; Fig. 4A) and six responded with a continuous discharge (Fig. 2B).

Mean arterial blood pressure invariably decreased, from 99.4 ± 3.1 to 54.3 ± 2.3 mm Hg, when bradykinin was injected into the left atrium (Figs. 2, 3, 4A). Pressure began to decrease 3–9 seconds after the injection and had largely returned to the control level 40–90 seconds later, although a small residual depression of 5–10 mm Hg often remained for several minutes. None of the chemosensitive endings was stimulated when we produced similar decreases in arterial or ventricular pressure by partially occluding the inferior vena cava. We therefore concluded that the firing evoked by bradykinin was not secondary to the hemodynamic effects of bradykinin but was due to direct chemical stimulation.

Four of the endings stimulated by injection of bradykinin appeared to be in or very near the epicardium, because we were able to stimulate them by lightly stroking the left ventricle with a fine bristle. These four endings were also stimulated when we dripped bradykinin (1 μg/ml) on to the epicardium (Fig. 4B), activity increasing from 1.3 ± 1.3 to 9.2 ± 4.8 impulses/sec, and remaining above control for 20–180 seconds (mean, 62 seconds). (The rather high control discharge of these four endings probably was a residual effect of the bradykinin previously injected into the left atrium.) Although blood pressure invariably decreased when bradykinin was injected into the left atrium (Figs. 2–4A), it increased by 5–30 mm Hg when bradykinin was dripped on the epicardium (Fig. 4B). None of the four endings was stimulated when we partially occluded the descending aorta to produce an increase in aortic arch pressure similar to that produced by applying bradykinin to the epicardium.

**Cardiovascular Mechanoreceptors**

We recorded impulses arising from 31 mechanoreceptors in the left ventricle, left atrium, or aortic arch. Fifteen had A-fibers (conduction velocities, 16.7–50.1 m/sec) and 16 had C-fibers (0.6–2.0 m/sec). None was stimulated by capsaicin or phenyl diguanide. All were stimulated by probing and distending the heart or aorta. When active, all invariably fired with an obvious cardiac rhythm.

Neither A- nor C-fiber mechanoreceptors were stimulated directly by bradykinin: all changes in firing appeared to be secondary to the hemody-
DYNAMIC EFFECTS OF THE CHEMICAL. FOR EXAMPLE, BRA-DYKININ INJECTED INTO THE LEFT ATRIUM DECREASED ARTERIAL BLOOD PRESSURE AND DECREASED THE FIRING OF AORTIC BARORECEPTORS WITH A-FIBERS (FIG. 2A). C-FIBER BARORECEPTORS (THORÉN AND JONES, 1977; KAUFMAN ET AL., 1978), WHICH HAVE A HIBERIOR HIGHER THAN THAT OF THEIR A-FIBER COUNTERPARTS, USUALLY WERE SILENT AND REMAINED SO DURING THE HYPOTENSION INDUCED BY INJECTION OF BRA-DYKININ. HOWEVER, WHEN BRA-DYKININ WAS APPLIED DIRECTLY TO THE EXPOSED EPICARDIUM, ARTERIAL BLOOD PRESSURE INCREASED, AN EFFECT WHICH IS ATtributed TO THE STIMULATION OF SYMPATHETIC CARDIAC AFFERENTS (STASZEWSKA-BARczAK ET AL., 1976). This increase in pressure, which invariably stimulated aortic baroreceptors with A-fibers, was sometimes sufficient to stimulate high-threshold aortic baroreceptors with C-fibers. The augmented discharge invariably retained its characteristic cardiovascular pattern, and we never observed a continuous or bursting discharge like that evoked when bradykinin stimulated chemosensitive endings. Similarly, changes in firing of A- and C-fiber mechanoreceptors in the heart appeared to be entirely secondary to the hemodynamic effects of bradykinin. Thus, bradykinin increases venous return and cardiac contractility (MAXWELL ET AL., 1962; ROWE ET AL., 1963; NAKANO, 1965), changes that probably accounted for the small increase sometimes observed in the firing of cardiac mechanoreceptors, both those with A-fibers and those with C-fibers (Fig. 4A and B). Effects of bradykinin on cardiac and aortic mechanoreceptors invariably could be mimicked by occluding the descending aorta or the inferior vena cava to produce the appropriate changes in cardiac or aortic pressure. Cardiac slowing, which occurred in about a quarter of the experiments (see below), undoubtedly contributed to the increased discharge of some cardiac mechanoreceptors.

AORTIC BODY CHEMORECEPTORS

We examined the effect of bradykinin on seven aortic body chemoreceptors; three had A-fibers (conduction velocities, 9.0–10.9 m/sec) and four had C-fibers (0.5–1.1 m/sec). Unlike the chemosensitive endings, aortic chemoreceptors were stimulated by ventilating the lungs with 5% O₂ in N₂, and by injecting NaCN into the left atrium. Chemoreceptor activity increased slightly, from 1.0 ± 0.4 to 3.0 ± 0.8 impulses/sec, when bradykinin was injected into the left atrium, the increase beginning 18.3 ± 3.8 seconds after the injection and lasting 17.0 ± 2.8 seconds. This small increase was probably due to the decrease in blood pressure, for a similar increase

A

B

FIGURE 4 Stimulation by bradykinin of a chemosensitive C-fiber (conduction velocity, 1.4 m/sec) whose ending was in the ventrolateral wall of the left ventricle near the epicardial surface. A: Bradykinin (0.5 µg/kg) was injected into the left atrium at the signal. Interval of 30 min between A and B. B: 1 ml bradykinin solution (1 µg/ml) was dripped on to the left ventricular epicardium at the signal. Note that blood pressure decreased when bradykinin was injected into the left atrium (A), but it increased when bradykinin was applied to the epicardium (B). In both A and B the ventricular C-fiber was the only active fiber in the vagal slip. IF, impulse frequency (impulses/sec). Other abbreviations as in Figure 1.
in firing occurred when we decreased pressure an equal amount by occluding the inferior vena cava.

**Effect of Bradykinin on Heart Rate**

The control heart rate before injection of bradykinin was 165.7 ± 4.2 beats/min. In 40% of experiments, heart rate increased by 10–52 (mean 20.8) beats/min when bradykinin was injected; in 23% it decreased by 12–52 (mean 27) beats/min; in the rest it varied less than ±6 beats/min. When we partially occluded the inferior vena cava to produce a decrease in blood pressure equal to that caused by bradykinin, heart rate invariably increased (from 157.0 ± 7.6 to 175.3 ± 9.3 beats/min).

**Discussion**

Bradykinin, in the concentrations used in these experiments, was highly selective in its action on vagal afferents in the heart and aorta, stimulating only C-fibers with chemosensitive endings. Changes in firing of all other endings, whether mechanoreceptors with A- or C-fibers, or aortic chemoreceptors, appeared to be secondary to the hemodynamic effects of bradykinin. These results provide further support for the notion that afferent vagal C-fiber endings in the heart are not a homogeneous group of polymodal endings equally sensitive to chemical and mechanical changes, but comprise at least two groups of endings, each responding primarily to either chemical or mechanical changes in the wall (Coleridge and Coleridge, 1977, 1979; Coleridge et al., 1979).

The chemosensitive endings, first identified in the ventricles (Coleridge et al., 1964; Sleight and Widdicombe, 1965) and later in the atria, aorta, and pulmonary artery (Coleridge et al., 1973), are stimulated by a number of foreign chemicals, including capsaicin, phenyl diguanide, nicotine, and the veratrum alkaloids, and also by the naturally occurring substances, bradykinin (present results) and PGF2α (Baker et al., 1979). These endings do not behave as conventional cardiac mechanoreceptors, for they never fire with a cardiac rhythm, but they are not totally unresponsive to vascular distension. Thus, Coleridge et al. (1973) found that some chemically sensitive C-fiber endings in the pulmonary artery and aorta were stimulated by abnormally high pressures (higher than 70 and 200 mm Hg, respectively), and a similar response to gross distension of the heart and aorta was observed in some of the present experiments (Fig. 1C). It is conceivable that the stimulation of C-fiber endings by such gross vascular distension involves a chemical mediator, for the prostaglandins, which stimulate vagal C-fiber endings in the heart (Baker et al., 1979), are known to act as stretch receptors or baroreceptors much like their myelinated counterparts. Although many of them are stimulated by nicotine and the veratrum alkaloids (Sleight and Widdicombe, 1965; Oberg and Thorén, 1972), they are not stimulated by four substances that stimulate the chemosensitive endings i.e., capsaicin, phenyl diguanide, and bradykinin (present results) and the prostaglandins (Baker et al., 1979).

Because the chemosensitive endings appear to be the only vagal afferents within the vascular territory of the coronary arteries to be directly stimulated by bradykinin, it seems likely that they constitute the afferent arm of the coronary depressor chemoreflex described by Neto et al. (1974). Some chemosensitive C-fibers began to fire 3–5 seconds after the beginning of the left atrial injection, the average delay being 8.8 seconds. Thus, when the difference in injection site is taken into account, the onset of afferent stimulation agrees well with the latency (3–5 seconds) of the reflex effects obtained by Neto et al. Some chemosensitive C-fibers continued to fire for as long as 6–7 minutes, a response in keeping with the relatively long duration (3–5 minutes) of the reflex changes. Since the reflex effects of aortic body stimulation are pressor rather than depressor (Daly and Ungar, 1966), a secondary increase in aortic chemoreceptor firing such as that observed in our experiments clearly could not contribute in a positive sense to the depressor chemoreflex evoked by bradykinin.

Our experimental preparation allowed us to identify the vagal cardiac afferents stimulated by bradykinin, but it was of limited value for demonstrating the reflex effects of stimulating these afferents because the left vagus nerve was partially dissected. Moreover, we injected bradykinin into the left atrium, and much of the resultant decrease in arterial blood pressure undoubtedly was due to a direct vasodilator effect. However, even though arterial blood pressure invariably decreased, cardiac slowing occurred in about a quarter of our experiments, an effect that was probably a manifestation of the vagal depressor chemoreflex.

Bradykinin also excites the cardiac endings of afferent fibers that travel to the spinal cord in sympathetic nerve branches (Uchida and Murao, 1974; Nishi et al., 1977; Baker et al., in press), but its action on sympathetic cardiac afferents is not confined, as it is in the case of the vagal cardiac afferents, to chemosensitive endings with unmyelinated fibers. Thus, among the sympathetic endings stimulated by bradykinin are mechanoreceptors with a prominent cardiac discharge, some having myelinated fibers, others unmyelinated ones (Uchida and Murao, 1974; Nishi et al., 1977; Baker et al., in press). Nevertheless, bradykinin does stimulate
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a particular group of sympathetic endings that possess several features in common with the vagal chemosensitive endings: their fibers are unmyelinated; their discharge, which is sparse and irregular under resting conditions, never acquires a cardiac rhythm; and most of them are relatively insensitive to mechanical distortion, but some are stimulated in an irregular fashion by gross distension of the heart (Baker et al., in press). There is at present no evidence to indicate whether the mechanosensitive or the chemosensitive types of sympathetic afferent, or both, are responsible for the reflex increase in blood pressure evoked by application of bradykinin to the epicardium (Staszewska-Barczak et al., 1976).

That application of bradykinin to the epicardium evokes reflex effects of sympathetic origin, whereas injection of bradykinin into the coronary circulation evokes reflex depressor effects of vagal origin (Fig. 4), may simply reflect the relative distribution of the two afferent systems innervating the heart, the majority of sympathetic afferent endings being near the epicardial surface, and the majority of vagal afferent endings being deeper in the substance of the myocardium (Coleridge et al., 1978). A further contributing factor may be that, when sympathetic and vagal cardiac afferents are stimulated simultaneously, as they probably are when bradykinin is injected into the coronary artery, the vagal input largely determines the reflex outcome—a vagal predominance that undoubtedly accounts for the fact that the demonstration of sympathetic cardiovascular reflexes often requires that the vagus nerves be cut (Coleridge et al., 1978). Similarly, recognition of the left ventricle as the preferential trigger zone for the vagal depressor (coronary) chemoreflex may simply reflect the especially rich afferent vagal C-fiber innervation of this particular chamber (Coleridge and Coleridge, 1979; Walker et al., 1978).

Although the existence of chemosensitive vagal C-fiber endings in the heart was first demonstrated in dogs with the aid of foreign chemicals such as capsaicin, veratridine, and nicotine (Coleridge et al., 1964a; Sleight and Widdicombe, 1965), their recent demonstration sensitivity to bradykinin (present results) and the prostaglandins (Baker et al., 1979)—substances that are known to be formed and released in the myocardium—gives some clue to their possible physiological role. To account for the cardiac actions of these endogenous substances, Needleman (1976) has suggested a hypothetical sequence of events which involves stimulation of chemosensitive nerve endings. He postulates that, in myocardial ischemia, bradykinin and prostaglandin E (or some precursor of the latter) act independently or together to dilate the coronary vessels and to stimulate sympathetic afferents evoking the warning sensation of pain, and also vagal afferents causing reflex bradycardia and hypotension. The latter vagal reflex mechanism might be expected to have a protective effect upon the myocardium, decreasing oxygen demand and thus possibly raising fibrillation threshold (Myers et al., 1974). The sympathetic chemosensitive endings with C-fibers, being relatively insensitive to changes in vascular pressure or volume, appear the most likely candidates for mediating the sensation of cardiac pain evoked by bradykinin. Their vagal counterparts—the chemosensitive C-fiber endings described in the present study—are almost certainly not involved in the conscious appreciation of pain, for their stimulation in conscious dogs by intrapericardial injection of nicotine evokes the characteristic vagal depressor effects but the dogs give no sign of pain (Sleight, 1964).

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