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Evidence for an Indirect Sympathetic Control of Atrial Stretch Receptor Discharge in the Dog

By Irving H. Zucker and Joseph P. Gilmore

ABSTRACT

Experiments were performed to determine the influence of cardiac sympathetic efferent nerve stimulation on the discharge rate of atrial type B stretch receptors in the anesthetized, open-chest dog. In all experiments, the left stellate ganglion was stimulated following volume expansion. To determine the effects of stellate stimulation, the responses of atrial receptors were observed during the withdrawal of blood in steps following intravascular volume expansion. Stimulation of the stellate ganglion decreased receptor discharge and left atrial pressure in all experiments. A change from a control left atrial pressure of 2.5 cm H2O (in peak left atrial v-wave pressure) resulted in a mean increase in receptor discharge of 6.6 ± 1.4 spikes/cardiac cycle during stellate stimulation; however, a change from a control pressure of 0.0 cm H2O resulted in a mean decrease in receptor discharge of 1.5 ± 1.5 spikes/cardiac cycle. The curves relating the change in atrial receptor discharge to the change in left atrial pressure during hemorrhage and the curve for these parameters during stellate stimulation were not significantly different from each other. Apparently, the decreased discharge during sympathetic stimulation was the result of a decline in left atrial pressure rather than a result of any direct effect on the receptor per se.

KEY WORDS

left atrial pressure stellate ganglion atrial type B receptors cardiac sympathetic nerves nerve stimulation atrial contractility vagus hemorrhage

Within the atria of several species there appear to be two types of receptors with fibers that traverse the vagus nerve. These receptors have distinctly different discharge patterns which have been designated type A and type B by Paintal (1). Type A receptors discharge during atrial systole, and type B receptors have a characteristic discharge pattern during the v wave, i.e., the period of filling during the atrial pulse. Type B receptor discharge is increased by stimuli that increase atrial pressure, i.e., by intravascular volume expansion (2) and by inflation of a balloon in the atria (3, 4). It has been suggested that type B receptors monitor atrial and intrathoracic blood volumes and provide the afferent limb of a reflex which controls the secretion of antidiuretic hormone (ADH) (5–9).

Although there have been several reports about the influence of sympathetic nerve activity on arterial baroreceptors (10–14), the extent to which efferent nerve activity can alter the activity of atrial type B receptors has not been determined. Therefore, the experiments presented in this paper were undertaken to determine if stimulation of cardiac sympathetic efferent nerves can modify type B atrial receptor discharge and, if so, to investigate the mechanisms involved.

Methods

Experiments were performed on mongrel dogs of both sexes (11–25 kg). Each dog was given morphine sulfate (0.5 mg/kg, sc); after 1 hour o-chloralose (100 mg/kg, iv) dissolved in polyethylene glycol (100 mg/ml) was administered. Supplemental doses of chloralose were given as needed. In addition to the anesthetic, several dogs were given gallamine triethiodide (1 mg/kg, iv) to preclude muscular movements. Gallamine triethiodide was always administered with supplemental doses of chloralose.

The trachea was intubated and the dog was connected to a positive-pressure respirator (Harvard Apparatus). The chest was opened through a transverse thoracotomy in the third intercostal space. To measure arterial blood pressure a polyethylene catheter (PE240) attached to a Statham transducer (P23Db) was inserted through a femoral artery into the ascending aorta close to the aortic valve. In addition, catheters (PE240) were placed in the left femoral artery to withdraw blood and in the right femoral vein to administer fluids and drugs. The pericardium was incised on the right and the left sides to expose both atrial appendages. The remainder of the pericardium was left intact. Either a stainless steel cannula was placed in the left atrium through the left

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atrial appendage or a catheter-tip transducer was placed in the left atrium through a pulmonary vein to measure left atrial pressure. In the dogs in which the stainless steel cannula was used to measure left atrial pressure, atrial pressure was referred to heart level. The catheter-tip transducer had a flat frequency response from d-c to 20 kHz and was zeroed at the level of the left atrium; the fluid-filled manometer systems had a natural frequency of 7 Hz (P23Bb) and 60 Hz (P23Db) with a 100-cm length of polyethylene tubing (P240). A Walton-Brodie strain-gauge arch was sutured to the right atrial appendage to obtain a qualitative index of changes in atrial contractility. The phase of respiration was determined using a thermistor placed between the intubation tube and the respirator. A bipolar silver-wire electrode was placed about the decentralized left stellate ganglion, and stimulation was accomplished electrically (1 msec, 5-15 v, 5-10 Hz) using a Grass S88 stimulator.

ATRIAL RECEPTOR RECORDING

Recordings of action potentials from vagal afferent fibers whose receptor endings were located in the atria were made according to the procedure described by Coleridge et al. (15) and Sinclair (16). Briefly, the left cervical vagus was exposed, and the outer and the inner sheaths were carefully removed. Slips of the vagus were dissected from the main nerve trunk, cut centrally, and placed over bipolar platinum electrodes for recording and audioamplification; the fibers which possessed a cardiac rhythm were isolated. These fibers were then progressively split until a single active unit was obtained. The recorded action potentials were amplified through a differential amplifier (Tektronix 3A9) and displayed on one channel of a dual-beam oscilloscope (Tektronix 565); a standard lead electrocardiogram (ECC) was recorded on the other channel. All strain-gauge outputs were recorded on a recorder (Beckman 411) and the output was displayed on an ultraviolet oscillograph recorder (Honeywell visicorder model 906) with a frequency response of 0-25 kHz along with the vagal fiber action potentials and the ECC. In some experiments, data were recorded on magnetic tape for subsequent analysis.

Identification of type B atrial receptors was based on the timing of the discharge relative to the EEG and the atrial and the arterial blood pressure pulses. All recordings were made with the respirator turned off at end-expiration. Atrial type B receptors were assumed to fire during atrial filling coincident with the c wave of the atrial pressure pulse and to cease at or just prior to atrial contraction. At the end of all experiments, the dog was bled and the location of the receptor was determined during cardiac standstill by obtaining a high-frequency discharge while probing with the finger and by then further localizing the receptor ending to a few square millimeters of tissue using a fine glass rod. Fourteen type B receptors from 13 dogs were studied. All but one of these receptors originated in the left atrium at the pulmonary venous-atrial junctions; the other receptor originated in the right atrium.

EXPERIMENTAL PROCEDURE

Following the identification of a type B atrial receptor, atrial pressure was increased either by infusing warm, isotonic saline into a femoral vein in 50- or 100-ml increments or by infusing a homologous blood-saline mixture which had been previously warmed to 37°C. After each increment in volume, a recording of the hemodynamic parameters and the fiber discharge was taken. Approximately 15-20 seconds were needed to take a representative record between each step increase in volume. Following volume expansion, atrial pressure was progressively decreased by withdrawal of 25- or 50-ml decrements of blood from the femoral artery with recordings taken at each step or by stimulation of the left stellate ganglion as previously described. Hemorrhage and stellate stimulations were alternated.

Receptor discharge was counted directly from the oscillographic records. The effects of stellate stimulation and hemorrhage on receptor discharge were compared using the two-tailed Student’s t-test.

Results

Figures 1 and 2 show the influence of cardiac sympathetic nerve stimulation on the discharge from left atrial type B receptors. Figure 1A illustrates a control tracing; note the typical firing pattern. Discharge begins at the beginning of the c wave of the left atrial pressure pulse and ceases at the end of the c wave when the atrioventricular valves open. Between Figure 1A and B, isotonic saline (150 ml, iv) was administered to increase left atrial pressure and, thus, receptor discharge. Between Figure 1B and C, left stellate ganglion stimulation was begun and continued while the tracing in C was obtained. This stimulation was associated with a large decrease in receptor discharge, an increase in atrial contractility (right atrial force), an increase in aortic pressure, and a decrease in left atrial pressure. The increase in right atrial force shown in Figure 1 was such that the galvanometer reached its limit; therefore the right atrial force tracing is sheared at its peak. The unusual aortic pressure in Figure 1C probably resulted because the tip of the aortic catheter was close to the aortic valve causing a high-velocity component to be recorded. Sympathetic stimulation decreased receptor discharge in each of the 14 fibers studied. In some cases (Fig. 1) almost total silencing of the receptor discharge was observed. Figure 2 illustrates a left atrial receptor during a control steady state (A), following infusion of 150 ml of saline (B), and during stellate stimulation (C). This receptor exhibited a high-frequency burst at the c wave of the atrial pressure pulse in addition to a prominent c-wave burst; the discharge of the receptor increased with increases in atrial c-wave

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SYMPATHETIC CONTROL OF ATRIAL RECEPTORS

To determine if the decrease in receptor discharge was due to a direct effect of sympathetic nerve stimulation or was secondary to the associated decline in atrial pressure that results from the increase in atrial contractility, experiments were performed in which atrial pressure was increased by volume expansion and then decreased by hemorrhage to obtain a relationship between receptor discharge and atrial pressure while unloading the receptor. This procedure was necessary because the relationship between atrial pressure and type B receptor discharge shows hysteresis (2). Since it has been shown (17, 18) that cardiac nerve stimulation decreases atrial pressure, it was necessary to establish an unloading curve in the absence of sympathetic stimulation and compare the results with those obtained during cardiac sympathetic nerve stimulation. The results from all of these experiments are shown in Figure 3. Cardiac sympathetic nerve stimulation decreased atrial receptor discharge and left atrial pressure in every experiment. However, when compared with the control curve (during hemorrhage) the decrease in receptor discharge was proportional to the decrease in atrial pressure, i.e., the two curves were not significantly different from each other except at A 1.0 cm H2O (P < 0.05) and at A 2.5 cm H2O (P < 0.02). Similar

FIGURE 1

Original tracing showing the influence of cardiac sympathetic nerve stimulation on the discharge of a left atrial type B receptor. A: Control. B: Record taken approximately 30 seconds after infusion of isotonic saline (150 ml). C: Record taken during stimulation of the decentralized left stellate ganglion (10 v, 1 msec, 5 Hz). Spikes = neurogram from atrial type B receptor, RAF = right atrial force, Ao.P. = aortic pressure, and LAP = left atrial pressure.

FIGURE 2

Effect of sympathetic stimulation on a left atrial type B receptor. ECG = electrocardiogram. All other abbreviations are the same as those in Figure 1. A: Control. B: Record taken after infusion of isotonic saline (100 ml). C: Record taken during stimulation of the left stellate ganglion (5 v, 1 msec, 5 Hz).
results were obtained when norepinephrine (5-10 \( \mu \text{g, iv} \)) was administered to increase atrial contractility. Figure 4 illustrates the effects of norepinephrine (5 \( \mu \text{g} \)) on the discharge from a left atrial receptor. Increases in heart rate were similar during stellate stimulation and hemorrhage; therefore, the relationship shown in Figure 3 is similar if spikes/min is used instead of spikes/cycle.

**Discussion**

Available data show that stimulation of sympathetic postganglionic fibers which originate from the superior cervical ganglion and innervate the carotid sinus decreases systemic blood pressure (10-12, 14). Evidence that the reduction in blood pressure is related to an increase in baroreceptor afferent nerve discharge has been presented by Koizumi and Sato (12) using the opossum and by Sampson and Mills (13) using the cat. Both groups have observed that stimulation of the sympathetic nerves which innervate the carotid sinus increases baroreceptor afferent nerve discharge. This effect appears to result from a decrease in the diameter and the dynamic elastic modulus of the carotid sinus (14) rather than from a direct effect of sympathetic nerve stimulation on the receptor (12).

The present experiments showed that the sympathetic nervous system could also modulate activity of atrial type B receptors. As with carotid sinus baroreceptors, the sympathetic control of atrial receptors was indirect rather than direct, and changes in type B receptor activity correlated well with the associated changes in atrial pressure. If the decrease in atrial type B receptor discharge in response to cardiac sympathetic efferent nerve stimulation was due to a direct effect of the latter on the receptor, the two curves shown in Figure 3 should be significantly different from each other.

The carotid sinus-sympathetic control system should function in a negative manner, since lowering carotid sinus pressure decreases carotid baroreceptor discharge, which, in turn, reflexly stimulates the sympathetic nervous system. This stimulation activates the postganglionic sympathetics that innervate the carotid sinus. Therefore, for any given intrasinus pressure, carotid baroreceptor discharge is increased, and this increase tends to reflexly attenuate sympathetic outflow, a response that is not homeostatically appropriate. However, Koizumi and Sato (12) have pointed out that, if a generalized increase in sympathetic activity occurs as it does dur-

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**FIGURE 3**

Relationship between the change in discharge from atrial type B receptors and the change in left atrial pressure prior to (control, open circles) and during stellate ganglion stimulation (closed circles). Vertical bars represent SE. Fourteen receptors were studied.

**FIGURE 4**

Effects of norepinephrine on the discharge of a left atrial type B receptor. Abbreviations are the same as those in Figures 1 and 2. A: Control. B: Record taken after infusion of isotonic saline (150 ml). C: Record taken after injection of 1-norepinephrine (5 \( \mu \text{g} \)).

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ing stress, the increase in sympathetic discharge to the carotid sinus functions in a homeostatically positive manner, since it attenuates the rise in systemic blood pressure.

There is evidence in the literature about the role of atrial receptors and the release of ADH (7). The atrial receptor–sympathetic control system appears to function as a positive-feedback system in the normal animal. For example, in oligemic hypotension, the decrease in venous return and atrial pressure decreases atrial type B receptor discharge and thereby presumably increases the secretion of ADH. Concomitantly, the associated reduction in aortic pressure leads to a reflex increase in cardiac sympathetic nerve discharge, which leads, in turn, to an increase in atrial contractility and a further reduction in atrial pressure (18); this process increases ADH secretion even further. This mechanism clearly operates to the advantage of the organism. With hypervolemia and the associated increase in atrial pressure, receptor discharge is increased, and ADH secretion is decreased. Also, if arterial blood pressure is increased because of an increase in cardiac output, there is a further increase in atrial pressure secondary to a reflexive decrease in cardiac sympathetic nerve discharge and an even further decrease in ADH secretion.

It might be argued that, since atrial distention causes an increase in heart rate that is mediated via the cardiac sympathetic nerves (19–21), the effect of the cardiac sympathetic nerves during volume expansion would be a decrease in atrial pressure; if this hypothesis is true the system operates as a negative-feedback mechanism. However, Furnival and associates (22) have shown that, when a tachycardia occurs with atrial distention, there is no concomitant positive inotropic effect on the heart. Although an increase is sympathetic activity to the left atrium from the uncut right sympathetic nerves during hemorrhage was possible in the present experiments, evidence presented by Linden (23) indicates that stimulation of the right ansa subclavia in the dog results in a very weak inotropic response to the left ventricle, suggesting either that few fibers traverse to the left side or that these fibers activate the muscle on the left side very poorly. Furthermore, anatomic and physiological evidence from Randall et al. (24) indicates that the stellate cardiac nerve from the right sympathetic nerves is distributed almost entirely to the region of the sinoatrial node and to the right atrium.

In a recent report, Greenberg and associates (25) observed that atrial type B receptor discharge was decreased in dogs in which the tricuspid valve was avulsed and the pulmonary artery was stenosed. Atrial receptor discharge was reduced in these dogs despite the fact that they exhibited obvious signs of congestive heart failure and had elevated central venous pressures. These authors (25) also considered the possibilities that “altered cardiac sympathetic drive in heart failure effected the discharge” to account for the decrease in receptor sensitivity. Results of the present study seem to preclude this possibility. Since the increased sympathetic discharge in heart failure tends to minimize the elevation of atrial pressure, the atrial receptor–sympathetic control system operates in a negative manner.

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