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Functional significance of coactivation of vagal and sympathetic cardiac nerves

(cardiac control/aortic blood flow/reflex patterns/reciprocal change/inotropic effects)

KIYOMI KOIZUMI, NAOHITO TERUI*, MARK KOLLAI†, AND CHANDLER MCC. BROOKS

Department of Physiology, State University of New York, Downstate Medical Center, Brooklyn, New York 11203

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ABSTRACT **Simultaneous recording of activity in the vagal and sympathetic supplies to the heart has revealed that in reflexly and centrally evoked activity these two "antagonists" do not necessarily change action reciprocally. Coactivation occurs in chemoreceptor reflexes and related reactions, upon stretching of the sinoatrial nodal region of the right atrium and when certain hypothalamic regions are stimulated. The objective of the present work was to assay the physiological importance of coactivation of the two potentially antagonistic cardiac nerves in anesthetized dogs. Output from the heart was monitored by recording volume flow in the thoracic aorta just below the aortic arch; cardiac contractility was measured as left ventricular *dp/dt*. Tape recordings of vagus and sympathetic nerve activity during chemoreceptor and baroreceptor reflexes, during reciprocal and nonreciprocal changes produced by hypothalamic stimulation, and during hypoxia and hypercapnia were used to trigger stimulators feeding a stimulus per action potential to cardiac vagus and sympathetic nerves after central connections were cut. The vagus stimulation alone produced a decrease in aortic blood flow; stimulation of the sympathetic nerve alone resulted in increased aortic blood flow. Simultaneous stimulation of vagus and sympathetic, however, produced an even greater cardiac output (measured by aortic blood flow). Intermediate degrees of heart rate and strength of myocardial contraction were maintained in coactivation. Obviously, an association of increased vagus and sympathetic actions, which can be effected reflexly or by action of higher centers, is of physiological benefit. In control reactions that relate cardiac function to body need, both reciprocal and synergistic actions (coactivation) of cardiac nerves are used.**

In previous studies (1–4) it was found that activities recorded simultaneously from vagal and sympathetic nerves innervating the heart do not necessarily change reciprocally in reflex action. In baroreceptor reflexes and in "spontaneously" occurring changes the two efferent systems do operate reciprocally. However, in reflex responses evoked by stretch of the sinus node region of the right atrium (1) and in chemoreceptor reflexes, activities in both nerves increases simultaneously (2, 5). Small alterations in blood P_{O_2} or P_{CO_2} which fall within the normal physiological range cause activities of both nerves to increase or decrease together, depending on the parameters of the stimulus (2, 4). It was also found that reciprocal and nonreciprocal reactions can be evoked by stimulating different areas of the hypothalamus (3).

The significance of reciprocal actions between the two divisions of the autonomic systems considered to have antagonistic actions on effector organs such as the heart is easily understood. Increased action of the inhibitory arm paired with cessation of activity in the excitatory arm of a cardiac reflex provides a powerful blocking effect and decreases heart function. The reverse, excitation of cardiac sympathetic activity and inhibition of the vagus, results in a powerful augmentation of chronotropic and inotropic effects. The functional significance of the other type of reflex response which also occurs, a nonreciprocal coactivation of "antagonistic" nerves, is more difficult to explain. Evidence that coactivation is functionally effective must be obtained before an explanation of the functional significance of this pattern of nerve action can be offered with confidence. The purpose of the present work was to make the required tests and measurements.

METHODS

Preparation. Eleven mongrel dogs weighing 9–14 kg were anesthetized by giving first ketamine hydrochloride (Ketalar, 25 mg/kg given intramuscularly) as an induction anesthetic followed by an intravenous injection of α-chloralose (5% chloralose in 3% sodium borate solution). The latter was given progressively in doses of 20 mg/kg until a total of 70–80 mg/kg was reached. A supplementary dose of chloralose (10 mg/kg) was given whenever necessary, usually every few hours.

After tracheotomy and cannulation of a femoral artery and vein for blood pressure recording and fluid or drug administration, the chest was opened under artificial ventilation. The CO_2 of the end-expired air was kept at 4–4.2%, and approximately 10% O_2 was added to inspired room air. Blood samples were taken from time to time and arterial P_{O_2} and P_{CO_2} as well as pH were measured (Radiometer, Copenhagen MBS3 MK2). Normal values [P_{O_2}, 89.1 mm Hg; P_{CO_2}, 36.8 mm Hg; pH 7.41; as determined in conscious dogs (6)] of blood gases were maintained by small adjustments of the amount of oxygen added and the ventilatory volume of the respiratory pump. The rate of the pump was kept at 23 strokes per min. Bicarbonate solution (4.2%) was given intravenously to adjust the acid–base balance. During nerve stimulation, succinylcholine hydrochloride (2 mg/kg) was used to prevent muscle movement.

Measurements of Cardiac Functions. Blood pressure was recorded from the femoral artery; heart rate was registered by a tachometer triggered from the pressure pulse or electrocardiogram (Grass 7 P4). For assessing the relative changes in cardiac output, a blood flow probe was attached to the thoracic aorta just below the aortic arch. The flow was measured by an electromagnetic blood flowmeter (Statham SP2202). The left ventricle was cannulated through the left carotid artery for measuring the left ventricular (LV) pressure and *dp/dt*. The latter indicated relative changes in the LV muscle contractility and was expressed as mm Hg per sec.

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Abbreviation: LV, left ventricular.

* On leave from Inst. of Basic Medical Sciences, Univ. Tsukuba, Ibaraki, Japan.
† On leave from Experimental Research Dept., Semmelweis Medical Univ., Budapest, Hungary.

Stimulation of the Cardiac Efferents. The right vagus nerve was severed at the neck and a cuff electrode was attached for peripheral stimulation. The left vagus nerve was also severed in half the experiments, but results were the same in both cases. The central connections of the stellate ganglia of both sides were severed and all branches from the ganglia except dorsal and ventral ansa and the inferior cardiac nerve were cut. Two small pin electrodes (insulated except at their tips) were inserted into the right stellate ganglion. In the earlier phases of the experiments the ventral ansa was stimulated by using a cuff electrode attached to the nerve. In three experiments, both right and left stellate ganglia were stimulated simultaneously and, in one, both vagi as well as the stellate were also simultaneously stimulated.

The cardiac nerves were stimulated by simulating the pattern of "natural" discharges in these vagal and sympathetic nerves to the heart. To accomplish this, the activity of both these nerves recorded simultaneously in previous experiments (2–4) was used to drive stimulators for each nerve—i.e., stimulating pulses were triggered by each recorded action potential. The frequency of stimulus used during "control periods" was that frequency of nerve action potentials recorded during basal condition; this generally was 3–10 pulses per sec. The duration of stimulating pulses was fixed at 0.5 msec, and the intensity was adjusted according to each situation but was kept constant for a set of trials. The intensity varied between 0.05 and 0.7 mA depending on the type of electrode used.

Experimental Procedures. When all preparations for recording were completed, systemic blood pressure, heart rate, LV pressure, LV dp/dt, and aortic blood flow were monitored for 30 min under stable conditions. After this period, central connections of both cardiac sympathetic and vagal trunks were severed as described previously. Stimulating electrodes were placed appropriately and stimuli were delivered according to the basal patterns of nerve activity previously recorded on the magnetic tape. Stimulus intensities applied to both sympathetic and vagal nerves were then adjusted to ensure effectiveness. This period of tape-driven stimulation of both nerves constituted our "control period." The stimulus parameters were then kept constant when varied situations were imposed. In most experiments, changes in heart rate caused by nerve stimulation during the "control period" approximately reversed the changes that occurred when central connections of cardiac sympathetic and vagal nerves were severed.

RESULTS

Coactivation of Sympathetic and Vagus Efferents. The reflex response that produces the most clear-cut increase in discharge of both sympathetic and vagal nerves to the heart is the one evoked by chemoreceptor stimulation (2–4). Patterns of coactivation of the efferent nerve activity thus produced were used to drive stimulators to the cardiac nerves; effects on cardiac functions were then examined (Fig. 1*A*). The top two tracings

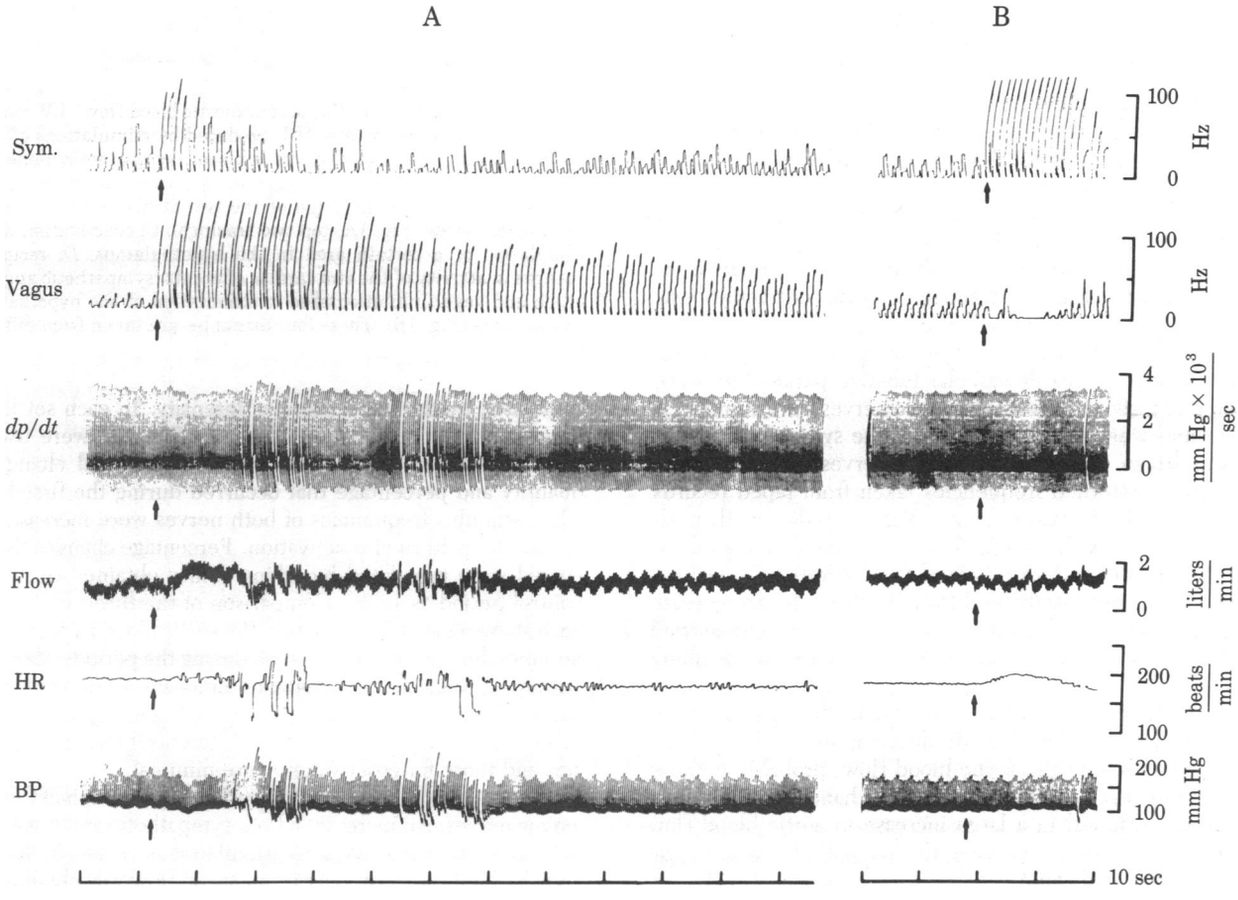

FIG. 1. Effects of coactivation of cardiac sympathetic (Sym.) and vagus nerves on the heart rate (HR), systemic blood pressure (BP), LV dp/dt, and aortic flow (Flow). The top two tracings are tape recordings: (*A*) increased activity in the two efferent cardiac nerves (at arrows) occurred 5 sec after injection of 10 μg of NaCN into the carotid sinus; (*B*) reciprocal changes produced by stimulation (arrows) of the hypothalamic "defense area." These tapes were used to trigger stimulators exciting centrally cut sympathetic and vagus nerves. Note the increase in aortic blood flow shortly after the arrow in *A* but no change in *B*. *A* and *B* were recorded within a short period of time from the same experiment. The stimulus intensities were kept constant.

show taped records of the nerve activity that occurred when chemoreceptors were stimulated by injection of sodium cyanide (10 μg) into the carotid sinus (2–4). The height of the excursion in the integrated records indicates the number of action potentials counted every second. Both sympathetic and vagus activities increased shortly (5 sec) after injection of the drug. The increase in sympathetic nerve activity terminated quickly when the increase in blood pressure evoked a baroreceptor reflex; the vagus nerve activity initially evoked remained high due to this baroreceptor excitation.

In this experiment, the basal heart rate after both nerves were cut was 168 beats per min. During the control period—i.e., when heart rate was established by tape-driven stimulation—the rate increased to 184 per min because of the high-frequency sympathetic stimulating pulses. After 2 min of stimulation at this level, during which all cardiovascular changes due to nerve stimulation were stabilized, an increase in stimulus frequency for both nerves followed, because changes in activity had occurred in nerves from which the tape recordings were taken after chemoreceptor stimulation (top two tracings at arrows). This simultaneous increase in stimulus frequencies evoked no great changes in heart rate, probably because the two counteracting effects of the sympathetic and vagal nerve on the heart beat were in balance. Blood pressure and LV contractility (measured as LV *dp/dt*) decreased slightly after 8 sec when the sympathetic activity (top record) decreased but vagal activity remained high. The aortic blood flow increased considerably, indicating an augmentation in cardiac output. The change was from 800 ml/min during the control period to 1600 ml/min, and this increase in cardiac output continued until the sympathetic activity returned almost to the control level. The fluctuations in heart rate shown in Fig. 1, which were maximal about 13 sec after the chemoreceptor-induced effects began, corresponded to a decrease in sympathetic discharge rate to below the control level while the vagal rate remained high.

This experiment demonstrated that coactivation—increased discharges in both vagal and sympathetic efferents to the heart—resulted in a larger aortic blood flow (i.e., relative increase in cardiac output) even though cardiac contractility was not much changed or was decreased.

Fig. 2 *A* and *B* shows two examples from another experiment in which changes in cardiovascular function parameters were compared in three situations: when two nerves were stimulated together and when the vagus alone or the sympathetic nerve alone was driven. In both experiments, nerves were stimulated by the same patterned frequencies taken from taped records shown in Fig. 1 (top two tracings). Fig. 2*A* indicates that, although activation of the sympathetic nerve alone increased LV *dp/dt*, heart rate, and aortic blood flow, additional vagal excitation further increased blood flow. In this case, an increase in vagal activity caused a slight decrease in heart rate as well as an increase in cardiac output, probably because cardiac filling became greater.

Fig. 2*B* shows a similar situation but in this case the sympathetic nerve activation alone produced an increase in LV *dp/dt* but no increase in the aortic blood flow, probably because the heart rate was too high. On the other hand, coactivation of both nerves resulted in a large increase in aortic blood flow compared to that obtained when the sympathetic or the vagal nerve was activated alone.

Table 1 shows actual values of changes in the aortic flow, the LV *dp/dt*, and heart rate to illustrate the effects produced by coactivation of cardiac efferents. One example was taken from each of seven different dogs. Changes in cardiac parameters were compared when a stimulus was applied to both autonomic nerves together and when one or the other nerve alone was

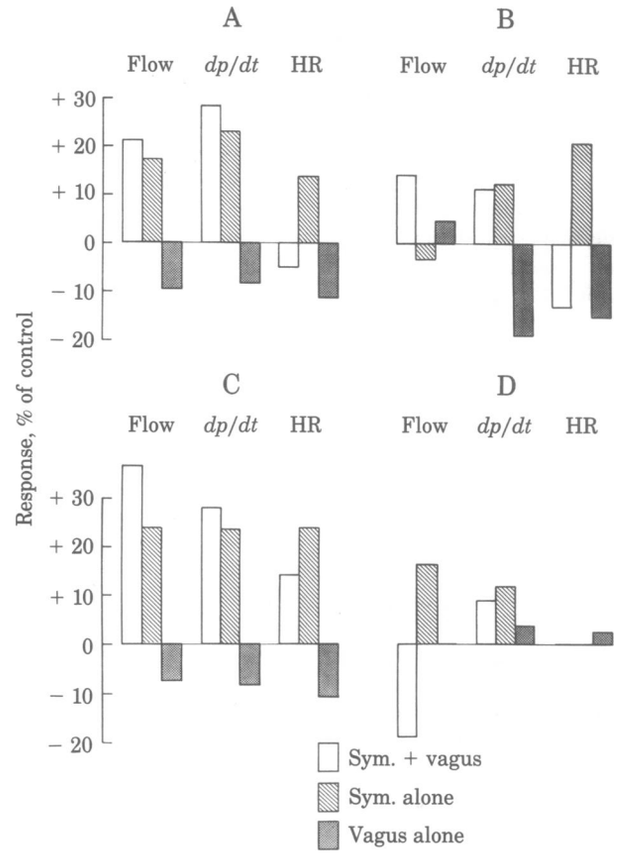

FIG. 2. Changes in cardiac output (aortic blood flow), LV contractility (*dp/dt*), and heart rate (HR) produced by stimulations of sympathetic (Sym.) and vagus nerves together, sympathetic alone, and vagus alone. Stimulators were triggered by action potentials recorded on tapes: *A* and *B*, coactivation of the two cardiac nerves in a chemoreceptor reflex (Fig. 1*A*, top two tracings); *C*, coactivation due to stimulation of a certain area in the hypothalamus; *D*, reciprocal changes in activity of the two cardiac efferents (sympathetic augmentation and vagal inhibition) due to stimulation of the hypothalamic defense area (Fig. 1*B*). These four examples are taken from different dogs.

stimulated by the same stimulus intensity. In each set listed, the same taped records (illustrated in Fig. 1*A*) were used to drive stimulators. The table shows the maximal changes in quantity and percentage that occurred during the first 10 sec when stimulus frequencies of both nerves were increased following the pattern of coactivation. Percentage changes that occurred were calculated by taking values obtained during the control period as 100%. Comparison of the three situations in each shows that, in five animals, the aortic blood flow increased far more during coactivation than during the periods when sympathetic or vagal nerve stimulation alone was carried out. In two cases, blood flow increased the most during stimulation of the sympathetic nerve alone, but the difference between these values and those for coactivation were minimal.

We also tried various other means of coactivation of the autonomic nerves. An increase in both sympathetic and vagal nerve activities could be evoked by stimulation of certain areas of the hypothalamus (3). An increase in aortic flow was obtained that was greater than that observed under sympathetic stimulation alone (Fig. 2*C*). Although the pattern of coactivation induced by direct hypothalamic stimulation was somewhat different from that during the chemoreceptor reflex (2–4), the effects on the three parameters of cardiac function were similar.

Another type of coactivation studied was that produced by

Table 1. Effects on aortic blood flow, cardiac contractility (LV *dp/dt*), and heart rate of coactivation of sympathetic and vagal efferents or activation of sympathetic nerve alone or vagus alone

	Blood flow		LV *dp/dt*		Heart rate	
Dog	Liters/min	%	mm Hg/sec	%	Beats/min	%
			Sympathetic + vagus			
2	+0.30	+23.1	−200	−8.0	−15	−10.5
3	+0.20	+20.0	0	0	−19	−9.8
4	+0.12	+22.2	+400	+11.1	−3	−1.8
6	+0.12	+14.3	+300	+11.5	−20	−13.3
7	+0.12	+15.4	+200	+7.7	+6	+5.3
9	+0.18	+21.4	+800	+28.6	−10	−5.0
11	+0.09	+9.0	+100	+3.4	−17	−9.0
2*	−0.30	−18.7	+200	+9.1	+16	+8.5
			Sympathetic alone			
2	0	0	+100	+3.8	+2	+1.2
3	0	0	+50	+1.7	+5	+3.3
4	+0.09	+16.7	+400	+11.8	+4	+2.4
6	−0.03	−3.4	+300	+12.5	+33	+21.2
7	+0.15	+17.0	+300	+12.5	+7	+5.8
9	+0.15	+17.2	+600	+23.1	+25	+11.8
11	+0.12	+12.0	+150	+6.4	+10	+5.2
2*	+0.20	+15.7	+300	+12.0	+7	+3.7
			Vagus alone			
2	0	0	−100	−5.2	−18	−12.9
3	−0.10	−8.3	−200	−7.6	−20	−16.0
4	−0.03	−6.7	−100	−2.9	−4	−6.0
6	+0.03	+4.8	−500	−19.2	−22	−15.3
7	−0.06	−7.7	0	0	−6	−5.3
9	−0.06	−9.5	−200	−8.3	−20	−11.4
11	−0.06	−7.4	−100	−4.2	−15	−8.6
2*	0	0	0	0	+4	+2.5

* Reciprocal action between sympathetic (augmentation) and vagal (inhibition) nerves.

low oxygen and asphyxia (2, 4). In these situations the increase in vagal discharge far exceeded that in the sympathetic. Thus, the combined stimulation always decreased heart rate considerably, yet aortic flow increased 8–25% above that during the control period.

Reciprocal Actions of Sympathetic and Vagus Efferents. In comparing the effects of coactivation and those produced by reciprocal actions of the autonomic nerves on cardiac function, we used reciprocal patterns of responses obtained during baroreceptor stimulation or other means to simulate the reciprocal action in the two efferents. Fig. 1*B* shows changes that occurred in the aortic blood flow, LV contractility, and heart rate when a reciprocal pattern was applied. This record was taken from the same experiment used in test of coactivation and obtained shortly after the results shown in Fig. 1*A* were recorded. Stimulus intensity for both nerves was kept constant, but in Fig. 1*B* a tape recording of reciprocal action was used to drive the stimulators. The top two tracings in Fig. 1*B* show a large increase in sympathetic activity and a simultaneous inhibition of vagal discharge produced by stimulation of the defense area of the hypothalamus (3). Although activation of the sympathetic nerve did cause an increase in LV *dp/dt* and heart rate, the aortic flow was not increased; it decreased somewhat.

Fig. 2*D* shows another reaction evoked by reciprocal-patterned stimulation. Although sympathetic stimulus alone caused an increase in contractility and aortic flow, a reciprocal activation in which sympathetic activity increased but vagal activity was decreased or inhibited resulted in a marked decrease in cardiac output.

Another example of reciprocal action is that which occurs in the baroreceptor reflex, but in this case the pattern of reciprocal change in sympathetic and vagal nerve activity is opposite to that which occurs after stimulation of the hypothalamic defense area. With the use of a baroreceptor-type pattern of stimulation, we found that both LV *dp/dt* and heart rate decreased due to decreased sympathetic stimuli accompanied by augmented vagal stimulation. The aortic flow also decreased in most instances. Fig. 3 illustrates changes in cardiac functions brought about by two types of reciprocal action as well as by coactivation of the autonomic nerves to the heart. All three results were taken from the same dog, and intensities of stimulation were kept constant in all cases. The figure indicates the advantage of coactivation of the autonomic nerves in producing an increased cardiac output.

However, one must be aware that, in natural situations, hemodynamic changes must also be considered; an increase in cardiac sympathetic nerve activity is accompanied by an increase in systemic blood pressure and flow in many instances. The increase in venous return thus created also can alter cardiac output. Hypothalamic defense area stimulation causes a tremendous increase in sympathetic discharge and this produces a sufficient increase in the blood pressure and inotropic action to cause an increase in aortic flow unless heart rate change is excessive. Another factor is revealed by manipulation of stimulus intensities applied to the two nerves. For example, too large a decrease in heart rate due to strong vagal exicitation can easily overshadow the sympathetic contribution to cardiac contractility, and the cardiac output decreases.

What we have shown is that activation of the two "antagonistic" cardiac nerves together can increase cardiac output significantly. This supports the concept that the coactivation seen in some reflex actions is of physiological benefit.

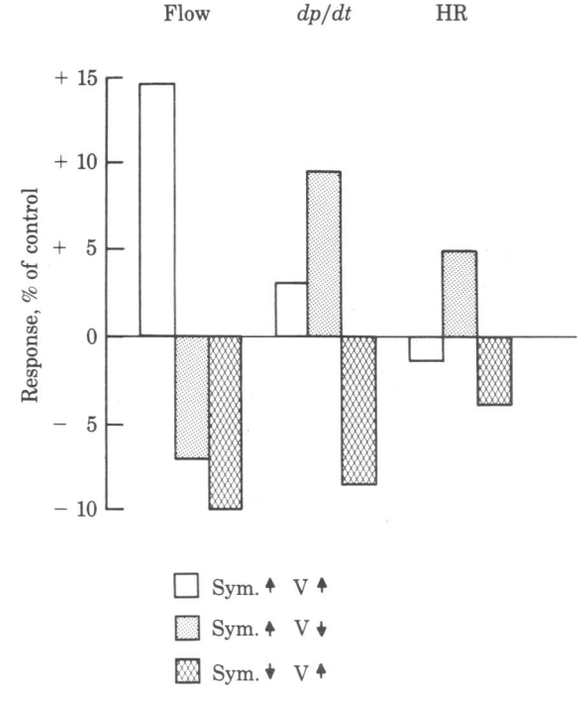

FIG. 3. Comparison of effects on cardiac functions produced by stimulating cardiac sympathetic (Sym.) and vagus (V) nerves in three different patterns. The patterns of stimulation frequencies used were derived from taped action potential recordings from two cardiac nerves during three manipulations: coactivation of the two cardiac nerves as shown in Fig. 1*A*; reciprocal changes as shown in Fig. 1*B*; reciprocal changes caused by baroreceptor stimulation. All data are from the same experiment, and stimulus intensities remained the same throughout.

DISCUSSION

Simultaneous recording of the activity in cardiac vagus and sympathetic fibers has permitted reexamination of frequently studied reflexes and the action of hypothalamic centers which regulate heart action. The initial observation (1) that stretch of the sinoatrial nodal region of the right atrium produced an increase in firing rate in both vagus and sympathetic fibers indicated that coactivation as well as reciprocal action can occur in reflexes controlling the heart. It is well recognized that a reciprocal response occurs when baroreceptors are stimulated (7) but it is less well known that excitation of chemoreceptors evokes a synergistic or coactivation of vagal and sympathetic fibers supplying the heart (2, 4).

The role of hypothalamic and other brain regions in control of heart action has been well studied. Reciprocal patterns of vagus and sympathetic discharge have been found consistently (8). For example, Gellhorn *et al.* (9, 10) obtained an enhancement of vagus activity and inhibition of the sympathetic by reflex or direct stimulation of the anterior hypothalamus; an augmentation of sympathetic activity and attenuation of vagal effects were obtained by stimulating "centers" in the posterior hypothalamus. Gebber and his coworkers (11, 12) also found that stimulating the anterior hypothalamus greatly facilitated the parasympathetic component of the baroreceptor reflex and inhibition of the sympathetic whereas stimulation of areas in the lateral and posterior hypothalamus augmented sympathetic activity and diminished reflex parasympathetic responses. In our own studies, reciprocal action was obtained particularly when centers evoking "alerting" and "defense reactions" (13) were stimulated. Coactivation such as observed in our studies (1–4) has seldom been reported. The problem was to determine whether or not coactivation is of any significance to cardiac function.

The efficacy of simultaneous vagus and sympathetic action on the heart was examined by recording aortic flow during electrical excitation of the right vagus alone, the right cardiac sympathetic alone, and then both together. It was found that the combined stimulus was more effective in producing an increase in cardiac output (14). The method of using physiologically induced coactivation of the cardiac nerves and testing their combined effect against action of vagus and sympathetics alone, as reported here, provides stronger support for the hypothesis that coactivation is a phenomenon of physiological importance.

This conclusion is physiologically reasonable. The objective of the sinoatrial reflex is to promote cardiac inflow and filling. The chemoreceptor reflex also acts to increase blood flow when need for oxygen and elimination of carbon dioxide is great. To increase cardiac output, a heart rate increase is beneficial but does not suffice. A good inotropic action and adequate filling are required. One can think of the vagus as maintaining a reasonably slow beat while the sympathetic exerts a degree of acceleration and a strong inotropic effect. The observation of synergistic action (coactivation) indicates that reflexes and centers modulate the potential antagonism to produce an association of actions beneficial to cardiac function.

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