Brief Reviews
Sympathetic-Parasympathetic Interactions
in the Heart
By Matthew N. Levy

It is generally recognized that the two divisions of the autonomic nervous system exert antagonistic effects on various aspects of the performance of the heart. However, these opposing influences are not algebraically additive; complicated interactions exist. Two major types of peripheral interactions have been described. The first type is manifested as an accentuated antagonism between the two divisions. In the second type, the peripheral components of one division are activated as a consequence of activity in the other; this will be designated reciprocal excitation.

ACCENTUATED ANTAGONISM

One of the earliest examples of the accentuated antagonism between sympathetic and vagal actions on the heart was described in 1934 by Rosenblueth and Simeone (1). They observed that in anesthetized cats the absolute reduction in heart rate produced by a given vagal stimulus was considerably greater when the basal heart rate was increased by tonic sympathetic stimulation. However, when the responses to vagal stimulation were expressed as fractions of the basal heart rates, the percent changes did not significantly differ in the presence and absence of tonic sympathetic stimulation. However, when the responses to vagal stimulation were expressed as fractions of the basal heart rates, the percent changes did not significantly differ in the presence and absence of tonic sympathetic activity. Therefore, Rosenblueth and Simeone interpreted their data to indicate a simple antagonism between the two divisions of the autonomic nervous system, and they minimized the existence of a significant interaction.

In a study published just one year later by Samaan (2), the chronotropic responses to autonomic stimulation of the heart were not algebraically additive, even when calculated in relative terms. The cardiac acceleration produced by strong sympathetic stimulation was usually overpowered, even by relatively weak vagal activity. These results have since been confirmed by more recent investigations, and the extent of the interaction has been expressed quantitatively (3, 4). A similar interaction between the chronotropic effects of the autonomic neurotransmitters, norepinephrine (NE) and acetylcholine (ACh), has recently been observed by Grodner et al. (5) in experiments on isolated atrial preparations. The effects of ACh were exaggerated in the presence of NE, and the inhibitory influence of ACh predominated over the adrenergically induced cardiostimulation in all cases.

The inotropic effects elicited by autonomic neural or humoral interventions also evince a prominent interaction. Hollenberg et al. (6) found that ACh infused into a coronary artery in dogs had only a slight negative inotropic effect on the ventricular myocardium. However, if the same infusion was administered during increased activity of sympathetic nerves to the heart or during a constant infusion of NE, the myocardial depression produced by ACh was much more pronounced. Dempsey and Cooper (7) described a similar accentuation of the antagonism.

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between ACh and NE in isolated cat hearts. An analogous interaction has also been observed (8-11) in response to autonomic stimulation of the heart: vagal stimulation produces a more profound depression of myocardial contractility against a background of tonic sympathetic activity than in the absence of appreciable sympathetic tone. This interaction appears to be specific for the adrenergic and cholinergic systems. Enhancement of myocardial contractility by a variety of nonadrenergic interventions failed to potentiate the negative inotropic effect of vagal stimulation, whereas cardiac sympathetic excitation consistently accentuated the vagal inhibition (11).

The disproportionate inhibition of the cardiostimulatory effects of sympathetic stimulation by cholinergic influences is probably accomplished in at least two ways: (1) a cholinergically induced reduction in the amount of NE released in response to a given level of sympathetic activity, and (2) a cholinergic attenuation of the magnitude of the response to a given adrenergic stimulus. These two processes are illustrated schematically in Figure 1.

With respect to the first of these processes, Burn and Rand (12) have proposed a cholinergic link in the release of NE by postganglionic sympathetic nerve fibers. Burn (13) has postulated two actions of ACh on the sympathetic fiber that are analogous to its effects on the myoneural junction: at lower concentrations, ACh induces the release of NE from sympathetic nerve terminals, whereas at higher concentrations, it impedes the release of NE in response to sympathetic stimulation. The inhibitory effect on the sympathetic terminals is represented in Figure 1 by the axon from the parasympathetic fiber which terminates near the sympathetic postganglionic nerve endings. Convincing evidence of a muscarinic inhibition of NE release from sympathetic nerve fibers to the heart has recently been adduced (14-16). In experiments on isolated rabbit hearts, Löffelholz and Muscholl (16) observed that ACh, at a concentration of $10^{-6}$ g/ml, reduced the NE output resulting from sympathetic nerve stimulation of the heart to about one-fifth of the level released in the absence of ACh infusion. This inhibitory effect of ACh could be blocked entirely by atropine. Also, contrary to the hypothesis advanced by Burn (13), this concentration of ACh was below that required to elicit NE release.

Muscarinic inhibition of NE release cannot be the sole mechanism responsible for the cholinergic attenuation of the cardiac response to sympathetic stimulation, because adrenergic-cholinergic interaction is prominent even when the adrenergic response is produced by humoral interventions. Thus, in the heart of the open-chest dog (6) and in the isolated cat heart (7), ACh antagonizes the positive inotropic effect produced by constant infusions of NE.

The precise mechanism responsible for this antagonism cannot be elucidated until the process by which NE evokes its cardiotoxic effect has been unraveled. Probably the principal theory currently being advanced to explain the actions of the catecholamines on the heart involves an increase in intracellular levels of cyclic AMP (adenosine 3', 5'-monophosphate) (17, 18). The adrenergic-cholinergic antagonism may therefore be mediated through the adenyl cyclase system. As illustrated in Figure 1, the NE liberated...
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during sympathetic nerve activity accelerates the synthesis of cyclic AMP. This process may be inhibited by the ACh released during vagal activity. Murad et al. (19) observed that ACh decreased the rate of formation of cyclic AMP in broken cell preparations of dog heart. In studies conducted on perfused guinea pig, rabbit, and cat hearts, Vincent et al. (20, 21) found that ACh completely inhibited the glycogenolysis produced by epinephrine. The accelerated glycogenolysis induced by the catecholamines is mediated by the increased formation of cyclic AMP. In the experiments of Vincent et al., however, the suppression of glycogenolysis evoked by ACh was not accompanied by an inhibition of the cardio tonic action of epinephrine when the heart rate was controlled. Meester and Hardman (22) reported that in perfused turtle and rabbit hearts, ACh did block the positive inotropic effects elicited by epinephrine and theophylline. Tissue levels of cyclic AMP are known to be increased by theophylline, by virtue of an inhibition of the phosphodiesterase that converts cyclic AMP to adenosine 5'-monophosphate. Therefore, the results of Meester and Hardman lend circumstantial support for the role of cyclic AMP in mediating the inotropic action of the catecholamines and in this type of adrenergic-cholinergic interaction. Additional confirmation has been provided by the recent study of LaRaia and Sonnenblick (23). They found that NE produced large positive inotropic effects in both atrial and ventricular tissues, and these effects were associated with parallel changes in myocardial cyclic AMP levels and adenyl cyclase activities. Also, carbachol evoked pronounced negative inotropic responses in atrial tissue, but relatively small inotropic changes in ventricular tissue. Correspondingly, this parasympathomimetic substance elicited proportionately large reductions in the cyclic AMP content and adenyl cyclase activity in the atrial tissue but much smaller reductions in the ventricular tissue.

**RECIProCAL EXCITATION**

Under a variety of experimental conditions, the effects on the heart exerted by one division of the autonomic nervous system may simulate those ordinarily evoked by the other division. The more common examples involve the production of positive chronotropic or inotropic effects by vagal stimulation or ACh administration, although instances of negative chronotropic or inotropic effects in response to sympathetic nerve stimulation of the heart have also been described.

Three principal mechanisms (Fig. 2) are responsible for the cardio stimulatory responses evoked by cholinergic interventions: (1) the presence of sympathetic fibers in a predominantly parasympathetic nerve trunk, (2) cholinergic stimulation of cardiac activity evoked by nonadrenergic mechanisms, and (3) cholinergic stimulation of the heart.

![Proposed mechanisms for the types of sympathetic-parasympathetic interactions which are manifested as reciprocal excitation of these two divisions of the autonomic nervous system. A: False interactions can occur as a consequence of the presence of cardiac sympathetic fibers in a combined vagosympathetic trunk, or as the result of direct cardio stimulatory (±) as well as cardioinhibitory (—) influences of ACh on the cardiac cells. The cardio stimulatory effects of ACh may be ascribable to an increase in the permeability of the cardiac cell membrane to calcium. B: Vagal activity can evoke cardio stimulatory responses by releasing NE from (1) chromaffin cells or (2) postganglionic sympathetic nerve terminals in response to the ACh released during vagal activity. Also, cardiac sympathetic activity can elicit the release of ACh from postganglionic parasympathetic fibers (PPF) by virtue of the action of NE at some presynaptic α-receptor.](image-url)
mediated by adrenergic mechanisms. Only the last of these three mechanisms constitutes a true adrenergic-cholinergic interaction.

False Interactions.—Concerning the first of the three mechanisms, the cervical sympathetic and vagal nerves of certain species (including the dog) are combined as a pair of single trunks, the vagosympathetic nerves (Fig. 2A). A fraction of the sympathetic fibers from this mixed nerve trunk terminate in the heart (24–28). Hence, adrenergic inotropic and chronotropic responses to vagosympathetic nerve stimulation may be evinced, especially after atropine (25, 26).

With respect to the second mechanism, several groups of investigators have described positive inotropic responses to cholinergic interventions which appear to be unrelated to adrenergic mechanisms. The potentialities for direct cardiostimulatory as well as cardioinhibitory influences of vagal activity are illustrated in Figure 2A. Hollenberg et al. (6) described a prominent increase in left ventricular contractile force immediately after cessation of an infusion of ACh into the coronary arteries in open-chest dogs. This so-called "rebound" appeared even after treatment with pronethalol, bretylium, or reserpine, and was abolished by atropine. Similar rebounds of left ventricular contractility have also been described immediately after cessation of vagus nerve stimulation (8, 27). Blinks (28) was able to excite the parasympathetic fibers selectively in isolated heart muscle preparations by means of field stimulation. He also observed a definite rebound in contractile force after cessation of stimulation. The rebound was unaffected by high concentrations of propranolol, but was abolished by atropine. Similar rebounds of left ventricular contractility have also been described immediately after cessation of vagus nerve stimulation (8, 27). Blinks (28) was able to excite the parasympathetic fibers selectively in isolated heart muscle preparations by means of field stimulation. He also observed a definite rebound in contractile force after cessation of stimulation. The rebound was unaffected by high concentrations of propranolol, but was abolished by atropine. In innervated cat atria preparations, Misu and Kirpekar (39) obtained biphasic responses to cervical vagal stimulation. The poststimulation excitatory response was not blocked by pronethalol, nor was it prevented by pretreatment with reserpine.

Endoh et al. (30) have recently described catecholamine-dependent and catecholamine-independent positive inotropic responses to ACh in blood-perfused canine papillary muscle preparations. The catecholamine-independent responses were induced by significantly lower doses of ACh than were the catecholamine-dependent responses. Also, they were always preceded by a phase of diminished contractility, which was not necessarily true of the catecholamine-dependent responses. The catecholamine-independent responses to ACh were abolished by atropine, but they were unaffected by ganglionic or β-receptor blocking agents or by tetrodotoxin. Hence, this type of enhanced contractility is probably similar to the rebound described by Hollenberg et al. (6), Blinks (28), and Levy et al. (8, 27).

Buccino et al. (31) and Friedman et al. (32) also described catecholamine-independent positive inotropic responses to ACh in isolated feline papillary muscle preparations. Such responses occurred only at low contraction frequencies and at high ACh concentrations and were not necessarily preceded by a negative inotropic response. It is therefore uncertain whether such catecholamine-independent responses are analogous to those described by Endoh et al. (30). It was postulated by Friedman et al. (32) that the catecholamine-independent responses in their experiments were ascribable to an ACh-induced enhancement of the permeability of the myocardial cell membranes to calcium. Such a possibility is included in Figure 2A. Chiang and Leaders (33) have demonstrated an increase in myocardial calcium exchange during a catecholamine-independent cardiostimulatory response to nicotine. Increased membrane permeability to calcium in response to ACh has been demonstrated in other tissues, but an ACh-induced alteration in calcium exchange in the myocardium remains to be established.

True Interactions.—Abundant evidence has been adduced to show that cholinergic interventions are capable of releasing NE from depots in the heart. In 1945, Hoffman et al. (34) reported that the injection of ACh produced positive inotropic and chronotropic effects in isolated perfused hearts of dogs, cats, rabbits, and guinea pigs after atropine. They were also able to demonstrate the presence of a sympa-
thomimetic substance in the perfusate of the hearts under such conditions. This substance has been characterized as a catecholamine, mainly NE, by a variety of surgical (7, 35, 36), pharmacological (7, 29, 35–43), and chemical (14, 15, 44, 45) techniques. The cardiostimulatory responses to cholinergic interventions have been attenuated or abolished by cardiac sympathectomy (7, 35, 36) or by pretreatment with reserpine (35, 36, 39, 41, 43), procedures which are known to deplete myocardial NE stores. Such cardiac stimulation has also been inhibited by ganglionic blocking agents (29, 34, 35, 37, 38, 40, 42, 43), by drugs which block axonal impulse conduction (29) or inhibit the release of NE from postganglionic sympathetic terminals (40), and by compounds which block α-receptors (34) and β-receptors (7, 29, 41).

The source of the NE which is released by cholinergic interventions remains controversial. Initially, Hoffmann et al. (34) postulated that the epinephrine-like substance which was shown to be liberated in their experiments was released from chromaffin tissue or sympathetic ganglion cells located within the heart. The termination of a vagal fiber on an intracardiac chromaffin cell is shown in Figure 2B. The conclusions of Hoffmann and his collaborators were based on the observation that the positive inotropic and chronotropic effects elicited by ACh were abolished by curare and nicotine, which are known to have ganglionic blocking activity. Similar conclusions were also reached by Heymans and Bennati (37), who found that the tachycardia evoked by ACh after atropine was abolished by the ganglionic blocking agent, tetraethylammonium. Subsequently, numerous other investigators (29, 35, 38, 40, 42, 43) have confirmed that the sympathomimetic activity engendered by cholinergic interventions can be attenuated or abolished by drugs whose principal action is ganglionic blockade.

In concurrence with these observations, Middleton et al. (38) reported that the ganglionic blocking agents nicotine, tetraethylammonium, and hexamethonium prevented the consistent positive inotropic effect of ACh on the cat papillary muscle after atropine. However, careful histological examination of these papillary muscles failed to disclose the presence of chromaffin tissue or ganglion cells. Similar histological findings were described by Lee and Shideman (35), who proposed that the source of the NE might be the sympathetic postganglionic nerve terminals. The termination of the parasympathetic postganglionic fibers in the vicinity of sympathetic nerve endings is shown in Figure 2B. Histochemical studies (46–48) indicate that almost all of the NE in the heart is located in sympathetic nerve fibers. ACh plays an integral part in the liberation of NE from sympathetic nerve fibers, according to the hypothesis of Burn and Rand (12, 13).

Considerable experimental evidence has accrued to support the concept that the NE released by cholinergic interventions originates from postganglionic sympathetic nerve terminals. Sympathetic denervation of the heart markedly attenuates or abolishes the cardiac sympathomimetic responses to cholinergic interventions (7, 35, 36). Such denervation is likely to deplete catecholamines in postganglionic sympathetic fibers but not in intracardiac sympathetic ganglion or chromaffin cells (48). Drugs, such as bretylium (49) and isocaramidine (41), which block the release of NE from sympathetic postganglionic terminals, also prevent the cardiostimulatory responses to cholinergic interventions. Electrophysiological studies involving the collision technique (50) and the recording of antidromic discharges (15) have provided strong supporting evidence for the excitation of postganglionic sympathetic nerve fibers by cholinergic stimuli. Finally, it has been shown that the traditional autonomic ganglionic blocking agents do not act exclusively at the ganglion, but block the action of ACh on the sympathetic postganglionic nerve fiber as well (51, 52), possibly by barring the entry of ACh into the nerve fiber. Hence, abolition of the cardiostimulatory effects of ACh by so-called ganglionic blocking agents does not necessarily constitute proof that ACh exerts its effects on ganglion or chromaffin cells.
The results of some recent studies have suggested, however, that the NE released by cholinergic interventions may be derived, at least in part, from extraneural stores. Chiang and Leaders (53) found that the magnitude of the cardiostimulatory phase following vagal stimulation was not significantly different in control and denervated hearts. Unfortunately, these investigators did not establish that the cardiostimulation was ascribable to NE release. Hence, the possibility exists that the positive inotropic and chronotropic responses to vagal stimulation might represent direct effects of the ACh released at the parasympathetic endings, such as those described in the preceding section. Copen et al. (43) observed a transient increase in heart rate after vagal stimulation. They concluded that this postvagal tachycardia was based on an adrenergic mechanism, since it could be abolished if the catecholamine stores were depleted by reserpine pretreatment. Infusion of NE in these animals resulted in the reappearance of postvagal tachycardia. Since others had reported that infusion of NE under these conditions did not restore the cardiac response to sympathetic nerve stimulation, Copen et al. postulated that the postvagal tachycardia resulted, at least in part, from the release of NE from sites other than postganglionic sympathetic endings, such as those described in the preceding section. Copen et al. (43) observed a transient increase in heart rate after vagal stimulation. They concluded that this postvagal tachycardia was based on an adrenergic mechanism, since it could be abolished if the catecholamine stores were depleted by reserpine pretreatment. Infusion of NE in these animals resulted in the reappearance of postvagal tachycardia. Since others had reported that infusion of NE under these conditions did not restore the cardiac response to sympathetic nerve stimulation, Copen et al. postulated that the postvagal tachycardia resulted, at least in part, from the release of NE from sites other than postganglionic sympathetic nerve endings, possibly from chromaffin cells. Supporting evidence for this contention was subsequently provided by additional experiments conducted in the same laboratory. Vassalle et al. (54) employed small doses of reserpine which were adequate to block responses to sympathetic nerve stimulation of the heart but not sufficient to deplete catecholamine stores in chromaffin cells. Under such conditions, postvagal tachycardia could still be elicited. Similarly, postvagal tachycardia was found to persist after doses of bretylium which were adequate to block sympathetic nerve endings but not large enough to prevent the release of catecholamines from chromaffin cells in the adrenal medulla.

Finally, experimental evidence has been provided which indicates that the reverse type of interaction may also occur: not only can parasympathetic activity stimulate sympathetic postganglionic fibers in the heart, but also sympathetic nerve activity apparently can excite parasympathetic fibers. Experimental data in support of this latter assertion are often difficult to interpret, because it is possible that ACh is released directly by sympathetic postganglionic fibers during the course of normal sympathetic impulse conduction, as proposed by Burn and Rand (12, 13).

In the studies on innervated atrial preparations from cats, Leaders (39) observed that after cessation of stimulation of the sympathetic nerves there was a period of cardioinhibition. This poststimulation response was enhanced by physostigmine and blocked by atropine, indicating the involvement of ACh. When sufficient hemicholinium was employed to abolish the effects of vagal but not of sympathetic stimulation, the phase of cardioinhibition after sympathetic excitation disappeared. Hence, it is likely that stimulation of the sympathetic nerves to the heart may result in the liberation of ACh from parasympathetic nerve fibers. Hashimoto et al. (55, 56) observed that injection of NE into the sinus node artery occasionally produced a sinus bradycardia which could be blocked by atropine and enhanced by physostigmine. When enough tetrodotoxin was administered to block transmission in the autonomic nerve fibers to the heart, this paradoxical response to NE injection was abolished (55). The paradoxical response was also effectively blocked by hexamethonium and phenoxybenzamine, suggesting to the authors that the injected catecholamine acted at a presynaptic α-receptor to induce the ultimate release of ACh from postganglionic vagal fibers (56). The termination of an axon from an intracardiac sympathetic fiber on the cell body of a parasympathetic postganglionic fiber is shown in Figure 2B.
Concluding Remarks

The neural control of the heart is extremely complex, in large part because of the dual innervation. Complicated interactions occur between the parasympathetic and sympathetic centers in the central nervous system, and peripheral interactions between fibers of these two divisions also take place within the tissues of the heart itself. Hence, information concerning the activity of one division or the other in isolation is certainly incomplete and may indeed be misleading. For example, vagal influences on heart rate so preponderate over sympathetic effects that the induction of complete sympathetic blockade might not result in a significant deceleration of the heart, even when substantial sympathetic tone exists. However, the failure of β-receptor blockade to produce an appreciable change in heart rate might lead to the erroneous conclusion that sympathetic tone was negligible.

The anatomical arrangement of the autonomic innervation of the heart appears to favor the occurrence of interactions between the terminal fibers of the two divisions. The postganglionic axons of both divisions are surrounded by specialized tissue which also envelops several muscle cells to form a closed system (57). This terminal apparatus transmits both adrenergic and cholinergic substances, and relatively short distances are required for diffusion of these neurotransmitters. Presumably, the transmitters released by the fibers of one division can readily diffuse to the nerve terminals of the other division, as well as to the cardiac cell surfaces.

One of the principal difficulties in interpretation of the data cited in this review is that of correlating the responses to administered adrenergic and cholinergic substances with the effects produced by neural activity. That is, it is difficult to determine the equivalent level of autonomic nerve activity represented by a given concentration of a neurotransmitter in an organ bath or in the coronary arterial blood. It has been shown experimentally (27) that a given coronary arterial blood concentration of ACh is equivalent to a certain frequency of vagal stimulation at one site in the heart (e.g., the sinoatrial node), whereas it corresponds to an entirely different frequency of vagal stimulation at some other locus (e.g., the ventricular myocardium). It is difficult to ascertain, therefore, whether the observed response to an administered neurotransmitter represents a physiological or a pharmacological process. Obviously, much more work is required.

References


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