SUMMARY When identical, successive single vagal stimulations, separated in time (T) by 2–60 seconds, are applied in the dog, the same dependence of AAV₂/AAV₁ on the first stimulus amplitude was also found when the amplitude was varied either by (1) changing the number of vagal fibers stimulated for both the first and second response, but at a constant AD (the delay in the cardiac cycle at which the stimulus was given), or (2) by stimulating the same number of fibers but changing AD for both the first and second response. Also the same characteristic of ∆AV₂/∆AV₁, plotted vs. T was found either (1) when both the first and second responses were produced by stimulation of the same nerve, or (2) when stimulation of the nerve from one side produced the first response and the alternate side the second response. The effects of abnormal atrioventricular nodal entry and excitation. Bipolar recording catheters were inserted into the right atrium through a small incision in the atrial appendage, and into the right ventricle through the right external jugular vein. The atrial catheter was secured tightly to the atrial appendage to eliminate timing errors due to changes in electrode position. The onset of the atrial electrogram was used as the reference event for all other measured, computed, and generated time intervals. The ventricular catheter was wedged against the ventricular wall and rarely changed position; however, any change in its position was noted easily from changes in wave shape of the electrogram recorded through it; these changes had a constant, minimal (less than 5 msec) effect on the measured AV interval. The catheters were connected to a Brush Mark 200 oscillograph to record the onset of atrial (A) and ventricular (V) activation.

The amplified A and V signals from the oscillograph were coupled capacitively to an analog/parallel-logic computer (EA1-580) which was used as previously described to derive the timing and gating signals with a resolution of 1 msec. (2) condition the A and V signals for input to the clock of a digital computer (Digital Equipment Corp., PDP-12), and (3) derive the analog signals proportional to the cardiac cycle duration (AA), the interval between A-onset and V-onset (AV), and the time from A-onset to the onset of the stimulus burst (AD). The systemic blood pressure, AV intervals, and stimulus signals were recorded on analog tape (Honeywell 7600). The digital computer was used to collect the AA, AV, and AD intervals for on-line data reduction and subsequent listing. The stimulus parameters generated by the analog computer were: pulse widths, 0.1–3 msec; pulse intervals, 3–9 msec; pulse amplitude, 10 V; and stimulus per burst, less than 10, and usually 1–4. The sets of conditioning and test bursts were separated by at least 75 seconds. These bursts will be referred to hereafter simply as the stimulus. Since the magnitude of the AV response depends upon the delay interval (AD) in the cardiac cycle at

WHEN A TEST stimulus is applied to the vagus nerve after a conditioning stimulus, the increment in cardiac cycle length or atrioventricular conduction time produced by the test stimulus may be considerably less than that produced by the first (conditioning) stimulus. This has been found both for a single stimulus and for pulse trains. In this study these conditioning phenomena were explored in an effort to analyze the mechanism by which they are produced.

Methods

Experiments were conducted on 18 mongrel dogs (10–15 kg) of both sexes; 16 yielded satisfactory results (in the other two dogs the responses to a repeated standard test stimulation of the vagus decayed to too great an extent with time to be usable). The dogs were anesthetized with morphine sulfate (2 mg/kg, im), followed 30 minutes later by chloralose dissolved in polyethylene glycol (75 mg/kg, iv).

Both cervical vagosympathetic trunks were dissected free from surrounding tissues, crushed, and ligated centrally. Either the left trunk, or both left and right trunks, were connected to a bipolar shielded electrode (Grass) at a point distal to the ligature. β-Adrenoreceptors were blocked with propranolol (1.0 mg/kg, iv) to abolish the effects of stimulation of cardiac adrenergic fibers contained in the vagosympathetic trunk. Adequacy of blockade was confirmed in selected dogs at 1-hour intervals by noting the absence of cardiac responses to periodic maximal stimulation of the right stellate ganglion. The heart was paced continually throughout the experiment at a rate just above the spontaneous rate; usually the paced cycle length ranged from 400 to 550 msec. After thoracotomy, the clip electrodes were attached near the sinoatrial node to minimize the effects of abnormal atrioventricular nodal entry and excitation. Bipolar recording catheters were inserted into the right atrium through a small incision in the atrial appendage, and into the right ventricle through the right external jugular vein. The atrial catheter was secured tightly to the atrial appendage to eliminate timing errors due to changes in electrode position. The onset of the atrial electrogram was used as the reference event for all other measured, computed, and generated time intervals. The ventricular catheter was wedged against the ventricular wall and rarely changed position; however, any change in its position was noted easily from changes in wave shape of the electrogram recorded through it; these changes had a constant, minimal (less than 5 msec) effect on the measured AV interval. The catheters were connected to a Brush Mark 200 oscillograph to record the onset of atrial (A) and ventricular (V) activation.

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which the stimulus is given, the experimental protocol consisted of placing the conditioning and test stimuli an integral number of (paced) cardiac cycles apart, but at the same value of AD in each of the two cycles.

Results

In the first series of experiments, an arbitrary set of stimulus parameters was used to produce a 50% maximal response (maximal being defined as that response just short of complete atrioventricular block). The independent variable was the integral number of cardiac cycles between conditioning and test stimuli. Figure 1 is a typical set of AV responses for one dog. For comparison among dogs, the data for all of them were normalized by computing the ratio of the peak of the second (test) response, $\Delta A V_2$ to that of the first (conditioning) response, $\Delta A V_1$. Thus $\Delta A V_2 / \Delta A V_1$ was slightly greater than unity for the top left panel of Figure 1 for this dog. As the time (T) between stimuli was increased progressively $\Delta A V_2 / \Delta A V_1$ declined markedly (left column of panels), reaching a minimum of 0.37 at T = 3.4 seconds. As T was further increased, $\Delta A V_2 / \Delta A V_1$ tended to rise, not necessarily monotonically, and did not reach a steady state value of unity until T exceeded about 50-60 seconds (not shown in Fig. 1); that is, the conditioning stimulus somehow altered this system so as to decrease the response to a second test stimulus when these two stimulus bursts were separated by less than about a minute.

In 11 dogs this was a consistent result for 15 experiments using either absolute or percent changes of AV from control. The $\Delta A V_2 / \Delta A V_1$ ratio were plotted as a function of T for each dog and for each experimental run. The closed circles of Figure 2 are a plot of the composite data showing the mean of all 15 experiments (the open circles of Figure 2 will be discussed below). Points at a T between one cardiac cycle length and about 1.5 sec are not included in Figure 2 because of their tremendous variability; $\Delta A V_2 / \Delta A V_1$ in this range fell between 0.8 and 2.5 (see Discussion). For the composite data the minimum $\Delta A V_2 / \Delta A V_1$ is not as low as shown for the representative experiment in Figure 1, mostly because the exact shapes of these curves are quite variable from dog to dog. Thus, the minimum points occur over about 2-10 seconds in individual experiments, and this raises the average minimum point to 0.67; the mean of the minimum of all $\Delta A V_2 / \Delta A V_1$ values, computed independently of time of occurrence, was 0.52.

Two subsequent sets of experiments were performed to help localize the mechanism responsible for the temporal dependence of $\Delta A V_2$ on $\Delta A V_1$. In the second set of experiments a possible relationship between this temporal dependence and the magnitude of the stimulus used was sought. For these experiments, the interval between stimuli, T, was held constant, but various stimulus parameters were increased from a minimum that barely elicited a response to a maximum that just avoided complete atrioventricular block. As before, identical conditioning and test stimuli were used, these being separated by the value of T that was found to produce a minimum $\Delta A V_2 / \Delta A V_1$. Successive pairs of stimuli were initiated at intervals greater than 1 minute.

Figure 3 shows composite plots of the two types of $\Delta A V_2 / \Delta A V_1$ dependence on stimulus amplitude found in seven dogs. For purposes of analysis, the $A_1$ amplitude was used as a measure of the stimulus amplitude. The abscissas of these curves are normalized to $A_m$, the maximum

![Figure 1](http://circres.ahajournals.org/)

![Figure 2](http://circres.ahajournals.org/)

![Figure 3](http://circres.ahajournals.org/)
obtainable change in AV at which complete atrioventricular block did not occur. Figure 3A illustrates the U-shaped curve that was obtained in five dogs, and Figure 3B the monotonic decrease in two other dogs. For all seven dogs, as the A1 response amplitude was increased up to about half of the Amax, the dependence of the second response upon the first was increased (ΔAV2/ΔAV1 decreased). In two dogs ΔAV2/ΔAV1 continued to decrease up to maximal levels of stimulation leading to complete atrioventricular block (Fig. 3B). In the other five dogs ΔAV2/ΔAV1 began to increase as the stimulus increased from about half-maximal to maximal (Fig. 3A). These results obtained despite variation of A1 either by changing the number of stimuli per burst and the pulse width or amplitude, or by changing AD, the point in the cardiac cycle at which a stimulus was given.

In the third set of experiments the conditioning stimulus was initiated on one vagal trunk, and the test stimulus on the contralateral trunk. Since identical stimuli applied to left and right vagi usually produce unequal response amplitudes, a modification of the protocol was necessary for these experiments, as illustrated in Figure 4. A narrower range of T periods was used because of the greater total number of stimulations required, and these were concentrated in the range of expected minimal ΔAV2/ΔAV1 values. The open circles of Figure 2 show the composite results of experiments on seven dogs; Student’s t-statistic confirmed that there was no significant difference (P > 0.5) between the curves represented by the two types of symbols.

Discussion

Previous work, both in our laboratory with single vagal stimuli1 and by others using pulse trains,2-3 showed that cardiac responsiveness to vagal stimulation depends on the time elapsed since a previous stimulus. The present work quantifies this dependence for single stimulus bursts, showing that the effect obtains even at brief, low levels of vagal stimulation. The composite data in Figure 2 show that when identical stimuli are applied the ratio of test to conditioning responses, ΔAV2/ΔAV1, decreases to a minimum as the time between stimuli is progressively increased. Thereafter the ratio increases gradually but does not reach unity until about a minute has elapsed between the two stimuli.

As shown in Figure 1, ΔAV2/ΔAV1 usually exceeds unity when T is less than about 1.5–2.0 seconds, and a value of 2.0 was exceeded in some dogs (not shown). This is most probably due to the fact that a small concentration of acetylcholine (ACh) is still present locally after the first stimulus, or due to diffusion of ACh from adjacent areas after the first stimulus. The response to the test stimulus (A2) then represents the effect of summated local ACh concentration. This can be explained better with the aid of Figure 5. The right tracing of each panel in Figure 5 shows the step changes of AV in time following a vagal stimulus, as in Figure 1. The maximal prolongation of the AV interval (ΔAV1 or ΔAV2) on the first or second cardiac cycle after the vagal stimulus is usually followed by a gradual return to control over the next 4–20 cardiac cycles. The next AV after the maximally prolonged AV can, however, be 30–60% of the maximal, as in Figure 1 and in the right panel of Figure 5A. The left panel of Figure 5A shows the characteristic of ΔAV vs. x, the postulated peak local ACh concentration which is related to the vagal stimulus burst intensity, as previously described from our laboratory. It is the non-linearity of this characteristic that can produce ΔAV2/ΔAV1 > 2.0 for small T. If the same Δx, that is, the same stimulus, of Figure 5A is applied at the second arrow of the right panel of Figure 5B, it will produce A2B since the same bolus of ACh (Δx) was added, but starting from some residual ACh concentration corresponding to A1B in Figure 5B. Also note that A2B – A1B is greater than A1B, again by virtue of the nonlinearity of the ΔAV vs. x characteristic. In Figure 5C the second...
stimulus has been placed one cardiac cycle closer, so that
now the second Δx is added starting from a level cor-
sponding to A'C. Now note that A''c - A'C is greater yet
than A''B and, in fact, the nonlinear characteristic has
produced a A''c - A'C greater than A''B - A'B. It is, thus,
this nonlinearity in combination with noninstantaneous
decay of local ACh concentration that can produce a
stimulus is apparently quite wide, thus preventing a mean-
ful composite summary of data in the T range of 1.5-2.0
seconds, therefore these values are not included in Figure 2.

Figure 2 is prepotent. Thus, we are not able to say how soon
after the first stimulus this ΔAV2/ΔAV1 dip actually begins.
However, it can be said that, for those dogs in which
ΔAV2/ΔAV1 < 1.0 for T < 1.5-2.0 seconds, the dip mechan-
ism has started in this T range because, as illustrated in
Figure 5, we should surely expect some ΔAV2/ΔAV1 in
excess of unity when the AV just prior to the second stimulus
(ΔAV' and AV' on Figure 5) is greater than control as a
result of residual ACh concentrations. The variability
among dogs in either or both the ΔAV vs. x characteristic
and in the decay of ACh concentration following the
stimulus is apparently quite wide, thus preventing a mean-
ful composite summary of data in the T range of 1.5-2.0
seconds, therefore these values are not included in Figure 2.

Possible mechanisms that could account for the temporal
dependence of A_n on A_1 of Figure 2 include (1) an increase in
cardiac excitability seen with acetylcholine under certain
pharmacologic constraints, (2) a reflex increase of sympa-
thetic activity or decrease of vagal activity, or both, (3)
simultaneous stimulation of adrenergic fibers in the vago-
sympathetic trunk, (4) a decreased release of ACh in re-
response to the test stimulus, or (5) altered receptor or ACh
inactivation processes.

ACETYLCHOLINE AUGMENTATION OF EXCITATION

ACh has been found to induce a tachycardia mediated by
norepinephrine at the cessation of a train of vagal stimuli.9
Although this may play a role in the ΔAV2/ΔAV1 dip, three
facts argue against it: (1) the postvagal tachycardia is
essentially over in 20 seconds, whereas, the ΔAV2/ΔAV1
lip lasts up to 1 minute; (2) a train of pulses is required for
the tachycardia, whereas the dip can be produced with single
vagal stimuli; and (3) propranolol was used to block the β-
receptors.

CHANGES IN AUTONOMIC ACTIVITY

A reflex increase in sympathetic activity can be eliminated
as a possible mechanism, because arterial pressure was
relatively constant in the paced heart preparation used here.
Further, propranolol was used to block any sympathetic
effects, including the possible effects of release of norepi-
ephrine from sympathetic nerve endings by ACh. Also, the
vagi were ligated, blocking any reflexes mediated by these
nerves. Thus, we were forced to focus on either (1) changes
in ACh release at vagal nerve endings or (2) altered ACh
inactivation or receptor sensitivity, as the mechanism re-
sponsible for the temporal dependence of ΔAV2 on ΔAV1
(the ΔAV2/ΔAV1 dip in Figure 2). In the remaining
discussion an attempt will be made to distinguish between
these two possibilities.

NERVE-ENDING PROCESSES

In all of the experiments summarized in Figure 2,
stimulation levels were used such that the control response
ΔAV1 was about half of the maximal level (maximal, A_m,
being that increase in atrioventricular conduction time just
short of complete atrioventricular block). To help distin-
guish between the two broadly defined mechanisms above
and further to apply these results to other situations, e.g., the
possible genesis of arrhythmias, the dependence of the
ΔAV2/ΔAV1 dip in Figure 2 on the stimulus intensity (and
thus also the amplitude of ΔAV1), also must be known.
Figure 3 shows that for the very small values of ΔAV2/ΔAV1
dip in Figure 2 on the stimulus intensity (and thus also the amplitude of ΔAV1), it is close to unity). Within limits, as ΔAV1 increases in amplitude with changing stimulus parameters, but with the same value of T, ΔAV2/ΔAV1 decreases, indicating an amplitude-dependence of the mechanism. The ratio reaches a minimal ΔAV2/ΔAV1 at about half-maximal
ΔAV1 levels in most dogs (Figure 3A) before rising toward
unity again near maximal ΔAV1; this subsequent rise in
the curve of Figure 3A is probably due to such a great
quantity of ACh being liberated for ΔAV1 in this maximal
stimulus range that significant local concentrations still
existed at the time of ΔAV2. For example, in two of the
five dogs represented in Figure 3A, ΔAV2/ΔAV1 exceeded

![Figure 5 Representation of amplitude dependence of the peak ΔAV response on vagal stimulus intensity, x; the identical characteristic is plotted as the curve at the left of each panel. The associated ΔAV time response to a vagal stimulus given at the vertical arrow is shown at the right of each panel. Panel A: a single stimulus of intensity Δx. Panels B and C: two stimuli such that the second response starts from the level of the second AV (panel B) and first AV (panel C) after the peak. Due to the nonlinear ΔAV vs. x dependence of A, on A, of Figure 2 include (1) an increase in
unity near maximal $\Delta AV$, and the value of $AV$ just prior to the second stimulus for these two dogs was 6–12 msec higher than that just prior to the first stimulus, suggesting a significant residual ACh concentration at this time. Again, as shown in Figure 5, the $\Delta AV$ response is a power (concave upward) function of stimulus intensity, so that as stimulus intensity is increased in equal increments, the increments of $\Delta AV$ become larger. Thus, a small residual concentration of ACh from $\Delta AV$ not yet inactivated at $\Delta AV$ will have a magnified effect when summated with the $\Delta AV$ stimulus response. In contrast, for the two dogs of Figure 3B, the value of $AV$ just prior to the second stimulus was within 2 msec, and usually within 1 msec, of control, and there is a continuous decline in the curve of Figure 3B.

One factor that could suggest involvement of nerve-ending processes in the mechanism of the $\Delta AV$/$\Delta AV$, dip in Figure 2 would be a dependence of ACh released by one fiber upon recent activity of the same or adjacent fibers, i.e., a negative feedback control system. The changes in $\Delta AV$, amplitude of Figure 3 were brought about by two methods, one being a change in stimulus parameters. It is assumed that this altered stimulus, at least for the case in which only stimulus pulse width and amplitude were changed, caused only the number of stimulated fibers to be changed. The hypothesis then is that the quantity of ACh released by a single fiber for $\Delta AV$ is inversely proportional to prevailing local concentrations of ACh, or possibly to another substance released with the ACh by the nerve terminal (evidence that it probably does not involve a mechanism inside the terminal will be discussed below). The curves of Figure 3 would indicate that such an inverse function would be nonlinear; that is, as the number of fibers stimulated is increased (at least up to the number producing about half the maximal response), the negative feedback inhibition is more severe (at constant $T$, $\Delta AV$/$\Delta AV$, nonlinearly decreases as $\Delta AV$ increases). Thus, the mechanism producing the $\Delta AV$/$\Delta AV$, dip in Figure 2 would be dose-dependent under this hypothesis. Such a hypothesis would be in accord with the curve of Figure 3B, but the curve of Figure 3A may militate against it if the above explanation for the rising phase of this curve is not valid.

Similar to that found for norepinephrine at sympathetic terminals, an inhibition of ACh release by the prostaglandins $E_1$ and $E_2$ has only recently been suggested for parasympathetic terminals. That is, parasympathetic terminals were shown to release $E_1$ and $E_2$ in the heart, and exogenous $E_2$ inhibits release of ACh. $E_1$ and $E_2$ are not metabolized in blood, but their effect is diminished by 90–100% on one passage through the lung. However, the speed of tissue washout of prostaglandins from rabbit heart (inferred from Figure 1 of Junstad and Wennmalm) seems to have a time constant on the order of 7–8 minutes. Thus, a hypothesis involving inhibition of ACh release for the temporal dependence of $\Delta AV$, on $\Delta AV$, does not seem reasonable, since the effect in Figure 2 is essentially over in about a minute. Also against this hypothesis was the fact that supramaximal vagal stimulus trains 10 minutes in duration were used to produce the low levels of $E$, measured, whereas in the present work the dip in $\Delta AV$/$\Delta AV$, of Figure 2 was produced by using single vagal stimuli.

No other reports were found to support such a dependence of ACh release on local ACh concentrations in vagal nerves, except that which occurs under the unphysiological condition of use of an anticholinesterase.

The effect shown in Figure 2 could also be the result of a ganglionic mechanism. Koelle postulated that an initial release of ACh serves to activate the additional release of ACh from presynaptic terminals of autonomic ganglia. Thus, local ACh concentrations conceivably could modulate ganglionic transmission to produce the dip of Figure 2. However, it would seem that if such were true, the characteristic shape of Figure 2 would be concave upward, not downward; that is, under the Koelle hypothesis, a residual ACh concentration from $\Delta AV$, at the time of $\Delta AV$, should augment ganglionic transmission, rather than inhibit it. Evidence that might support a ganglionic mechanism is that ACh inhibits the uptake of choline into rat brain synapto
tosomes, thus decreasing the supply of precursor for ACh synthesis. A decreased synthesis of ACh for $\Delta AV$ could result in the dip of Figure 2. It is not known whether a similar mechanism operates in autonomic ganglia.

The $\Delta AV$, amplitude in Figure 3 also was varied by changing $AD$, the delay in the cardiac cycle at which a stimulus is given, for both $\Delta AV$, and $\Delta AV$. The dependence of the $\Delta AV$,/$\Delta AV$, ratio on the amplitude of $\Delta AV$, here was identical to that found when $\Delta AV$, was changed by altering the stimulus parameters. However, changing $AD$ does not alter the number of fibers stimulated or, presumably, the local ACh or prostaglandin $E_1$ and $E_2$ concentrations. It is likely that only the sensitivity of the atrioventricular nodal membrane is altered by these changes in timing of the vagal stimulus. Under these conditions, there is also an identically strong dependency of the $\Delta AV$,/$\Delta AV$, ratio on $\Delta AV$, but now it no longer can be said that this dependence is due to an inverse functional relationship of ACh release on local ACh or $E$, concentration. It does not seem reasonable to postulate both that there is, and that there is not, an inverse functional dependence of $\Delta AV$,/$\Delta AV$, on ACh or $E$, concentration ($\Delta AV$, amplitude) to account for the identical characteristic of Figure 3 being produced by either technique. Rather, it is more likely that the identical characteristics were produced by the identical mechanisms. This argument points away from involvement of ACh release processes in the mechanism of the $\Delta AV$,/$\Delta AV$, dip in Figure 2.

**CHANGES IN RECEPTOR SENSITIVITY ON ACh INACTIVATION**

The third set of experiments strengthens the concept that ACh release mechanisms are not responsible for the dip in $\Delta AV$,/$\Delta AV$, Here $\Delta AV$, and $\Delta AV$, each were produced by stimulating different nerves entirely, therefore the stimulus causing $\Delta AV$, could not have affected any ACh release processes internal to the nerve terminal caused by the second stimulus. Such a conclusion would be invalid if minute local concentrations of liberated ACh could somehow affect...
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subsequent release of ACh by any other nearby nerve ending. This is so for ACh, since the $\Delta AV_2/\Delta AV_1$ dip occurs at such times (2 seconds to about 1 minute) that the ACh released for $\Delta AV_1$ is virtually ineffective in prolonging AV, thus presumably at very low concentrations ($\Delta AV$ is only 1–2 msec just prior to $\Delta AV_1$ at these half-maximal stimulus levels). Also, as noted above, no evidence has been found to link ACh release to local ACh concentrations over the time scale represented by the dip of Figure 2. The conclusion that the stimulus causing $\Delta AV$, could not have affected the ACh release processes, for $\Delta AV_2$ also depends upon there being no convergence of left and right vagal efferents upon common parasympathetic ganglia. Convincing evidence that there is no convergence has been presented by Kött et al. The evidence presented here thus points toward a mechanism involving alterations in receptor sensitivity or ACh inactivation as being responsible for the reduced responsivenessto the second of a closely spaced pair of vagal stimuli. It is possible that cholinesterase activity may somehow be increased (over 2–60 seconds) following an initial vagal stimulus, although no work appears to have been done to support this concept. Another possibility is a time-dependent desensitization of the receptor to ACh. This has been suggested for the sinoatrial node by Satow, who used this concept to partially explain vagal escape. The present results, no matter what the mechanism, similarly provide an explanation for the phenomenon of vagal escape.

Finally, the present work suggests a note of caution in using the magnitude of cardiac vagal responses as an indicator of assumed relative local ACh concentrations, as has been done by several workers (e.g.,) in the past. If the argument is true that the $\Delta AV_2/\Delta AV_1$ ratio is due to altered receptor sensitivity or cholinesterase dynamics, and not to alteration of ACh synthesis, storage, or release at the nerve ending, then cardiac vagal responses are obviously not directly indicative of ACh concentrations if the vagal stimuli are separated by less than about a minute.

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Depression of atrioventricular sensitivity in the dog by successive brief bursts of vagal stimulation.

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