Mathematical Model of the Changes in Heart Rate Elicited by Vagal Stimulation

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We developed a mathematical model of the underlying cellular mechanisms responsible for the changes in sinus cycle length (SCL) elicited by vagal stimulation in intact animals. The model incorporated a stimulation-mediated depletion of the releasable pool of acetylcholine (ACh) in the nerve endings, the in vitro reaction kinetics of acetylcholinesterase, and the electrical activity of a pacemaker cell with six membrane ionic currents. SCL increased linearly with the frequency of simulated vagal stimulation, as it does in animal experiments, because the concentration of ACh in the neuroeffector junction ([ACh]) saturated as the frequency of stimulation was increased and because SCL increased geometrically in response to increases in [ACh]. The dependence of SCL on the timing of vagal stimulation in the cardiac cycle resulted, in part, from the dependence of [ACh] on SCL. Simulated vagal stimulation entrained the sinus node because the rate of activation and inactivation of ACh-activated K⁺ channels depended only weakly on membrane potential during diastolic depolarization. SCL increased geometrically with [ACh], because 1) during diastolic depolarization, the amplitude of the ACh-activated K⁺ current was approximately equal to the amplitude of the sum of the other ionic currents, 2) [ACh] was low enough to saturate neither acetylcholinesterase nor the cellular system that activates the ACh-activated K⁺ channels, 3) the pacemaker cell membrane behaved electrotonically like a capacitor, and 4) the sum of all the ionic currents increased linearly with the amplitude of the ACh-activated K⁺ current. (Circulation Research 1989;65:1330-1339)

Our goal is to explain the cellular basis for the changes in sinus cycle length (SCL) elicited by vagal stimulation by using mathematical models of the underlying cellular physiology. In recent papers, we have presented mathematical models of the release of acetylcholine (ACh) from vagal nerve endings, the degradation of ACh in the neuroeffector junctions of the sinus node, and the changes in SCL elicited by ACh. By combining these mathematical models of the underlying cellular physiology, we create a more complete mathematical model that predicts the changes in SCL elicited by vagal stimulation in the intact animal. Our principal goal is to determine how the underlying cellular physiology, which we represented mathematically in our computer model, causes changes in SCL.

Methods

Mathematical Models

ACh release. ACh release evoked by activation of postganglionic vagal nerve endings may deplete a neuronal pool of releasable ACh. Let v (Table 1) represent the dimensionless quantity of ACh, 0 ≤ v ≤ 1, that is available for release (Figure 1); the letter v was chosen because the releasable pool of ACh may be stored in intracellular vesicles. Let r equal the fastest rate of renewal of the releasable pool of ACh. Let p equal the fraction of the releasable pool of ACh, v, that is released by each vagal stimulus. Each stimulus in a brief burst of vagal stimuli releases progressively less ACh because the quantity of ACh that is available for release decreases.

A vagal stimulus inhibits subsequent ACh release for more than 100 msec but less than 600 msec. To estimate r from these experimental data, assume...
that the difference between \((1-v)\) and 1 is halved every 200 msec, that is, \(r = \ln(2/200) = 0.0035\) msec. As a result, 600 msec after \(ACh\) release, the difference between \(1-v\) and 1 will have been halved three times; that is, the releasable pool will have been nearly renewed.

\[ \frac{d[ACh]}{dt} = -k[ACh] + R(t) \]  

where \(k\) equals the sum of the rates of \(ACh\) hydrolysis and washout (Figure 1); that is, \(k\) equals the rate of \(ACh\) degradation. We used \(k = 0.00139/msec\) in our simulations; this value of \(k\) corresponds to a half-life of 500 msec. Equation 3 may be inaccu-
rate when acetylcholinesterase is inhibited because diffusion would then be the principal means of ACh degradation; the rate of diffusion may depend not only on [ACh] but on SCL as well.

**Sinus node.** We used a Hodgkin-Huxley type mathematical model to predict the changes in SCL elicited by ACh (Figure 1). Briefly, the time change in membrane potential (V) is given by

\[
dV/dt = -(1/C)I_T
\]

where C is the membrane capacitance and \( I_T \) is the sum of six membrane ionic currents: \( I_{Na^+} \), a fast Na\(^+\) current; \( I_s \), the slow inward current; \( I_{Ko} \), a hyperpolarization-activated current; \( I_{Kt} \), a K\(^+\) current; \( I_L \), a leakage current; and \( I_{KAO} \), the ACh-activated K\(^+\) current. \( I_{Na} = (I_T - I_{KAO}) \).

Each of the six ionic currents is a nonlinear function of V and the six ionic gates, which are solutions to a coupled system of seven nonlinear ordinary differential equations. The ionic gates determine the ionic currents that change V, which subsequently affects the ionic gates and currents. Equations for the ionic currents and gates are listed in Table 1 of Reference 7. SCL was calculated by finding the time between maxima of dV/dt.

The free-running period (\( \tau \)) of the pacemaker cell is its SCL in the absence of any ACh. To adjust \( \tau \), we added a voltage and time-independent current to some of the dog experiments that we simulated, from the sinus node to the right atrium. We incorporated a delay of 50 msec in our model (Figure 1) to adjust for the difference between the measured and simulated latencies. The 50-msec discrepancy may represent, at least partially, the time required for ACh to diffuse in neuroeffector junctions from vagal nerve endings to pacemaker cells.

**Latency and conduction delay.** The total delay (\( t_d \)) in the model (Figure 1) equals the sum of 1) the latency between the time of vagal stimulation and the beginning of right atrial depolarization was considered to be the beginning of each cardiac cycle.

The simulated (Equations 1, 2, and 4) latency between vagal stimulation and hyperpolarization of pacemaker cells equals 30 msec. The latency between stimulation and hyperpolarization equals 80 msec in the rabbit; we do not know the value in the dog. We incorporated a delay of 50 msec in our model (Figure 1) to adjust for the difference between the measured and simulated latencies. The 50-msec discrepancy may represent, at least partially, the time required for ACh to diffuse in neuroeffector junctions from vagal nerve endings to pacemaker cells.

Measurements of the sinoatrial conduction time in normal dogs vary widely: 60–110 msec, 30–175 msec, and 80 msec. The estimates of the sinoatrial conduction time may differ so much because the accuracy of a measurement depends on the ability to locate the portion of the sinus node from which electrical activity originates. We used a sinoatrial conduction time of 60 msec in our simulations. Therefore, \( t_d = 50 + 60 = 110 \) msec.

**Sinoatrial conduction time varies by as much as 20 msec depending on the timing of vagal stimulation in the cardiac cycle.** Nevertheless, \( t_d \) is a constant. We discuss the significance of this assumption in the discussion section “Phase Response Curves.”

**Numerical methods.** We solved simultaneously Equations 1–4 by the hybrid method of Moore and Ramon. The temporal stepsize was 0.5 msec. We stored the voltage-dependent constants in computer-generated lookup tables whenever possible; we used voltage increments of 0.1 mV. Simulations were performed using MC68881 microprocessor running FORTRAN.

We considered SCL to be steady when two criteria were satisfied. First, the simulated time had to exceed twice the half-life of ACh, that is, \( t > 2[\ln(2)/k] \). Second, for three cardiac cycles, SCL had to be within twice the stepsize of each other.

The phase (\( \text{AST} \)) of a burst of vagal stimuli in the cardiac cycle was defined to be the time from the upstroke of a right atrial electrogram until the beginning of the first stimulus in a brief burst of vagal stimuli. By “brief” we mean that the duration of the burst is less than 90 msec. We refer to a “phase response curve” (PRC) as the relation between AST and SCL. Let \( \text{AST}_{\text{max}} \) be the longest AST for which \( (\text{AST} + t_d < \text{SCL}) \). We simulated PRC starting with \( \text{AST} = -t_d \). After each cardiac cycle, AST was increased by 10 msec until \( \text{AST} = \text{AST}_{\text{max}} \). Because PRCs are periodic, vagal stimulation at \( \text{AST} = -t_d \) is identical to stimulation at \( \text{AST} = \text{AST}_{\text{max}} \). Therefore, to permit comparison of experimental data from Yang and Levy with our simulation results (Figure 5), we plotted our simulations from \( \text{AST} = 0 \) to \( \text{AST} = \text{AST}_{\text{max}} + t_d \).
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FIGURE 2.  Graphs showing dependence of sinus cycle length on the frequency of vagal stimulation. Mean interstitial concentration of acetylcholine ([ACh]) refers to the mean [ACh] over time. The data points in panel C were generated by holding [ACh] constant at the specified level.

Results
Effect of the Frequency of Stimulation on SCL
We simulated the changes in SCL elicited by vagal stimulation at frequencies above 6 Hz; $\tau=318$ msec and $[ACh]=50$ or 100 msec. The simulated (Figure 3) and experimentally recorded action potentials3,8,14 resembled each other. Let diastolic depolarization refer to the slow increase in V from $V_{min}=-59$ mV to $V_{max}=-42$ mV. The repolarization and fast depolarization phases of the action potential precede and follow diastolic depolarization, respectively. The duration of repolarization was nearly independent of [ACh] (Figure 3). Similarly, the duration of fast depolarization was nearly independent of [ACh] (Figure 3). Raising [ACh] increased the duration of diastolic depolarization.

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During diastolic depolarization, $|I_{KAC}| \approx |I_{sum}|$; that is, the magnitude of $I_{KAC}$ is approximately equal to the sum of all the other ionic currents (Figure 3). ACh was, therefore, a major determinant of V during this phase of the action potential. Thus, ACh prolonged the duration of diastolic depolarization. During fast depolarization and repolarization, $|I_{KAC}| \ll |I_{sum}|$ (Figure 3); therefore, ACh did not change the duration of fast depolarization or repolarization.

To understand the geometric dependence of the duration of diastolic depolarization (Dur) on [ACh] (Figure 2C), we plotted mean $I_{KAC}$ versus [ACh] (Figure 4A) mean $I_1$ versus mean $I_{KAC}$ (Figure 4B), and Dur versus mean $I_1$ (Figure 4C). “Mean” refers to the mean value during diastolic depolarization. A raise in [ACh] increased mean $I_{KAC}$ linearly (Figure 4A). It can be shown by using the Hodgkin-Huxley regression equations that predict the kinetics of $I_{KAC}$ and linear systems theory25 that $I_{KAC}$ was proportional to [ACh] because $[ACh]<<4.2\times10^{-6}$ M. Because the physiological [ACh] was low, the cellular systems that activate and inactivate ACh-activated K+ channels were not saturated. Increases in mean $I_{KAC}$ were associated with linear increases in mean $I_1$ (Figure 4B); equivalently, an increase in mean $I_{KAC}$ decreased the magnitude of $I_1$ because $I_1<0$. Therefore, an increase in [ACh] increased mean $I_1$, linearly during diastolic depolarization.
During diastolic depolarization, changes in $I_T$ as a function of time were minimal (Figure 3). Therefore, by integrating equation 4 for a constant $I_T$,

$$V_{max} = V_{min} - (1/C)I_T \cdot \text{Dur}$$

As a result,

$$\text{Dur} = C(V_{min} - V_{max})/I_T$$

In words, the duration of diastolic depolarization was reciprocally related to $I_T$ (Figure 4C). Note that $V_{min} - V_{max}$ and $I_T < 0$; thus, increases in $I_T$ increased $\text{Dur}$ geometrically. Therefore, the duration of diastolic depolarization was geometrically related to $[\text{ACh}]$ because ACh increased $I_T$ linearly (Figures 4A and 4B).

Phase Response Curves

PRCs are graphs that show the dependence of SCL on ASI and the number of pulses in each burst of vagal stimuli. We simulated two PRCs (3 or 5 pulses/burst); we set $\tau = 318$ msec, $m = 73$ nM, and the increment between pulses = 9 msec (Figure 5A). The amplitude of a PRC was calculated by finding the difference between the maximum and minimum SCL. The amplitude was greater when we included five rather than three pulses in each burst (583 – 473 = 110 msec vs. 500 – 439 = 61 msec). Decreasing the number of pulses per burst from five to three increased the difference between the ASI that produced the minimum and the ASI that produced the maximum SCL (280 – 170 = 110 msec vs. 270 – 120 = 150 msec). SCL had a tendency to oscillate for ASI that corresponded to the negative slope region of the PRC. These simulation results resemble the corresponding experimental results in dogs.

We investigated how the phase-dependent response of the sinus node to ACh affects the shape of PRC. Once during each cardiac cycle, we abruptly increased $[\text{ACh}]$ from 0 nM to a nonzero level of $[\text{ACh}]$. We maintained $[\text{ACh}]$ at that level for 40 msec, and then we instantaneously degraded all of the ACh. We picked ACh concentrations (4.6 and 18.6 μM) that yielded PRC with mean SCL over the entire PRC (Figure 5B) that equaled the mean SCL produced by vagal stimulation (Figure 5A). The PRC (Figure 5B) resembled the equivalent experimentally generated PRC.

The simulation results that were obtained by decreasing the number of pulses per burst (Figure 5A) were matched qualitatively by decreasing $[\text{ACh}]$ directly (Figure 5B). First, decreasing $[\text{ACh}]$ from 18.6 μM to 4.6 μM decreased the difference between the amplitudes of the PRC (674 – 303 = 371 msec vs. 616 – 298 = 318 msec). Second, decreasing $[\text{ACh}]$ from 18.6 μM to 4.6 μM increased the difference between the ASI of application of ACh pulses that produced the minimum and the ASI that produced the maximum SCL (190 – 180 = 10 msec vs. 190 – 170 = 20 msec). However, the PRCs that were generated by simulated vagal stimulation (Figure 5A) and by simulated ACh pulses (Figure 5B) differed quantitatively. Most strikingly, the amplitude of PRC produced by ACh pulses exceeded the amplitude of PRC generated by vagal stimulation (674 – 303 = 371 msec for 18.6 μM vs. 583 – 473 = 110 msec for 5 pulses/burst).
When the vagus was stimulated once per cardiac cycle, the mean [ACh] per cardiac cycle depended on SCL. We plotted mean [ACh] from the simulation shown in Figure 5A against ASi (Figure 5C). An increase in SCL decreased mean [ACh] (comparing Figures 5A and 5C). In particular, for simulated vagal stimulation with five pulses per burst, vagal stimulation prolonged SCL the most when ASi=190 msec (Figure 5A). At the same ASi, mean [ACh] was at its lowest level (Figure 5C).

On the one hand, an increase in SCL allowed more time between bursts of vagal stimuli for acetylcholinesterase to degrade the ACh in the neuro-effector junctions and, thus, lower the mean [ACh] per cardiac cycle. On the other hand, an increase in SCL increased the time between vagal bursts,
FIGURE 6. Graphs showing cellular basis of phase response curves. The data in Figure 5B were replotted (panel A) as time from stimulus to upstroke versus time from upstroke to stimulus (AST). The fractions of acetylcholine (ACh)-activated K+ channels that were open immediately after the pulse of ACh ended and immediately before fast depolarization began were plotted against AST (panel B). The simulation in Figure 5B was then repeated (panel C); however, instead of applying pulses of ACh, ACh-activated K+ channels were activated directly by the same fraction.

which increased ACh release (Equation 2).\(^2,23\) The dominant effect of an increase in SCL was to decrease mean [ACh].

**Positive Slope of the Phase Response Curve**

We replotted those data points in Figure 5B that corresponded to the positive slope region of the PRC as STA (the time from the stimulus to the upstroke of the subsequent action potential) versus AST (Figure 6A). STA was virtually constant; therefore, an increase in AST increased SCL (Figures 5A and 5B).

To determine why changing AST did not alter STA, we examined the dependence of V and the ionic gates on AST (Figure 6B). In particular, the rates of activation and inactivation of the ACh-activated K+ channels depended on [ACh] and varied with t, but depended only weakly on V over the range of V during diastolic depolarization.\(^7,9\) As a result, the fraction of ACh-activated K+ channels that were open immediately after the pulse of ACh ended and immediately before the subsequent action potential upstroke started did not depend on AST.

We tested the significance of this observation. When we applied pulses of ACh (Figure 5B), we computed the fraction of the ACh-activated K+ channels that were open immediately after the ACh was instantaneously degraded. Applying pulses of ACh indirectly changed V and the ionic gates of the other channels. We repeated the original simulation (Figure 5B); however, instead of applying pulses of ACh, we directly activated ACh-activated K+ channels by the same proportion. The PRC that was generated by this simulation (Figure 6C) resembled qualitatively the PRC that was generated by applying pulses of ACh in the original simulation (Figure 5B).
Oscillations on the Negative Slope of Phase Response Curves

SCL frequently oscillates (sinus arrhythmia) in dogs during vagal stimulation at AS1 values that correspond to the negative slope region of the PRC.14,25 The vagus was stimulated at a phase (AS1=320 msec) that corresponded to the negative slope region of a PRC (τ=400 msec, m=45 nM, 9 pulses/burst, and an interval between pulses of 9 msec). SCL alternated between 472 and 915 msec (Figure 7).

One mechanism of the sinus arrhythmia involved an interaction between [ACh] and V (Figure 7). Some bursts of vagal stimuli (St1 in Figure 7) arrived 430 msec after the upstroke of the action potential (i.e., AS1+t=320+110=430 msec). SCL of the shorter cycle equaled 472 msec. Therefore, some ACh was released very close (472-430=42 msec) to the end of the shorter cycle, and some was released after the shorter cycle had ended. Because [ACh] was high at the start of the subsequent sinus cycle, SCL was prolonged. As a result, the subsequent burst of vagal stimuli (St2 in Figure 7) arrived during the middle of the cardiac cycle. [ACh] was low when the next cycle started, and a short SCL resulted. Thus, the next burst (St3) arrived late in the cardiac cycle. In effect, the mean [ACh] was greater during the longer cycle than during the shorter cycle. A variation in the mean [ACh] per cardiac cycle from cycle to cycle is sufficient to produce oscillations in SCL; that is, SCL oscillated (Figure 7), in part, because acetylcholinesterase degraded ACh rapidly enough for the mean [ACh] to vary from cardiac cycle to cardiac cycle.

The other process that contributed to the generation of the sinus arrhythmia (Figure 7) was the dependence of SCL on AS1. During rapid depolarization, |I_{Kca}|<|I_{Na}| (Figure 3). Therefore, the ACh that was released late in the cardiac cycle (St1 in Figure 7), and consequently exerted its influence during rapid depolarization of the next action potential, had little effect on SCL (Figures 5A and 5B). On the other hand, during diastolic depolarization, |I_{Kca}|>|I_{Na}| (Figure 3). Therefore, the ACh that was released in the middle of the cardiac cycle (St2 in Figure 7), and consequently exerted its influence during diastolic depolarization, significantly prolonged SCL (Figures 5A and 5B).

Sinus Arrhythmias During Stimulation at Constant Frequency

Vagal stimulation over a certain range of frequencies can, in dogs, entrain the sinus node23; that is, heart rate equals the frequency of vagal stimulation. SCL oscillates during stimulation at constant frequencies that are slightly above or below this frequency range.2,27

Our model (Figure 1) predicts these experimental results and provides insight into the cellular mechanisms of these behaviors. We set τ=425 msec and m=75 nM. SCL remained steady during vagal stimulation at 1.3 or 1.5 Hz but oscillated during stimulation at 1.1 Hz (Figure 8A). SCL equaled 666 msec (which corresponds to a frequency=1,000/666=1.5 Hz) during vagal stimulation at 1.5 Hz. Similarly, SCL equaled 768 msec (1.3 Hz) during vagal stimulation at 1.3 Hz. Increasing the frequency of stimulation from 1.3 to 1.5 Hz decreased SCL from 768 msec (1.3 Hz) to 666 msec (1.5 Hz) because the sinus node was entrained to the periodic vagal stimulation.28

The cellular mechanisms responsible for the sinus arrhythmia produced by simulated vagal stimulation at 1.1 Hz (Figure 8A) were the same as those that caused the sinus arrhythmia produced by repetitive vagal stimulation at a constant AS1 (Figure 7). Oscillations occurred, in part, because acetylcholinesterase degraded ACh rapidly enough for the mean

![Graph showing vagal stimulation at a constant low frequency.](Figure 8)
[ACh] to vary significantly from cycle to cycle (Figure 8B). Oscillations also occurred, in part, because vagal stimuli released ACh at different ASt (Figure 8C) and, thus, elicited different SCL (Figure 5A).

**Discussion**

**Stimulation at a Constant Frequency**

The change in SCL elicited by vagal stimulation (Figure 2A) depends on the interaction of two nonlinear processes. [ACh] increases the duration of diastolic depolarization because, during diastolic depolarization, $$|I_{K_{ACh}}| \approx |I_{nACh}|$$ (Figure 3). [ACh] is too low to saturate the cellular system that activates ACh-activated K+ channels or acetylcholinesterase. Therefore, raising [ACh] increases $$I_{K_{ACh}}$$ linearly. Increasing $$I_{K_{ACh}}$$ is associated with a linear increase in $$I_{T}$$ (Figure 4B) or, equivalently, a decrease in $$|I_{nACh}|$$. During diastolic depolarization changes in $$I_{T}$$ as a function of time are minimal; thus, the pacemaker cell membrane behaves electrotonically like a capacitor that is being discharged. Consequently, the duration of diastolic depolarization is inversely related to $$I_{T}$$ (Figure 4C, Equation 5), and raising [ACh] increases SCL geometrically.

SCL not only increases geometrically with [ACh], but it also increases with the concentrations of adenosine, verapamil, and nifedipine. The first two agents generate hyperpolarizing currents; the second two agents block depolarizing currents. Despite their disparate mechanisms of action, all four agents act to increase $$I_{T}$$ during diastolic depolarization. As a result, raising the concentration of ACh, adenosine, verapamil, or nifedipine increases the duration of diastolic depolarization geometrically and, by extension, SCL.

**Phase Response Curves**

The model predicts the effect of varying ASt and the number of pulses per burst on SCL. The model represents the sinus node by a single pacemaker cell (Figure 1). The simulated results (Figure 5A) closely resemble those obtained experimentally in intact dogs. Therefore, the dependence of the shape of PRC on the number of pulses per burst of vagal stimuli does not require an interaction among pacemaker cells in the sinus node.

The differences between PRC observed in simulated cells by application of ACh pulses (Figure 5B) and in vivo by vagal stimulation (Figure 5A) can be accounted for by the dependence of the mean [ACh] per cardiac cycle on ASt (Figure 5C). In the simulated in vivo situation, an increase in SCL increases the time available between bursts of vagal stimuli for acetylcholinesterase to degrade the ACh in the neuroeffector junctions, and thus causes mean [ACh] to decrease. As a result, the sharp PRC generated by directly applying ACh to cells (Figure 5B) is smoothed to produce the PRC produced by vagal stimulation (Figure 5A).

The shapes of PRC can be related to the underlying cellular physiology. ACh that is applied to pacemaker cells at ASts that correspond to the negative slope region of PRC has little effect on SCL because the ACh is applied during fast depolarization, when $$|I_{K_{ACh}}| >> |I_{nACh}|$$ (Figure 3). By the time diastolic depolarization starts, much of the ACh has been hydrolyzed. ACh that is applied to pacemaker cells at ASts that correspond to the positive slope regions of PRC can prolong SCL because the ACh is applied during diastolic depolarization, when $$|I_{K_{ACh}}| >> |I_{nACh}|$$ (Figure 3).

The rates of activation and inactivation of ACh-activated K+ channels do not depend significantly on V, over the range of V included in diastolic depolarization. Therefore, for all ASts on a positive slope of a PRC, ACh pulses open the same number of ACh-activated K+ channels (Figure 6B). Similarly, the time that it takes for most of the open ACh-activated K+ channels to close does not depend significantly on ASt (Figure 6B). Fast depolarization does not begin until the proportion of ACh-activated K+ channels that are activated has decreased sufficiently for $$I_{T}$$ to be strongly inward. As a result of the V-independence of the ACh-activated K+ channels during diastolic depolarization, ASt is a constant independent of ASt (Figure 6A). Stimuli applied early in diastolic depolarization produce the same ASt as stimuli applied later. Thus, stimuli applied early increase SCL less than do stimuli applied later. In other words, the slope of the PRC is positive (Figures 5A and 5B).

We add one caveat to our explanation. If the rates of activation and inactivation of the ACh-activated K+ channels depended significantly on V during diastolic depolarization, the slope of the PRC would not necessarily be negative for all ASt. For example, if an increase in V decreased the rate of inactivation of ACh-activated K+ channels, the positive slope region of the PRC would become steeper. The V-independence of the ACh-activated K+ channels was sufficient to produce PRC with positive slopes. Nevertheless, many other classes of V-dependencies can generate PRC with positive slopes, as well.

$$t_\phi$$ includes the sinoatrial conduction time, which varies by as much as 20 msec depending on ASt. A 20-msec variation in $$t_\phi$$ only alters SCL when ASt falls on the negative slope region of PRC (Figure 5A). At no ASt does a 20-msec variation in $$t_\phi$$ alter the shape of the PRC. Therefore, the simulations suggest that
normal variation in sinoatrial conduction time does not significantly alter the changes in SCL elicited by vagal stimulation. In addition, inhomogeneities of cell types and innervation within the sinus node may affect activation of the atrium by the sinus node. Such inhomogeneities affect SCL by altering $t_d$. Our simulation results are insensitive qualitatively to physiological inhomogeneities because they do not produce changes in $t_d$ that are large enough to significantly alter the shape of the PRC.

Entrainment

Our model (Figure 8A) and corresponding experimental data indicate that vagal stimulation over a certain range of frequencies can entrain the sinus node. Levy used arguments based on control theory to show that vagal stimulation at a constant frequency can entrain the sinus node when ASF falls on the positive slope region of PRC (Figure 5A). As explained above, the PRC has a positive slope because the rates of activation and inactivation of ACh-activated $K^+$ channels depend only weakly on $V$ during diastolic depolarization. Therefore, the cellular mechanism of entrainment can be explained on the basis of the relative independence of the ACh-activated $K^+$ channels on $V$ during the diastolic depolarization phase of the action potential.

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