Muscarnic potassium channels augment dynamic and static heart rate responses to vagal stimulation

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Submitted 23 March 2007; accepted in final form 22 May 2007

Vagal control of heart rate (HR) is mediated by a cascade of multiple neurotransmission mechanisms involving various receptors and ion channels. The direct action of acetylcholine (ACh) via muscarinic potassium channels (KACh) in the sinoatrial node cells contributes to the quickness of the heart rate response to vagal stimulation. On the contrary, the indirect action of ACh utilizes the faster membrane-delimited mechanisms involving adenylyl cyclase. Given the rapidity of vagal HR control compared with sympathetic control (2, 14, 31), we hypothesized that the direct action of ACh via KACh channels mediates approximately 75% of the steady-state negative chronotropic effect relative to the maximum carbachol-induced bradycardia in the isolated rabbit heart (i.e., static HR response to vagal stimulation). However, in this study, the role of KACh channels in the dynamic HR response to vagal stimulation was not analyzed quantitatively. Because HR changes dynamically in response to daily activities, quantification of dynamic and static characteristics is equally important. For instance, information on the dynamic HR response is key to understanding the generation of HR variability. Berger et al. (2) used transfer function analysis to identify the dynamic characteristics of the HR response. Saul et al. (29) demonstrated the utility of transfer function analysis for insight into cardiovascular regulation. The present study aims to expand our knowledge of the involvement of KACh channels in dynamic HR control by the vagal system.

MATERIALS AND METHODS

Surgical preparations. Animal care was consistent with the “Guiding Principles for Care and Use of Animals in the Field of Physiological Sciences,” of the Physiological Society of Japan. All protocols were reviewed and approved by the Animal Subjects Committee of the National Cardiovascular Center. Nine Japanese White rabbits (2.5–3.2 kg body wt) were anesthetized by a mixture of urethane (250 mg/ml) and α-chloralose (40 mg/ml); initiation with a bolus injection of 2 ml/kg and maintenance with continuous administration at 0.5 mg/ml.

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ml·kg\(^{-1}\)·h\(^{-1}\). The rabbits were intubated and mechanically ventilated with oxygen-enriched room air. Arterial pressure (AP) was measured by a micromanometer (model SPC-330A, Millar Instruments, Houston, TX) inserted into the right femoral artery and advanced to the thoracic aorta. HR was measured with a cari- diotachometer (model N4778, San-ei, Tokyo, Japan). A double-lumen catheter was introduced into the right femoral vein for continuous anesthetic and drug administration. Sinoaortic denervation was performed bilaterally to minimize changes in the sympathetic efferent nerve activity via arterial baroreflexes. Bilateral section of the cardiac postganglionic sympathetic nerves minimized any possible interaction between the vagus and sympathetic nerves. The vagi were sectioned bilaterally at the neck. A pair of bipolar electrodes were attached to the cardiac end of the sectioned right vagus for vagal stimulation. Immersion of the stimulation electrodes and nerves in a mixture of white petroleum jelly (Vaseline) and liquid paraffin prevented drying and provided insolation. Body temperature was maintained at 38°C with a heating pad throughout the experiment.

**Experimental procedures.** The pulse duration of nerve stimulation was set at 2 ms. The stimulation amplitude of the right vagus was adjusted to yield an HR decrease of \(-50\) beats/min at a stimulation frequency of 10 Hz. After this adjustment, the amplitude of vagal stimulation was fixed at 1.8–6.0 V. Initiation of vagal nerve stimulation over 1 h upon completion of surgical preparations allowed stable hemodynamics. A preliminary examination indicated that the response of HR to vagal stimulation was stable for up to 3 h in our experimental settings (10 min of dynamic vagal stimulation at 50-min intervals; data not shown).

**Dynamic protocol.** For estimation of the dynamic transfer characteristics from vagal stimulation to HR response, the right vagus was stimulated by a frequency-modulated pulse train for 10 min. The stimulation frequency was switched every 500 ms at 0 or 10 Hz according to a binary white-noise signal. The power spectrum of the stimulation signal was reasonably constant up to 1 Hz. The transfer function was estimated up to 1 Hz, because the reliability of estimation decreased as a result of the diminution of input power above this frequency. The selected frequency range sufficiently spanned the physiological range of interest with respect to the dynamic vagal control of HR.

**Static protocol.** For estimation of the static transfer characteristics from vagal stimulation to HR response, step-wise vagal stimulation was performed. Vagal stimulation frequency was increased from 5 to 20 Hz in 5-Hz increments. Each frequency step was maintained for 60 s.

The dynamic and static transfer functions from vagal stimulation to HR response were estimated under control and \(K_{ACh}\) channel blockade conditions. After the control data were recorded, a bolus injection (30 nmol/kg iv) of a selective \(K_{ACh}\) channel blocker, tertiapin (Peptide Institute, Osaka, Japan), was administered, and vagal stimulation protocols were repeated 15 min thereafter. The control data were obtained first in all animals, because the long-lasting (>2 h) effects of tertiapin (data not shown) did not permit the subsequent acquisition of control data. A >5-min interval between dynamic and step-wise stimulation protocols confirmed that AP and HR returned to baseline levels. Dynamic and step-wise vagal stimulation protocols were randomly assigned under control and \(K_{ACh}\) channel blockade conditions.

**\(\beta\)-Adrenergic blockade protocol.** A supplemental experiment was performed under \(\beta\)-adrenergic blockade (\(n = 3\)) eliminated any effect of sympathetic activity. At \(\sim 10\) min after a bolus injection of propranolol (1 mg/kg iv) (22), HR and AP reached a new steady state. The dynamic and static transfer functions from vagal stimulation to HR response were estimated before and after tertiapin treatment, both under \(\beta\)-adrenergic blockade.

**Data analysis.** A 12-bit analog-to-digital converter was used to digitize data at 200 Hz, and data were stored on the hard disk of a dedicated laboratory computer system. The dynamic transfer function from binary white-noise vagal stimulation to HR response was estimated as follows. Input-output data pairs of the vagal stimulation frequency and HR were resampled at 10 Hz; then data pairs were partitioned into eight 50%-overlapping segments consisting of 1,024 data points each. For each segment, the linear trend was subtracted, and a Hanning window was applied. A fast Fourier transform was then performed to obtain the frequency spectra for vagal stimulation \([\text{SN}_f(\omega)]\) and HR \([\text{HR}_f(\omega)]\) (4). Over the eight segments, the power of vagal stimulation \([\text{SN}_f(\omega)]\), the power of HR \([\text{HR}_f(\omega)]\), and the cross power between these two signals \([\text{SN}_f\text{-HR}_f(\omega)]\) were ensemble averaged. Finally, the transfer function \([H(f)]\) from vagal stimulation to the HR response was determined as follows (1, 20)

\[
H(f) = \frac{\text{SN}_f\text{-HR}_f(f)}{\text{SN}_f(f)} \quad (1)
\]

The transfer function from vagal stimulation to HR response approximated a first-order, low-pass filter with a lag time in previous studies (14, 21–24); therefore, the estimated transfer function was parameterized as follows

\[
H(f) = \frac{-K}{1 + \frac{f}{f_c}} e^{-2\pi f c} \quad (2)
\]

where \(K\) represents the dynamic gain (or, more precisely, the steady-state gain, in beats·min\(^{-1}\)·Hz\(^{-1}\)), \(f_c\) denotes the corner frequency (in Hz), \(L\) denotes the lag time (in s), and \(f\) and \(f_j\) represent frequency and the imaginary unit, respectively. The negative sign in the numerator indicates the negative HR response to vagal stimulation. The steady-state gain indicates the asymptotic value of the relative amplitude of the HR response to vagal nerve stimulation obtained in the frequency of input modulation approaching zero. The corner frequency represents the frequency of input modulation at which gain decreases by 3 dB from the steady-state gain in the frequency domain and reflects the readiness of the HR response for vagal stimulation in the time domain. The dynamic gain, corner frequency, and lag time were estimated by an iterative nonlinear least-squares regression. The phase shift of the transfer function indicates, with respect to the input signal, a lag or lead in the output signal normalized by its corresponding frequency of input modulation.

To quantify the linear dependence of the HR response on vagal stimulation, the magnitude-squared coherence function \([\text{Coh}(f)]\) was estimated as follows (1, 20)

\[
\text{Coh}(f) = \frac{[\text{SN}_f\text{-HR}_f(f)]^2}{\text{SN}_f(f) \cdot \text{HR}_f(f)} \quad (3)
\]

Coherence values range from zero to unity. Unity coherence indicates perfect linear dependence between the input and output signals; in contrast, zero coherence indicates total independence between the two signals.

To facilitate the intuitive understanding of the system dynamic characteristics, we calculated the system step response of HR to 1-Hz nerve stimulation as follows. The system impulse response was derived from the inverse Fourier transform of \(H(f)\). The system step response was then obtained from the time integral of the impulse response. The length of the step response was 51.2 s. We calculated the maximum step response by averaging the last 10 s of the step response. The 90% rise time of the step response was determined as the time required for the response to reach 90% of the maximum step response. The time constant of the step response was calculated from the corner frequency of the corresponding transfer function as follows

\[
\text{time constant} = \frac{1}{2\pi f_c} \quad (4)
\]

where the time constant is related inversely to the corner frequency without influence of the lag time.
The static transfer function from step-wise vagal stimulation to HR was estimated by averaging the HR data during the final 10 s of the 60-s stimulation at each stimulation frequency.

**Statistical analysis.** Values are means ± SD. Student’s paired t-test was used to test differences in fitted parameters and calculated step response between control and $K_{ACCh}$ channel blockade conditions. For hemodynamic parameters, a two-way ANOVA, with drug and vagal stimulation as the main effects, was used to determine significant differences. For percent reduction from the control conditions in each parameter, one-way ANOVA was used to determine significant differences. $P < 0.05$ was considered significant.

**RESULTS**

**Dynamic characteristics.** Figure 1A shows typical recordings and corresponding power spectra of vagal stimulation and HR response under control and $K_{ACCh}$ channel blockade conditions. Random vagal stimulation decreased HR intermittently. Tertiapin-mediated $K_{ACCh}$ channel blockade attenuated the amplitude of the variation and the speed of the HR response to vagal stimulation. In the power spectral plot, tertiapin decreased the HR power. The decrease in the HR power was

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**Fig. 1.** A: representative recordings of heart rate (HR) obtained utilizing binary white-noise vagal stimulation (top) and corresponding vagal stimulation (VS, bottom). Traces were recorded before (control, left) and after tertiapin infusion (30 nmol/kg iv) for muscarinic K+ ($K_{ACCh}$) channel blockade (right). Insets: power spectra of each parameter. Tertiapin attenuated amplitude of HR variation and speed of response of HR to vagal stimulation. B: dynamic transfer function relating vagal stimulation to HR responses averaged from all animals (pooled data, $n = 9$). Top: gains; middle: phase shifts; bottom: coherence (Coh) functions. Frequency on abscissa (gain and phase) indicates frequency of input modulation, rather than stimulation frequency. C: calculated step response to 1-Hz tonic vagal stimulation averaged from all animals (pooled data, $n = 9$). Solid lines, means; dashed lines, SD. Thin line, control; thick line, $K_{ACCh}$ channel blockade with tertiapin (30 nmol/kg iv). Tertiapin decreased transfer gain and increased phase shift with increasing frequency, and tertiapin decreased maximum step response and slowed initial step response.
Table 1. Effects of tertiapin infusion on AP and HR before and during dynamic vagal stimulation

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<th>Control</th>
<th>Tertiapin</th>
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<tr>
<td>AP, mmHg</td>
<td></td>
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<tr>
<td>Before stimulation</td>
<td>82.4 ± 20.5</td>
<td>77.6 ± 20.7</td>
</tr>
<tr>
<td>During stimulation</td>
<td>77.9 ± 20.0</td>
<td>74.8 ± 18.6</td>
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<tr>
<td>HR, beats/min</td>
<td></td>
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<tr>
<td>Before stimulation</td>
<td>247.3 ± 24.7</td>
<td>248.1 ± 32.7</td>
</tr>
<tr>
<td>During stimulation</td>
<td>212.4 ± 22.3</td>
<td>231.1 ± 25.9</td>
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Values are means ± SD (n = 9). Tertiapin was infused at 30 nmol/kg iv. AP, arterial pressure; HR, heart rate. Vagal stimulation significantly decreased HR (P < 0.01), but no significant effect of drug (P = 0.28) or interaction (P = 0.32) was observed by 2-way ANOVA.

more potent in the higher (>0.1 Hz) than in the lower frequency range.

Table 1 summarizes the mean values of AP and HR before and during vagal stimulation averaged from all animals. Dynamic vagal stimulation significantly decreased the mean HR (P < 0.01), but not the mean AP. Tertiapin did not significantly affect mean AP or HR before or during stimulation.

Figure 1B illustrates the dynamic transfer functions characterizing the vagal HR response averaged from all animals under control and tertiapin-mediated K\textsubscript{ACh} channel blockade conditions. Gain plots, phase plots, and coherence functions are shown. Tertiapin attenuated the dynamic gain compared with the control conditions; the extent of the attenuation was greater in the higher frequency range: 63.0 ± 11.6, 74.4 ± 8.3, 93.0 ± 2.5, and 93.3 ± 3.9% at 0.01, 0.1, 0.5, and 1 Hz, respectively, as normalized to the control condition (P < 0.01 by ANOVA). The peak in the gain at 0.6 Hz observed during tertiapin-mediated K\textsubscript{ATP} channel blockade would be caused by the artificial respiration (respiratory rate = 35–40 min\textsuperscript{-1}), because the low coherence value (~0.1) at 0.6 Hz indicates the independence of the input and output signals. This peak was masked by the large HR response to vagal stimulation under the control condition. The phase approached π radians at the lowest frequency and lagged with increasing frequency under the control condition; tertiapin caused the phase difference between the two conditions in the frequency range of 0.03–0.7 Hz, which disappeared at 1 Hz. The fitted parameters of the transfer functions are summarized in Table 2. Tertiapin significantly decreased the dynamic gain and the corner frequency without changing the lag time. Coherence was near unity in the overall frequency range in the control condition, whereas a decrease in the coherence function from unity was noted at >0.6 Hz with K\textsubscript{ACh} channel blockade.

Figure 1C shows the calculated step response of HR to vagal stimulation averaged from all animals in the control condition and during K\textsubscript{ACh} channel blockade. Tertiapin slowed the transient response (time constants = 0.6 ± 0.1 to 2.7 ± 0.5 s, P < 0.01) and attenuated the HR response to vagal stimulation (maximum step response = −4.5 ± 1.2 to −1.8 ± 0.6 beats/min, P < 0.01) in the time domain. Furthermore, tertiapin significantly delayed the 90% rise time of the step response, which was calculated as an index of system readiness (1.6 ± 0.5 to 5.0 ± 1.4 s, P < 0.01).

Static characteristics. Figure 2A shows typical recordings of step-wise vagal stimulation and the HR response in the control condition and during K\textsubscript{ACh} channel blockade. The step-wise vagal stimulation decreased HR in a step-wise manner. Tertiapin attenuated the static reductions of HR from the baseline HR.

Figure 2B summarizes changes in HR in response to step-wise vagal stimulation. The step-wise vagal stimulation significantly decreased HR with increasing stimulus frequency under both conditions. Tertiapin significantly attenuated the static reductions of HR. The attenuation of HR reduction normalized to control conditions increased with increasing stimulus frequency: 45.8 ± 21.3, 58.2 ± 17.9, 64.7 ± 14.6, and 68.0 ± 11.4% at 5, 10, 15, and 20 Hz, respectively (P < 0.05 by ANOVA).

\(\beta\)-Adrenergic blockade protocol. In the supplemental protocol (n = 3) with \(\beta\)-adrenergic blockade, tertiapin decreased the dynamic gain from 2.4 ± 0.6 to 1.3 ± 0.5 beats·min\textsuperscript{-1}·Hz\textsuperscript{-1} and the corner frequency from 0.23 ± 0.05 to 0.06 ± 0.02 Hz without changing the lag time (0.36 ± 0.01 vs. 0.43 ± 0.00 s). In terms of the static characteristics, tertiapin significantly attenuated the vagal stimulation-induced HR decrease by 43 ± 10, 50 ± 8, 56 ± 7, and 61 ± 8% at stimulus frequencies of 5, 10, 15, and 20 Hz, respectively.

DISCUSSION

We have quantified the role of the K\textsubscript{ACh} channels by examining the transfer characteristics. The major findings in the present study are that K\textsubscript{ACh} channel blockade with intravenous tertiapin administration decreased the dynamic gain and corner frequency without changing the lag time of the dynamic transfer function from vagal stimulation to HR. These findings support our hypothesis that direct action of ACh via KACh channels contributes to the quickness of the HR control in response to electrical vagal stimulation.

Effect of tertiapin on dynamic transfer characteristics. Our results indicate that K\textsubscript{ACh} channels contribute to a rapid component in vagal HR control. Tertiapin slowed the dynamic HR response to vagal stimulation, since tertiapin attenuated the gain of the transfer function significantly in the high frequency range (Fig. 1B). Moreover, the calculated step response clearly demonstrated this point (Fig. 1C). Tertiapin prolonged the time constant and 90% rise time of the step response by 2.1 and 3.4 s, respectively. Since quickness is a hallmark of the vagal control of HR relative to sympathetic control, these results highlight the importance of K\textsubscript{ACh} channels in the rapidity of vagal HR control. Because tertiapin did not affect the lag time (Table 2), the increase in the 90% rise time to the step response due to tertiapin (~3.4 s) may primarily reflect the slowed transient response.

Our results are consistent with and may partly explain the earlier studies in which transgenic mice were used to investigate the role of K\textsubscript{ACh} channels (8, 33). Using the G protein-

Table 2. Effects of tertiapin infusion on parameters of the transfer function relating dynamic vagal stimulation to HR

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<th>Tertiapin</th>
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<td>Dynamic gain, beats·min\textsuperscript{-1}·Hz\textsuperscript{-1}</td>
<td>5.0 ±1.2</td>
<td>2.0 ±0.6*</td>
</tr>
<tr>
<td>Corner frequency, Hz</td>
<td>0.25 ±0.03</td>
<td>0.06±0.01*</td>
</tr>
<tr>
<td>Lag time, s</td>
<td>0.37 ±0.04</td>
<td>0.39 ±0.05</td>
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Values are means ± SD. Tertiapin was infused at 30 nmol/kg iv. *P < 0.01 vs. corresponding control.
 gated inwardly rectifying potassium (GIRK) channel family subunit GIRK4, which is a component of K Ach channels (5, 16), Wickman et al. (33) indicated that the spectral power of HR was lower at 1.5–5.0 Hz, which is predominantly vagally mediated, but not at 0.4 Hz, in GIRK4-knockout than in wild-type mice. Another study using transgenic mice with a reduction in functional βγ-subunits of the G i proteins also showed impaired vagal HR control, such as reductions in carbachol-induced bradycardia, HR variability, and baroreflex sensitivity (8). In the present study, tertiapin significantly attenuated the dynamic gain compared with the control conditions in the frequency bands from 0.01 to 1 Hz; the extent of the decreases in dynamic gain was augmented with increasing frequency of input modulation. This finding also supports the notion that K Ach channels play a large part as a rapid component of vagal control of HR. Furthermore, increased phase shift due to tertiapin in the higher frequency range (0.03–0.7 Hz) would support the interpretation that the K Ach channel current played an important role in the rapid HR response to vagal stimulation.

Tertiapin-mediated changes in fitted parameters of the transfer function from vagal stimulation to HR suggest that, at the postjunctional effector sites, the K Ach channels play a key role in determining the dynamic properties of transduction from vagal nerve activity to HR. To quantitatively elucidate vagal and sympathetic control of HR, our research group used a transfer function analysis to examine the system characteristics. First, the transfer function from dynamic vagal nerve stimulation to HR approximated the characteristics of a first-order, low-pass filter, whereas the transfer function from dynamic sympathetic nerve stimulation to HR approximated the characteristics of a second-order, low-pass filter (14). Dynamic gain of vagal stimulation to HR was increased by concomitant sympathetic nerve stimulation (14) and pharmacologically induced accumulation of cAMP at the postjunctional effector sites (23) and decreased by high plasma norepinephrine (21). These perturbations of the indirect action of ACh did not affect the quickness of vagal HR control; i.e., neither corner frequency nor lag time was altered. On the contrary, inhibition of cholinesterase by neostigmine decreased the corner frequency.

Fig. 2. A: representative recordings of HR (top) and corresponding vagal stimulation (bottom) obtained utilizing a step-wise stimulation. Traces were recorded before (control, left) and after tertiapin infusion (30 nmol/kg iv) for K Ach channel blockade (right). K Ach channel blockade attenuated amplitude of HR variation to tonic vagal stimulation. B: static transfer function relating step-wise vagal stimulation to HR responses averaged from all animals (pooled data, n = 9). Basal HR was not different between control and K Ach channel blockade (see Table 1). K Ach channel blockade decreases static HR response, and static reductions in bradycardic effect were greater at higher stimulation frequencies.
KACh channels contribute to earlier study by Yamada (34). This consistency suggested that stimulus intensity of 20 Hz. This value is consistent with the and selectively blocked the KACh channel in cardiac myocytes vs. indirect action should be carefully interpreted. ACh in the present study. Therefore, the percentage of direct by tertiapin may have in turn affected the indirect action of these studies, Hashimoto et al. (10) demonstrated that tertiapin (30 nmol/kg iv) used in the present study should be sufficient to block KACh channel current in vivo.

Effect of tertiapin on the static transfer characteristics. Tertiapin attenuates the static reduction of HR in accord with the attenuation of the gain of the dynamic transfer function at the lowest frequency of input modulation. This suggests that KACh channels contribute to the static, as well as the rapid, component of vagal HR control. The relative attenuation of HR reduction increased with increasing stimulus frequency (Fig. 2B), suggesting that direct action of ACh in the static properties of transduction from vagus nerve activity to HR is augmented by an increase in the amount of available ACh. Although it is well established that the muscarinic response to static vagal stimulation depends on the stimulation frequency (26, 27), whether the contribution of the KACh channel pathway to the total HR response depends on the stimulus frequency remains unknown. The basal mean HR of GIRK-knockout mice (33) and transgenic mice with a reduction of βγ-subunits of the G i proteins (8) is the same as that of wild-type mice, suggesting that KACh channels are not involved in mean HR control in the basal state. At low-to-moderate levels of vagal activity, vagal control of HR is due to changes in cAMP-modulated I n, often referred to as “pacemaker” current (6). KACh channels might play an essential role in HR control at high levels of vagal activity.

In the present study, tertiapin decreased the HR response to vagal stimulation by ~70% of the control condition at a stimulus intensity of 20 Hz. This value is consistent with the earlier study by Yamada (34). This consistency suggested that KACh channels contribute to ~70% of the maximum negative chronotropic effects to pharmacologically and/or electronically induced vagal stimulation. However, changes in HR induced by tertiapin may have in turn affected the indirect action of ACh in the present study. Therefore, the percentage of direct vs. indirect action should be carefully interpreted.

Limitations. There are several limitations to this study. First, we did not confirm the completeness of KACh channel blockade. Kitamura et al. (15) demonstrated that tertiapin potently and selectively blocked the KACh channel in cardiac myocytes in a muscarinic receptor- and voltage-independent manner. Furthermore, Drici et al. (7) showed that tertiapin blocked KACh channels with an IC50 of ~30 nM with no significant effect on major currents associated with the cardiac repolarization process or atrioventricular conduction. On the basis of these studies, Hashimoto et al. (10) demonstrated that tertiapin (12 nmol/kg iv) significantly prolonged the atrial effective refractory period during vagal stimulation in their in vivo canine study. Therefore, we believe that the dose of tertiapin (30 nmol/kg iv) used in the present study should be sufficient to block KACh channel current in vivo.

Second, data were obtained from anesthetized animals. Since the anesthesia would affect the autonomic tone, the results may not be directly applicable to conscious animals. However, because we cut and stimulated the right cardiac vagal nerve, changes in autonomic outflow associated with anesthesia might not have significantly affected the results.

Third, in the present study, we stimulated the vagal nerve according to binary white noise and a step-wise pattern, which was quite different from the pattern of physiological neuronal discharge. However, although nonphysiological patterns of stimulation could theoretically bias the system identification results, because coherence was near unity over the frequency range of interest, by virtue of their inherent linearity, the system properties would not vary much with differing patterns of stimulation.

In conclusion, KACh channel blockade with intravenous tertiapin administration decreased the dynamic gain and corner frequency without changing the lag time of the transfer function from vagal stimulation to HR. In the time domain, tertiapin prolonged the time constant and 90% rise time of the step response. Additionally, tertiapin decreased the static reductions of HR from baseline HR to less than half of the control response with increasing vagal stimulus frequency. These results suggest that KACh channels accelerate the dynamic HR response to vagal stimulation and contribute more to the static HR response for more potent tonic vagal stimulation in vivo.

Perspectives

To simply identify the role of KACh channels in vagal HR control, a previous study (34) and the present study completely and/or partially excluded background sympathetic tone. However, in the physiological condition, sympathetic tone affects vagal control of HR and vice versa [e.g., accentuated antagonism (17)]. Pathophysiological conditions such as chronic heart failure (25), hypertension (19), and obesity (30) reveal increased basal sympathetic nerve activity compared with the normal condition. Tertiapin did not affect basal AP or HR (Table 1), suggesting that tertiapin did not affect sympathetic tone in the present experimental settings. Furthermore, under β-adrenergic blockade (the supplemental protocol), tertiapin decreased the dynamic gain and corner frequency, suggesting that the effects of tertiapin cannot be explained by the background sympathetic tone. However, the experimental design of the present study did not allow separate assessment of the direct vs. the indirect action of ACh, because the indirect action of ACh was not manipulated intentionally. Further investigation is needed to clarify the effects of sympathetic tone on the contribution of KACh channels to negative chronotropic effects.

GRANTS

This study was supported by Health and Labour Sciences Research Grants H15-Physi-001, H18-Nano-ippan-003, and H18-Iryo-Ippan-023 from the Ministry of Health, Grant-in-Aid for Scientific Research promoted by the Ministry of Education, Culture, Sports, Science and Technology in Japan 18591992, and the Ground-Based Research Announcement for Space Utilization project promoted by the Japan Space Forum. This study was also supported by Industrial Technology Research Program Grant 06B44524a from the New Energy and Industrial Technology Development Organization of Japan.

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AJP-Heart Circ Physiol • VOL 293 • SEPTEMBER 2007 • www.ajpheart.org
K_ACh ACCELERATES AND ENHANCES VAGAL HR CONTROL


