Nicotine Is a Potent Blocker of the Cardiac A-Type $K^+$ Channels

Effects on Cloned Kv4.3 Channels and Native Transient Outward Current

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Background—Nicotine is a main constituent of cigarette smoke and smokeless tobacco, known to increase the risk of sudden cardiac death. This study aimed at establishing ionic mechanisms underlying potential electrophysiological effects of nicotine.

Methods and Results—Effects of nicotine on Kv4.3 and Kv4.2 channels expressed in Xenopus oocytes were studied at the whole-cell and single-channel levels. The effects of nicotine on the transient outward $K^+$ current ($I_{to}$) were studied by use of whole-cell patch-clamp techniques in canine ventricular myocytes. Nicotine potently inhibited Kv4 current. The concentration for half-maximal inhibition ($IC_{50}$) was 40±4 nmol/L, and the current was abolished by 100 µmol/L nicotine. The $IC_{50}$ for block of native $I_{to}$ was 270±43 nmol/L. The steady-state activation properties of Kv4.3 and $I_{to}$ were unaltered by nicotine, whereas positive shifts of the inactivation curves were observed. Of the total inhibition of Kv4.3 and $I_{to}$ by nicotine, 40% was due to tonic block and 60% was attributable to use-dependent block. Activation, inactivation, and reactivation kinetics were not significantly changed by nicotine. Nicotine reduced single-channel conductance, open probability, and open time but increased the closed time of Kv4.3. The effects of nicotine were not altered by antagonists to various neurotransmitter receptors, indicating direct effects on $I_{to}$ channels.

Conclusions—Nicotine is a potent inhibitor of cardiac A-type $K^+$ channels, with blockade probably due to block of closed and open channels. This action may contribute to the ability of nicotine to affect cardiac electrophysiology and induce arrhythmias. (Circulation. 2000;102:1165-1171.)

Key Words: nicotine • ion channels • potassium

Use of cigarettes and smokeless tobacco is a considerable public health problem. Conversely, nicotine also has the potential to be a valuable pharmacological agent.1 Nicotine is known to increase the risk of cardiovascular disease, sudden coronary death, hypertension, and stroke.2–5 It is believed that nicotine promotes sudden cardiac death by provoking lethal ventricular arrhythmias.6–8 Indeed, nicotine is implicated in a wide spectrum of cardiac rhythm disorders, including transient sinus arrest and/or bradycardia, sinus tachycardia, atrial fibrillation, sinoatrial block, AV block, and ventricular tachyarrhythmias.3,6–9

Nicotine binds to the nicotinic cholinergic gating site on ion channels in receptors (nAChRs) throughout the body, stimulating the release of neurotransmitters, including catecholamines from the adrenal medulla. The cardiac effects of nicotine have been ascribed to this enhanced release of catecholamines.10 However, accumulating evidence has shown that nicotine can also exert its effects without involvement of nAChRs and catecholamine release. Studies under conditions devoid of nAChR stimulation demonstrated the ability of nicotine to alter action potential (AP) characteristics in guinea pigs,11 rabbits,12 and dogs13 in different tissues such as sinus node,14 atrium, ventricle, and Purkinje fibers. The most noticeable changes were decreases in resting potential and prolongation of later AP phases. It is therefore quite conceivable that nicotine might be able to interact directly with ion channels.

$K^+$ currents are critical for membrane repolarization and maintaining resting potentials of cardiac cells.15 The A-type $K^+$ current, also called transient outward $K^+$ current ($I_{to}$), governs the initial phase of cardiac repolarization and influences the participation of other currents and membrane transport processes by affecting the voltage-time trajectory of the AP. $I_{to}$ is altered in many heart diseases and is a target for many drugs. Native $I_{to}$ is encoded by A-type $K^+$-channel genes such as Kv1.4, Kv4.2, and Kv4.3.16–19 The participation of Kv4.3 has been convincingly demonstrated in rats,18 rabbits,16 dogs,17 and humans.16 In light of the ability of
nicotine to prolong APD and to alter the propensity to arrhythmias, we hypothesized that nicotine might be able to block K⁺ channels. To explore whether the long-recognized effects of nicotine on cardiac electrophysiology could be accounted for, at least partially, by the effects of nicotine on A-type channels, we performed detailed analyses on Kv4.3 and Kv4.2 channels expressed in Xenopus oocytes and on native Iₛᵣ.

Methods

In Vitro Transcription and Functional Expression

Procedures for in vitro transcription and oocyte injection have been described previously.16,20 Kv4.2 (subcloned into PRC-CMV vector) and Kv4.3 (pSP64-A vectors) were kind gifts from Dr. Jeanne Nerbonne, Washington University, St Louis, Mo. cRNAs were prepared with mMESSAGE mMACHINE (Ambion) using T7 (for Kv4.2) and SP6 (for Kv4.3) RNA polymerases. All whole-cell and single-channel recordings were obtained in stage V to VI Xenopus oocytes injected with 46 nL of cRNA.

Two-Electrode Voltage-Clamp Recording

Electrodes filled with 3 mol/L KCl had a resistance of 1 to 3 MΩ when measured in the bath solution containing (in mmol/L) NaCl 100, KCl 0.3, MgCl₂ 2, and HEPES 10 (pH 7.4). Electrodes were connected to a GeneClamp-500 amplifier (Axon). The pClamp suite of programs was used for data acquisition and analysis. Experiments were conducted at room temperature (22°C to 23°C). Leak was subtracted for all current records. When the sustained current component at the end of the 400-ms pulse was >10% of the total current amplitude, the oocytes were rejected.

Single-Channel Recording

Single channels were recorded in cell-attached patches in the inside-out mode.16 Fire-polished glass electrodes had a tip resistance of 10 MΩ when filled with the extracellular solution, which had the same composition as the bath solution described for the two-electrode experiments. The bath solution (intracellular side) contained (in mmol/L) NaCl 136, KCl 5.4, MgATP 5, HEPES 10, and phosphocreatine 5 (pH 7.3). The Tyrode’s solution for cell isolation and whole-cell patch-clamp recording contained (in mmol/L) NaCl 136, KCl 5.4, MgCl₂ 1, HEPES 5, glucose 10, and CaCl₂ 1 (pH 7.4).

Series resistance and capacitance were compensated and leak currents subtracted. Sodium current was suppressed by holding cells at −50 mV. CdCl₂ (200 µmol/L) was used to inhibit Ca²⁺ current and Cd²⁺-activated chloride current. ATP-sensitive current was blocked by glyburide (10 µmol/L) in the superfuse and ATP (5 mmol/L) in the pipette. Dofetilide (1 µmol/L) and 293B (20 µmol/L) were used to block delayed-rectifier K⁺ currents. APs were recorded in current-clamp mode and elicited by twice-threshold, 1.5-ms pulses.

Data Analysis

Group data are expressed as mean±SEM. Iₛᵣ amplitude was measured as the difference between peak and residual currents at the end of depolarizing pulses. Statistical comparisons among groups were performed by ANOVA followed by t test with Bonferroni correction. A 2-tailed P<0.05 was taken to indicate a statistically significant difference. A nonlinear least-squares program (CLAMPFIT or Graphpad Prism) was used for curve-fitting.

Results

Effects of Nicotine on Kv4.3 and Kv4.2 Currents in Xenopus Oocytes

Superfusion for 10 minutes with nicotine at concentrations of 10 nmol/L to 100 µmol/L inhibited Kv4.3 currents (Figure 1). Significant block was seen at 10 nmol/L, and complete inhibition was achieved at 100 µmol/L. The IC₅₀ was 40±4 nmol/L (Hill coefficient=0.3, Figure 2). 4-Aminopyridine (4-AP), a prototype A-type K⁺ current blocker, inhibited Kv4.3 with an IC₅₀ of 1.7±0.2 mmol/L (Hill coefficient=0.5, Figure 2).

The voltage-dependent activation curve was not significantly affected by nicotine at concentrations up to 10 µmol/L (Figure 3A). On the contrary, inactivation was shifted toward...
more positive potentials (Figure 3B). Half-maximal inactivation voltage \( V_{1/2} \) values were \( -50 \pm 6 \), \( -42 \pm 4 \) (\( P<0.05 \) versus control), \( -37 \pm 4 \) (\( P<0.01 \)), and \( -32 \pm 3 \) (\( P<0.01 \), n=6/group) mV for control, 0.1, 1, and 10 \( \mu \)mol/L nicotine, respectively.

The activation (Figure 4A) and inactivation (Figure 4B) time constants were not altered by nicotine at concentrations up to 10 \( \mu \)mol/L. Kv4.3 channel reactivation (Figure 4C) was similarly unaffected (time constant, 198±24 ms without and 224±27 ms with 10 \( \mu \)mol/L nicotine, \( P>0.05 \), n=4).

The use-dependence of nicotine action was evaluated with 10 consecutive pulses to 150 mV at 0.1, 1, and 2 Hz. The first pulse after a 60-second quiescent period at a holding potential of -80 mV was taken as tonic block, and the reduction in subsequent pulses was considered use-dependent inhibition. There was a significant tonic block (≈24%), as indicated by the reduced current amplitude in the first pulse (Figure 5). Further decrease in the current amplitude was observed with pulsing, but this use-dependent inhibition was seen only at a frequency of 1 Hz, and statistical significance (\( P<0.01 \), ANOVA, F test, n=5) was achieved only at 2 Hz.

Figure 2. A and B, Kv4.3 currents at a test potential of +10 mV, showing effects of nicotine (Nic) and 4-AP, respectively. C, Dose-response curves for Kv4.3 block by nicotine (n=6) and 4-AP (n=4). Symbols are experimental data, and curves are best-fit Hill equations: \( B(\%)=100[1+(IC_{50}/D)^n] \), where \( B(\%) \) is percent change in Kv4.3 current at a drug concentration D and n is Hill coefficient.

Figure 3. A, Effects of nicotine on Kv4.3 activation curve. Tail currents (I) on repolarization to -50 mV (arrow) after 10-ms activating pulses to voltages between -40 and +60 mV were normalized to maximum value \( I_{\text{max}} \) at +60 mV and plotted against activation potential. Symbols are experimental data (n=5), and curves are best-fit Boltzmann equations: \( \frac{I}{I_{\text{max}}} = \frac{1}{1+\exp[(V_{1/2}-V)/k]} \), where \( V_{1/2} \) is half-maximal activation voltage and k is a slope factor. B and C, Shift of inactivation curves by nicotine. Prepulses (2 seconds) were followed by 400-ms test pulses, providing mean±SEM values in B. Normalization of currents at each prepulse potential to value at -100 mV provided data in C.

Figure 4. A and B, Average (n=6) Kv4.3 activation and inactivation time constants (\( \tau \)) calculated from currents recorded with voltage protocols shown in Figure 1. C, Reactivation time course of Kv4.3 current, as determined by twin-pulse protocol shown in inset. Symbols are experimental data (n=5), and curves represent single-exponential fits.

Figure 5. Use-dependent effects of nicotine (100 nmol/L) on Kv4.3 currents elicited by 10 consecutive 200-ms depolarizing pulses to +50 mV at varying pulse frequencies, with each train of voltage steps delivered after \( \geq 60 \) seconds at -80 mV. A, Pulse-to-pulse changes in Kv4.3-current amplitude normalized to first-pulse current as a function of pulse number. B, Nicotine-induced percent change in current amplitude relative to control. \( P<0.01 \) for use-dependence, n=5.
Kv4 channels. (Figure 5B). The use-dependence was rapid (rate constant of 0.3±0.0 pulses).

Figure 6 summarizes the blocking properties of nicotine on Kv4.2 channels. The current was diminished ≈42% at a concentration of 100 nmol/L and ≈82% at 100 μmol/L, similar to the effects on Kv4.3. No significant endogenous currents were recorded in water-injected oocytes before or after superfusion with nicotine (Figure 1A). Pretreatment with or coapplication of mecamylamine (100 μmol/L, an nAChR antagonist), atropine (1 μmol/L, a muscarinic AChR antagonist), prazosin (2 μmol/L, an α1-adrenoceptor antagonist), or propranolol (1 μmol/L, a β-adrenoceptor inhibitor) did not alter the inhibitory effects of nicotine on Kv4 channels.

**Effects on Single-Channel Currents**

Depolarization of cell-attached patches to potentials positive to +30 mV produced brief channel openings at the onset of the voltage step and infrequent subsequent reopenings (Figure 7A). The ensemble average of 200 consecutive recordings (Figure 7A, bottom) is typical of I_{k,Na}, with rapid activation and inactivation. Nicotine suppressed single-channel and ensemble-average currents (Figure 7A) and slightly reduced slope conductance (from 18±3 to 13±3 pS, P<0.05, n=4, 0.1 μmol/L nicotine, Figure 7B). Open probability was reduced (Figure 7C), closed time lengthened (Figure 7D) from 1.8±0.4 to 3.3±0.5 ms (P<0.05, n=4) for the fast component and from 16.5±2.6 to 19.2±3.1 ms for the slow component (P=NS), and open time shortened (Figure 7E).

**Effects on Native I_{Na]**

Ten minutes after baseline recording, nicotine was applied to the bath, and I_{Na} recordings were repeated after a 15-minute exposure period (Figure 8A). After we had verified that mecamylamine (100 μmol/L, n=4 cells), atropine (1 μmol/L, n=3), prazosin (2 μmol/L, n=3), and propranolol (2 μmol/L, n=3) had no influence on the effects of nicotine, these compounds were also included in the superfusate (Figure 8B). Approximately 15%, 25%, and 56% decreases in I_{Na} were seen with 0.01, 0.1, and 1 μmol/L nicotine, respectively (Figure 8C). The IC_{50} (Figure 8D) averaged 0.39±0.05 μmol/L.

Like its effects on Kv4.3, nicotine did not alter the activation curve (V_{1/2} values, 6±1 and 9±2 mV for control and 10 μmol/L nicotine, respectively, P>0.05, n=4). The inactivation curve (Figure 9A and 9B) was shifted to more positive potentials by nicotine (V_{1/2} = −33±4 and −20±3 mV for control and 1 μmol/L nicotine, respectively; P<0.05, n=5). No significant changes in reactivation time constants were observed (12.9±1.8 ms for control versus 15.4±2.3 ms for nicotine 1 μmol/L). Nicotine at concentrations up to 50 μmol/L did not alter the activation and inactivation time courses determined by the same methods as for Kv4.3.

As with Kv4.3, nicotine produced 2 phases of block: tonic block and use-dependent block (Figure 9C). The degree of tonic block (determined from the current reduction with the first pulse of the depolarizing train to +50 mV) was ≈12% at 0.1 μmol/L. Use-dependent block with subsequent pulses quickly reached steady state (≈23%), with a rate constant of 0.6±0.1 pulses.

**Effects on Canine Ventricular APs**

Nicotine caused a concentration-dependent (0.01 to 1 μmol/L) lengthening of AP duration (APD) and an eleva-
Use-dependent inhibition of K<sub>A</sub>. C, SEM inactivation data (n=10, curve is best-fit Hill equation). Data in C and D are obtained in presence of receptor antagonists. 

Figure 9. Effects of nicotine on steady-state I<sub>K</sub><sub>A</sub> inactivation. A, Original recordings. B, Mean±SEM inactivation data (n=5). C, Use-dependent inhibition of I<sub>K</sub><sub>A</sub> (n=5). Use-dependence was assessed by 10 consecutive depolarizing pulses from −50 to +50 mV at 1 Hz after a 60-second quiescent period. Symbols are experimental data, and curve is single-exponential fit (data obtained in presence of receptor antagonists).

Discussion

We have performed a detailed characterization of nicotine block of Kv4.3 currents expressed in Xenopus oocytes and native I<sub>K</sub><sub>A</sub> in canine ventricular myocytes at both the whole-cell and single-channel levels. Our major novel finding is that nicotine is a potent direct blocker of cardiac A-type channels and significantly delays canine ventricular repolarization.

Previous Studies of the Effects of Nicotine on K<sup>+</sup> Channels

In our study, the effects of nicotine were not reversed by mecamylamine (an nAChR antagonist),<sup>24</sup> atropine (a muscarinic AChR antagonist), prazosin (an α<sub>1</sub>-adrenoceptor antagonist), and propranolol (a β-adrenoceptor inhibitor). These results indicate that nicotine block of A-type K<sup>+</sup> currents are most likely the consequence of direct interactions between drug molecules and channel proteins. Reports on the effects of nicotine on ion channels are sparse. Hamon et al<sup>25</sup> first reported that nicotine inhibited slowly inactivating K<sup>+</sup> currents in rat cultured striatal neurons. The effects were attributed to stimulation of nicotinic receptors, because the nicotinic antagonist dihydro-β-erythroidine reversed and nicotinic agonists reproduced the block.<sup>25</sup> Direct effects on K<sup>+</sup> channels were not revealed until recently by Tang et al,<sup>26</sup> who used vascular smooth muscle cells, and by our laboratory.<sup>27</sup> Tang et al found that nicotine caused dual effects on the rapidly activating and slowly inactivating K<sup>+</sup> current in rat artery smooth muscle cells: an increase in current amplitude at concentrations <0.3 mmol/L and a decrease at >0.3 mmol/L. We have reported preliminary findings<sup>27</sup> that nicotine directly blocks K<sup>+</sup> currents, with effects on I<sub>K</sub><sub>A</sub> at much higher concentrations compared with those on I<sub>K</sub><sub>A</sub>. To date, no detailed studies on the interactions between nicotine and cardiac K<sup>+</sup> channels have been published. The present work provides insight into potential mechanisms underlying nicotine block of A-type currents. Approximately 40% of the total inhibition could be ascribed to tonic block, with the remainder (60%) due to use-dependent block, for both Kv4.3 and I<sub>K</sub><sub>A</sub>. This would imply that nicotine binds to I<sub>K</sub><sub>A</sub> channels in the closed state. A decrease in the slope conductance of Kv4.3 single channels and increases in closed times by nicotine are in line with this notion. Nicotine did not alter voltage-dependent activation, whereas the inactivation curve was shifted to more positive potentials and block was relieved slightly with more positive holding potentials that rendered more channels in the inactivated state. At the single-channel level, nicotine reduced the channel conductance, open time,
and open probability but increased the closed time of Kv4.3. These data are consistent with the closed and open channel block indicated at the macroscopic level.

**Potential Implications**

It has been shown that the average blood concentration of nicotine in regular smokers is 220 nmo/L and that the level can reach \( \approx 440 \) nmo/L after consumption of a single cigarette.\(^{10,26}\) It has been estimated that the typical single dose of nicotine in chewing tobacco is \( \approx 15 \) times greater than for an average-strength cigarette.\(^{5,24}\) Moreover, for a daily intake of 100 mg nicotine with regular nicotine chewing gum use, blood nicotine can accumulate for 6 to 8 hours.\(^{28}\) Longer retention of nicotine occurs in the heart, possibly accounting for the predisposition of the heart to pathological manifestations.\(^{29,30}\) Although we have shown that nicotine blocks multiple K\(^+\) currents, the IC\(_{50}\) values for other currents (\( \approx 4 \) nmo/L for \( I_{Ks} \), 165 nmo/L for \( I_{K2.1} \), 1.3 nmo/L for \( I_{K1} \), and 17 nmo/L for HERG)\(^{27}\) are \( \approx 10 \) times higher than blood concentrations of nicotine. Only the concentrations of nicotine effective in Kv4.3 and \( I_{Ks} \) inhibit in our study are relevant to the blood levels in heavy cigarette smokers and smokeless tobacco users.

It has been suggested that Kv4.3 and Kv4.2 are the major molecular constituents of native cardiac \( I_{Ks} \).\(^{16,18}\) The ability of nicotine to block Kv4.3 and Kv4.2 might contribute to the previously observed lengthening of cardiac APD in many preparations.\(^{11–13}\) Nicotine preferentially prolongs initial repolarization and the subsequent plateau phases,\(^{11}\) consistent with the participation of \( I_{Ks} \) in early phases of repolarization. The ability of nicotine to slow repolarization was confirmed in our experiments. Blockade of \( I_{Ks} \) may also provide an explanation for the observed nicotine-induced alterations (morphology, height, and duration) in the T wave of the ECG,\(^{6}\) because \( I_{Ks} \) has been proposed to be responsible for cardiac memory,\(^{31}\) an altered T-wave morphology after tachycardia.

A-type K\(^+\) channels are not limited to cardiac cells. Both cloned and native A-type currents have been identified in a variety of tissues, including brain and vascular smooth muscle. The A-type K\(^+\) current in vascular smooth muscles is believed to act as a “brake” to counteract depolarizing influences that may induce spontaneous AP activity or oscillatory vasoconstriction.\(^{32}\) Nicotine is known to have vasoconstrictive properties that contribute to the elevation of blood pressure and stroke risks induced by this compound.\(^{3–5,7,8}\) Nicotine readily crosses the blood-brain barrier and is distributed throughout the brain. Impairment of the vascular brake due to inhibition of A-type K\(^+\) currents in vascular smooth muscle could contribute to the increased risk of hypertension and stroke after nicotine exposure. Future studies are warranted to clarify this notion.

To the best of our knowledge, nicotine is one of the most potent blockers of A-type channels. 4-AP is in widespread use as a pharmacological tool for its ability to inhibit A-type K\(^+\) current selectively. However, as documented in many previous reports, several hundred micromolar to several millimolar concentrations of 4-AP are necessary to block Kv4.3 and \( I_{Ks} \).\(^{33–35}\) In the present study, the potency of nicotine for Kv4.3 block was \( \approx 4 \times 10^4 \)-fold higher than that of 4-AP (IC\(_{50}\)=40\( \pm \)4 nmo/L for nicotine versus 1.7\( \pm \)0.2 nmo/L for 4-AP, Figure 2). Phrixotoxins PaTx1 and PaTx2, purified from the venom of the tarantula Phrixotrichus auratus, probably represent the only substance with an inhibitory potency for Kv4.3 (5\(<\)IC\(_{50}\)<70 nmo/L)\(^{36}\) comparable to that of nicotine. Although we have shown that nicotine blocks multiple K\(^+\) currents, the IC\(_{50}\) values for other currents are \( \approx 10 \) times higher than that for Kv4.3/\( I_{Ks} \). Thus, nicotine can potentially be a useful pharmacological probe to study the role of A-type channels in cardiac electrical activity and the outcome of pharmacological interventions on A-type channels.

**Potential Limitations**

There are some unexplained issues in the present study. Although blockade of A-type channels may account in part for the ability of nicotine to broaden APD, our data did not allow us to draw any conclusions as to whether this property is beneficial (antiarrhythmic) or deleterious (proarrhythmic). Many antiarrhythmic agents act by inhibiting \( I_{Ks} \), and this would imply that inhibition of \( I_{Ks} \) should confer antiarrhythmic efficacy.\(^{37–40}\) However, excessive block of \( I_{Ks} \) could also be proarrhythmic. Obviously, the arrhythmic consequences of nicotine action on A-type current await further study. Furthermore, the observations on nicotine in in vitro conditions are not necessarily the same as those in vivo. The effects of nicotine on A-type current could be modulated by the action on \( I_{Ks} \) produced by stimulation of \( \alpha_1 \)-adrenoceptors by nicotine, because it is known that nicotine can enhance release of norepinephrine, and it has also been reported that \( \alpha_1 \)-adrenergic stimulation can alter \( I_{Ks} \).\(^{41}\) In addition, nicotine may also directly or indirectly affect other ion channels, such as calcium and sodium channels. Thus, the overall outcome of nicotine actions in in vivo situations would be determined by different aspects of nicotine pharmacology and pathophysiological conditions of the heart in an integrated manner.

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