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Rate-dependent effects of ajmaline and propafenone on atrioventricular conduction

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Abstract

The aim of the present study was to characterize the time dependence of the depressant effects of ajmaline and propafenone on the Ca^{2+}-channel-dependent tissue of the atrioventricular node in isolated guinea pig hearts perfused by the method of Langendorff. Ajmaline at a concentration of 0.03 μM and propafenone at a concentration of 0.3 μM caused a significant and comparable prolongation of the His bundle and atrioventricular conduction time (AVCT). When the pacing cycle length was abruptly shortened from 240 to 180 ms, the mean time constant (τ_{on}) of the rate-dependent AVCT prolongation was comparable for ajmaline and propafenone. In contrast, if the pacing cycle length was abruptly increased from 180 to 240 ms the mean time constant (τ_{off}) for ajmaline was significantly higher than for propafenone. The rate-dependent increase of the atrioventricular effective refractory period was significantly more pronounced in the presence of ajmaline than of propafenone. Ajmaline and propafenone affect the Ca^{2+}-channel-dependent tissue of the myocardium. The more pronounced rate-dependent effect of ajmaline on the atrioventricular effective refractory period may be explained by a slower dissociation kinetic from the channel.

Keywords: AV-node; Ajmaline; Propafenone; Rate dependence; Time constant

1. Introduction

Ajmaline and propafenone are recognized as highly effective antiarrhythmic drugs for the treatment of a wide variety of tachyarrhythmias, both ventricular and supraventricular (Callans et al., 1991; Manz et al., 1992; Manz and Lüderitz, 1993).

Propafenone is a potent class I antiarrhythmic drug with moderate β-blocking activity and weak Ca^{2+} channel blocking actions (Ledda et al., 1981; Bryson et al., 1993; Fei et al., 1993). Propafenone is well established in the treatment of atrial and AV-nodal junctional re-entrant tachycardias, Wolff-Parkinson-White tachycardias involving accessory pathways, and ventricular and atrial tachyarrhythmias (Lüderitz and Manz, 1992).

Ajmaline, a *Rauwolfia* alkaloid, prolongs the refractory periods and slows conduction in the atrial and ventricular myocardium. Ajmaline also slightly prolongs the atrioventricular conduction and QT interval (Padrini et al., 1993). The pronounced effect of ajmaline on the accessory pathway led to the use of this substance in patients with Wolff-Parkinson-White syndrome. Ajmaline is also used to convert atrial fibrillation to sinus rhythm (Lüderitz and Manz, 1992).

If atrial fibrillation is converted to sinus rhythm pharmacologically, a resulting sinus tachycardia may cause higher ventricular rates than before cardioversion (Hindricks et al., 1994). Therefore, class I antiarrhythmic drugs with additional rate-dependent effects on atrioventricular conduction may prevent an increase in the ventricular rate after conversion of atrial fibrillation to sinus node tachycardia. If a class I antiarrhythmic had additional effects comparable to that of Ca^{2+} channel antagonists on atrioventricular conduction, the ventricular rate during atrial fibrillation would be reduced whether atrial fibrillation was converted to sinus rhythm or not. Such drugs may decrease heart rate or even terminate tachycardia when used in the acute treatment of AV nodal re-entrant tachycardia.

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Class I antiarrhythmic drugs such as ajmaline and propafenone have a broad spectrum of action on the cardiac conduction system and thus are used so frequently in the treatment of supraventricular tachycardias (Lüderitz and Manz, 1992).

The aim of the present study was to describe the time dependence of the depressant effects of ajmaline and propafenone on the calcium-channel-dependent tissue of the atrioventricular node.

2. Materials and methods

2.1. Animals

Twenty white guinea pigs of either sex, weighing 200–300 g, fed ad libitum, were divided into two groups of 10 animals. Complete results were obtained from 15 of 20 preparations studied.

2.2. Experimental protocol

Guinea pigs of either sex weighing 250–300 g were injected intraperitoneally with 250 IU of heparin 1 h before being killed by dislocation of the neck. Hearts were quickly removed, rinsed in ice-cold Tyrode's solution and afterwards attached to a modified non-recirculating Langendorff perfusion system (Anton Paar Ges.m.b.H., Graz, Austria). All procedures met the guidelines set by the Animal Care Committee at our medical center. Tyrode's solution, saturated with a mixture of oxygen (95%) and carbon dioxide (5%), and warmed to 36°C, was used as perfusate (in mM: NaCl 132.1, KCl 2.7, $CaCl_2$ 2.5, $MgCl_2$ 1.15, $NaHCO_3$ 24.0, NaH_2PO_4 0.42, D-glucose 5.6). Electrocardiographic (ECG) recordings were taken from the epicardiac surface. The perfusion rate was adjusted to the atrioventricular conduction time which has to be shorter than 65 ms and the spontaneous sinus rate which has to be about 200 beats/min (maximal perfusion rate was 8 ml/min and maximal perfusion pressure was 60 cmH_2O). Each heart was allowed to equilibrate for 30 min. Atrioventricular conduction time is a sensitive parameter for acute ischaemia in this preparation. If rhythm irregularities occurred during the equilibration period, the heart was discarded.

Two $FeCl_3$ chlorided silver wire electrodes (wire ∅ 0.3 mm, ∅ 1.5 mm electrode tip) were placed on the epicardial surface of the heart free to move with the contractions. His-bundle activity was visible in the bipolar ECG signals which were monitored on a digital storage oscilloscope and stored on a tape-recorder sampling at 5 kHz. Details of this high resolution ECG recording technique are described in earlier publications (Stark et al., 1989). The ECG signals were further digitised by an analog to digital converter (TL-125, Axon Instruments, USA) and monitored and stored on a personal computer (486/50 MHz) for further analysis.

2.3. Parameters measured

Changes in sinus rate, AV-nodal (AH-interval), His-bundle (HV-interval) and intraventricular (QRS-interval) conduction as well as the repolarization time (QT-interval) were evaluated in the two groups during control conditions and 20 min after the addition of 0.03 μM ajmaline and 0.3 μM propafenone. The compounds were continuously injected by a perfusion pump near the aorta to the Tyrode's solution to avoid unspecific binding in the perfusion system. Twenty minutes after the addition of each substance to the perfusate the atrioventricular effective refractory period was estimated at a basic stimulation cycle length of 200 and 180 ms. Thereafter the time constant characterizing the changes in atrioventricular conduction time after abruptly increasing (τ_{on}) or decreasing (τ_{off}) the pacing rate was evaluated.

2.4. Pacing protocol

The time constants for the changes in atrioventricular conduction time (AVCT) were estimated after an abrupt increase (pacing cycle length: 240 to 180 ms) and a subsequent decrease (pacing cycle length: 180 to 240 ms) in the pacing rate at a concentration of 0.03 μM ajmaline and 0.3 μM propafenone whereby a comparable prolongation of the atrioventricular conduction time during sinus rhythm was induced. Twenty minutes after addition of each drug the AVCT was measured at an atrial pacing cycle length of 240 ms. After 2 min of atrial pacing at an intensity of twice the late diastolic threshold, the pacing cycle length was abruptly shortened from 240 to 180 ms, and kept at this new rate for another 2 min. Afterwards the pacing cycle length was abruptly increased from 180 to 240 ms. The AVCT was measured continuously, beat to beat, throughout the experiment (Fig. 1). To exclude ischaemic effects during rapid pacing, in a prior series of experiments the creatine kinase concentration in the coronary effluent was measured before and immediately after the rapid stimulation period. No increase in the creatine kinase concentration could be observed (Stark et al., 1995).

A nonlinear regression analysis (Sigma Plot software package) was performed. $AVCT_n = (AVCT_{ss} - AVCT_0) * (1 - \exp(-n/\tau_{on}))$, where $AVCT_n$, $AVCT_0$, and $AVCT_{ss}$ are the AVCT of the nth beat, of the last paced beat at a cycle length of 240 ms, and of the steady state at a pacing cycle length of 180 ms; τ_{on} is a time constant expressed as a number of beats. τ_{off} was evaluated by the following equation: $AVCT_n = (AVCT_0 - AVCT_{ss}) * (1 - \exp(-n/\tau_{off}))$, where $AVCT_n$, $AVCT0$, and $AVCT_{ss}$ are the AVCT of the nth beat, of the last paced beat at a cycle length of 180 ms, and of the steady state at a pacing cycle length of 240 ms. In the presence of ajmaline and propafenone the frequency-dependent changes of the AVCT were described by a time constant for the initial fast phase and for a following slow phase which was

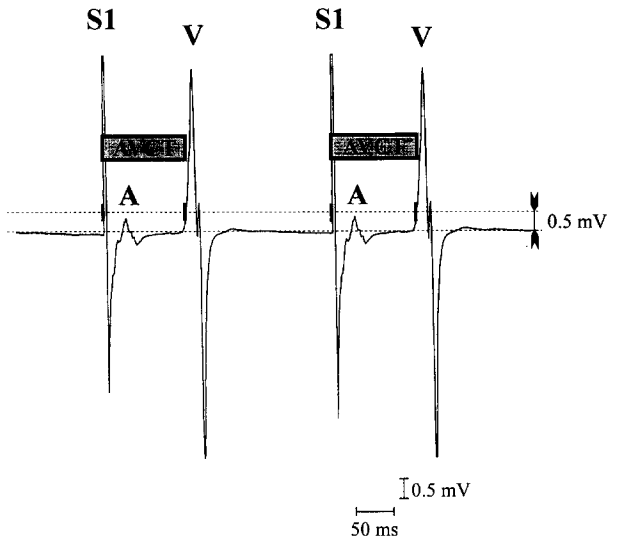

Fig. 1. Computerized measurement of atrioventricular conduction time (AVCT) measured automatically by a computer from the beginning of the stimulus (S1) to the beginning of the ventricular complex (V) at a level of 0.5 mV of depolarization (Stark et al., 1995). Vertical bars on the upper dotted line indicate the points of measurement. A = atrial signal.

noted only in the presence of drugs. The initial fast phase could be described by a time constant of one beat for the drugs used as well as for control conditions.

2.5. Stimulation protocol for evaluation of the atrioventricular effective refractory period

The effective refractory period of the atrioventricular conduction was determined under control conditions and 20 min after the addition of each drug concentration. The stimuli were delivered through Teflon-coated silver wire electrodes placed on the epicardial surface of the left auricle for the measurement of atrioventricular nodal refractoriness. The stimulation threshold was evaluated at the beginning of the pacing protocol. A programmable stimulator with separate constant current output delivered rectangular stimuli of 2 ms duration at an intensity of twice the late diastolic threshold. The effective refractory period of the atrioventricular node was evaluated with a conditioning train of 10 basic stimuli (S1). The S1–S1 interval was 200 and 180 ms and the S1–S2 interval was shortened in steps of 1 ms. After each step the heart was allowed to recover from pacing for 1 s. The longest S1–S2 interval for a stimulus that failed to conduct through the AV-node and to produce a His bundle response (H2) was defined as the AV-nodal effective refractory period (AV-ERP).

2.6. Expression and statistical analysis of the results

All values are expressed as means ± standard error of the mean (S.E.M.). The data were compared using a Wilcoxon test after a test of homogeneity of variance on a personal computer using a statistical software package (Statgraphics, version 6.0).

2.7. Drugs

Ajmaline and propafenone (SIGMA, Germany) were dissolved in Tyrode's solution saline before each experiment. The measurements were performed after a perfusion period of 20 min. In pilot experiments ($n = 3$, data not presented) we have shown that 20 min of perfusion with ajmaline and propafenone are necessary to get a steady state of the electrophysiological effects. Control measurements were made in the presence of Tyrode's solution. Ajmaline (0.03 μM) corresponds to a low and 0.3 μM propafenone to a medium therapeutic concentration (with regard to plasma protein binding) (Dhein et al., 1993). At these concentrations both drugs caused a comparable prolongation of the atrioventricular conduction time.

3. Results

3.1. Effects on sinus rate and conduction intervals

Ajmaline (0.03 μM) and propafenone (0.3 μM) caused a comparable and significant prolongation of the atrioventricular conduction time. His bundle conduction time was also prolonged significantly to a comparable degree by both substances. The sinus rate was slightly depressed by both substances and reached significance in the presence of ajmaline. The QT interval remained unchanged by 0.03 μM ajmaline and 0.3 μM propafenone (Table 1).

3.2. Rate-dependent effects of ajmaline and propafenone

In control experiments abrupt changes of heart rate, caused by a shortening and subsequent prolongation of the pacing cycle length from 240 to 180 and back to 240 ms,

Table 1
Changes in conduction intervals and sinus rate during perfusion with propafenone and ajmaline

Parameter	Control ($n = 8$)	$< P >$	Propafenone 0.3 μM ($n = 8$)
AH interval (ms)	47.4 ± 0.7	0.01	54.8 ± 0.9
HV interval (ms)	9.9 ± 0.2	0.05	11.6 ± 0.6
QRS interval (ms)	28.7 ± 0.5	NS	29.7 ± 0.8
QT interval (ms)	164 ± 8	NS	172 ± 11
Sinus rate (beats/min)	226 ± 14	NS	207 ± 6
	Control ($n = 8$)	$< P >$	Ajmaline 0.03 μM ($n = 8$)
AH interval (ms)	49.8 ± 0.9	0.01	57.6 ± 1.3
HV interval (ms)	10.0 ± 0.5	0.05	11.7 ± 0.6
QRS interval (ms)	30.9 ± 1.1	NS	31.4 ± 1.9
QT interval (ms)	154 ± 5	NS	161 ± 7
Sinus rate (beats/min)	249 ± 7	0.05	229 ± 7

Values are mean ± S.E.M.

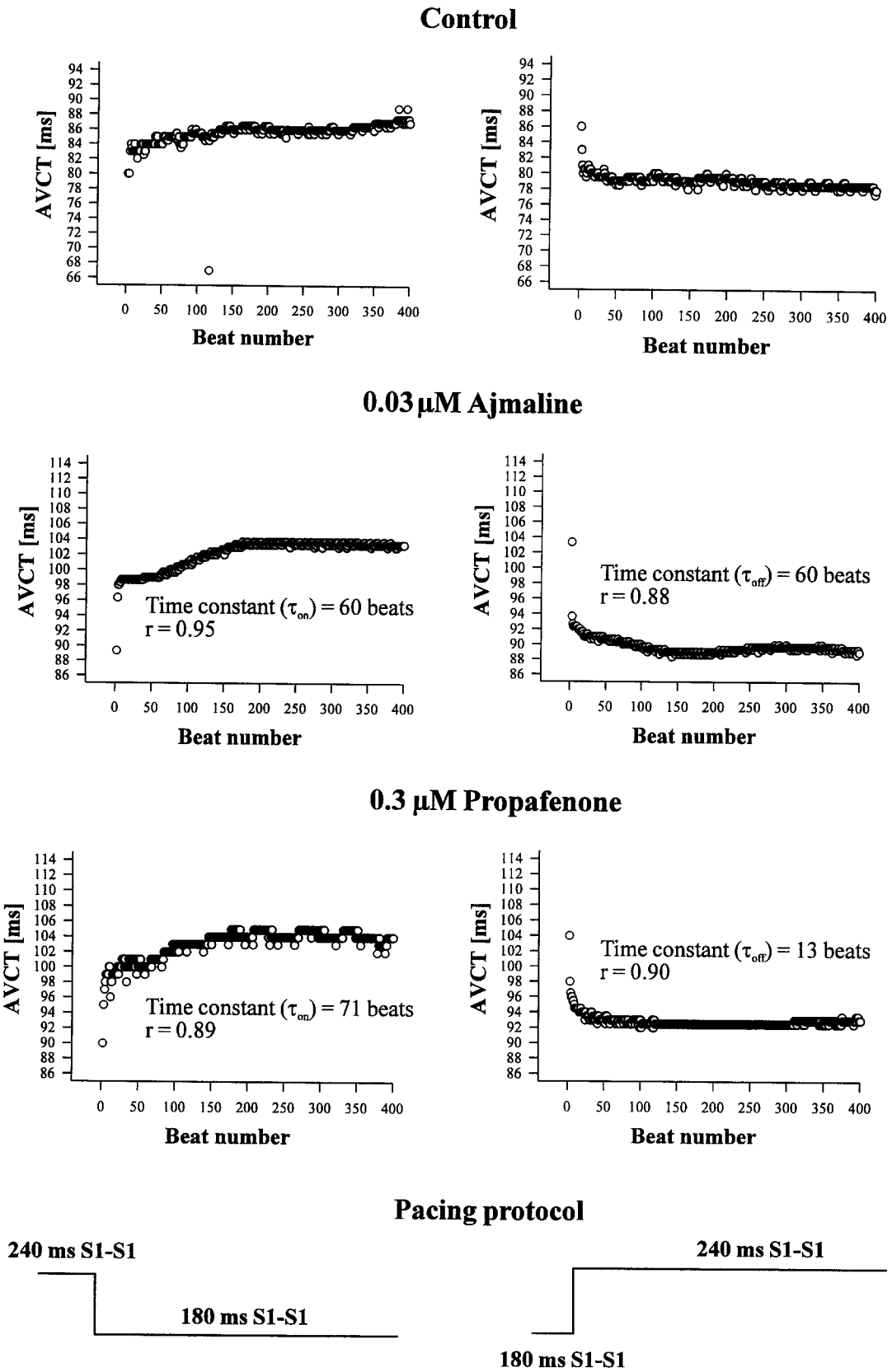

Fig. 2. Beat to beat plot of atrioventricular conduction time (AVCT) changes after abrupt decrease (240 to 180 ms) or increase (180 to 240 ms) of the atrial pacing rate in the presence of ajmaline and propafenone. At beat 0 the pacing cycle length was changed abruptly. The time constant (τ_{on}, τ_{off}) for the best nonlinear regression fit is expressed in beats. r = nonlinear correlation coefficient.

Table 2
Time constant for drug-induced changes in atrioventricular conduction time

Parameters	Propafenone 0.3 μM	< P >	Ajmaline 0.03 μM
n	8		7
τ_{on} (beats)	90 ± 11	NS	81 ± 16
r	0.97 ± 0.03		0.89 ± 0.06
τ_{off} (beats)	19 ± 2 [a]	< 0.01	90 ± 18
r	0.91 ± 0.03		0.93 ± 0.03
Magnitude (ms)	16 ± 2	NS	14 ± 1

n = number of experiments with analyzable kinetic data; τ = time constant; Magnitude = drug-induced prolongation of intraventricular conduction time after decrease in pacing cycle length from 240 to 180 ms; r = nonlinear correlation coefficient.
Values are mean ± S.E.M. [a] $P < 0.01$ compared to τ_{on}.

did not produce any rate-dependent AVCT changes. In the presence of ajmaline and propafenone AVCT increased progressively as an exponential function of the beat number after abrupt shortening of the pacing cycle length and decreased after the pacing cycle length was switched back to 240 ms. Both drugs exhibited a clear rate-dependent adaptation of the AVCT. The mean time constant (τ_{on}) of the rate-dependent AVCT prolongation after shortening of the pacing cycle length from 240 to 180 ms was comparable for ajmaline and propafenone. In contrast, if the pacing cycle length was abruptly increased from 180 to 240 ms, the mean time constant (τ_{off}) for ajmaline was significantly higher than for propafenone (Fig. 2, Table 2).

3.3. Effects of ajmaline and propafenone on the atrioventricular effective refractory period

In the presence of ajmaline and propafenone the AV-ERP was significantly prolonged when evaluated at an interstimulus interval of 200 and 180 ms compared to control conditions. There was a significant ($P < 0.05$) further increase of the AV-ERP when evaluated at an interstimulus interval of 180 ms compared to 200 ms in the presence of both substances, indicating the rate-dependent effect on the AV-nodal refractoriness. The AV-ERP, evaluated at a pacing cycle length of 180 ms, was significantly higher in the presence of ajmaline than of propafenone (Fig. 3).

4. Discussion

Antiarrhythmic drugs with class I effects slow ventricular conduction by blocking Na^+ channels. This conduction slowing is rate-dependent (Hauswirth et al., 1972; Starmer et al., 1984). In the present study the two Na^+ channel blockers, ajmaline and propafenone, showed a rate-dependent prolongation of atrioventricular conduction and refractoriness. Ajmaline had a more pronounced rate-dependent effect than propafenone on AV nodal refractoriness.

Ajmaline is a class Ic drug that acts on atrial and ventricular myocardium. Ajmaline prolongs the refractory periods and slows conduction in atrial and ventricular structures (Bussmann et al., 1978; Lüderitz and Manz, 1992). The pronounced effect on the accessory pathway led to the use of ajmaline in patients with Wolff-Parkinson-White syndrome (Chen et al., 1994). Additionally ajmaline is able to terminate AV node re-entrant tachycardia (Sethi et al., 1984).

Propafenone is also a class Ic drug that increases atrial and ventricular refractoriness. Propafenone has also been reported to prolong AV node conduction and so may as well be beneficial in terminating AV node re-entrant tachycardia (Manz and Lüderitz, 1993).

The rate-dependent effect of ajmaline and propafenone on ventricular conduction and refractoriness is well documented, but there is less information on the effects of these two drugs on the AV nodal conduction (Chen et al., 1994; Stark et al., 1994). The occurrence of AV node re-entry is determined by the excitation and refractoriness properties of AV node slow-channel tissue (Zipes, 1988). It is thus important to analyze the direct rate-dependent effects of ajmaline and propafenone on AV nodal conduction and refractoriness. In canine Purkinje fibers there is a close relation between recovery time constant for effects on V_{max} and conduction (Nattel, 1986). The precise relation between the time dependence of measures of inward current and conduction in the presence of antiarrhythmic drugs is still uncertain. Nonetheless, considerable evidence shows that, at least for drugs that alter Na^+ conductance, the frequency dependence of inward current changes is closely related to use-dependent changes in conduction (Hondeghem and Katzung, 1977; Morady et al., 1985). It

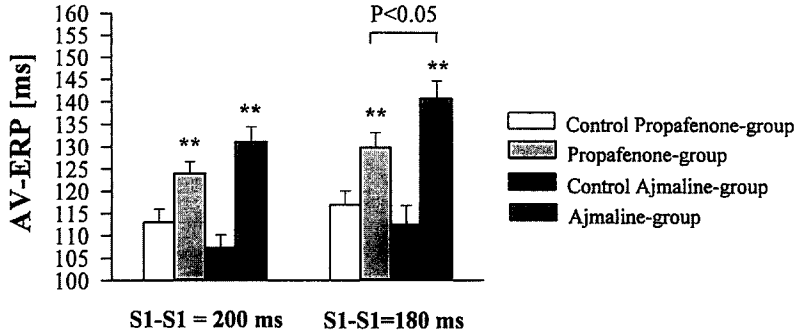

Fig. 3. Effects of ajmaline (0.03 μM) and propafenone (0.3 μM) on the atrioventricular effective refractory period (AV-ERP) evaluated at an interstimulus interval (S1–S1) of 200 and 180 ms. $n = 8$ in the ajmaline and propafenone group. ** $P < 0.01$ compared to control.

could be expected that this fact is also the reason for slowing of atrioventricular conduction during abrupt changes of heart rate in the presence of drugs with Ca^{2+} channel blocking properties.

Both ajmaline and propafenone showed a clear rate-dependent depressing effect on atrioventricular conduction, indicating a slight calcium-antagonistic effect of these two drugs (Fei et al., 1993). The time constant characterizing the rate-dependent effect of ajmaline and propafenone on atrioventricular conduction after abrupt increase of the heart rate is comparable to that of the Ca^{2+} channel antagonist, diltiazem (Stark et al., 1995). The kinetic of the beat to beat induced prolongation of the AV conduction time after the abrupt increase of the heart rate in the presence of ajmaline and propafenone may be defined by a specific binding kinetic to the Ca^{2+} channel. After abrupt decrease of the heart rate to baseline values, the AV conduction time recovered faster in the presence of propafenone than of ajmaline; this is indicated by a shorter time constant for propafenone. This phenomenon can be explained by a different, drug-specific dissociation kinetic from the Ca^{2+} channel.

As demonstrated for local anaesthetics in nerve and heart, the interaction with the binding site is use- and voltage-dependent (Heistracher, 1971; Cahalan, 1978). The identical phenomenon was also shown for Ca^{2+} channel antagonists (McDonald et al., 1980; Hondeghem and Katzung, 1984). The drug apparently blocks the channel when it is activated. Removal of the block is fastest when the channels are in the rested state. Drug-bound channels recover at a rate determined by the diastolic dissociation of the blocking drug from the channel.

The slow dissociation kinetic of ajmaline from the Ca^{2+} channel may lead to drug accumulation at the channel and may be responsible for its more pronounced effect on the rate-dependent AV-nodal effective refractory period than propafenone.

A second explanation for the effects of ajmaline and propafenone on atrioventricular conduction and refractoriness is that ajmaline and propafenone slow AV node conduction by inhibiting a Na^+ current-dependent contribution to conduction in the atrioventricular node. Although Ca^{2+} current is widely accepted as the main inward current determining conduction in the atrioventricular node, the ability to carry tetrodotoxin-sensitive Na^+ current can clearly be demonstrated in voltage-clamped AV node preparations (Zipes, 1988; Kokubun et al., 1982). The Na^+-dependent component of phase 0 is more prominent in AV node cells outside the N region than would be expected from the more negative resting potential and greater phase 0 upstroke velocity in the proximal and distal portions of the atrioventricular node (Ruiz-Ceretti and Zumino, 1976; Billette, 1987). Thus the rate-dependent effect of ajmaline and propafenone on atrioventricular conduction and refractoriness may be induced additionally by the use dependence of drug-induced Na^+ channel blockade. Further studies are needed to determine the ionic mechanism of the action of ajmaline and propafenone on the atrioventricular node.

Acknowledgements

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