Analysis of the Ventricular Repolarization in Relation to the Development of Proarrhythmic Effects Induced by Non-Cardiac Drugs in Mammalian Hearts

PhD Thesis

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1. Introduction

Prolongation of the effective refractory period (ERP) by lengthening of the cardiac action potential duration (APD) is a common mechanism in the mode of action of certain dysrhythmic drugs which was termed by Vaughan Williams as Class III antiarrhythmic action. The delayed rectifier potassium current (I_K) is a major outward current responsible for ventricular muscle action potential repolarization. The I_K in most species including man consists of both a rapid (I_{Kr}) and slow (I_{Ks}) component. Specific I_{Kr} blockers greatly prolong APD and several are well recognized as useful in ablating cardiac arrhythmias. Although lengthening repolarization can terminate both ventricular tachycardia and atrial fibrillation, it can, in certain situations, also evoke torsade de pointes (TdP) ventricular arrhythmias, which may degenerate into ventricular fibrillation, causing sudden death. The proarrhythmic potential of Class III antiarrhythmic drugs greatly limits their usefulness in therapy.

The APD increase induced by selective I_{Kr} blockade displays *reverse use-dependency*. The revese use dependent prolongation of cardiac repolarization means greater increases in APD at long diastolic intervals than at short ones. Thus, when the time between successive action potentials is long, I_{Kr} block produces a far greater increase in APD. Long APDs due to block of I_{Kr} at long diastolic intervals and slow heart rates are associated with induction of early after depolarizations (EAD) believed to trigger TdP ventricular arrhythmias.

Previously, selective I_{Ks} block has generally been assumed to increase APD and refractoriness in a frequency-independent manner. Because of this, the search for selective I_{Ks} blockers has intensified as they may represent novel antiarrhythmic agents devoid of the risk of TdP arrhythmia induction. Some compounds have recently been reported to selectively block $I_{Ks.}$ Available published results of describing chromanol 293B and L-735821 effects, in fact, have often contradicted each other. These contradictory findings have caused us to question whether these differences may be due to species variations in I_{Ks}. The effects of these compounds on QT_c and cardiac action potential configuration have not been characterized in the rabbit, which represents a species widely used to determine the effects of new antiarrhythmic agents intended for use in man. Therefore, one of the major objectives of this study was to characterize the effects of chromanol 293B and L-735,821 on whole heart QT_c, papillary muscle APD, and isolated myocyte membrane current in rabbit, a species widely used for antiarrhythmic drug testing. We compared the effects of the two I_{Ks} blockers to those of E-4031, a recognized I_{Kr} blocker.

Under normal conditions block of one type of outward potassium channel is not likely to cause excessive and potentially dangerous APD lengthening, since the other types of potassium channels provide sufficient repolarization strength which was termed as "*repolarization reserve*". The different potassium channels may compensate each other to secure the repolarization process. If repolarization is excessively lengthened due to drug induced I_{Kr} block, hypokalaemia, genetic abnormality, or bradycardia, the subsequent increase in APD would favour I_{Ks} activation and provide a negative feedback mechanism to limit further APD lengthening. Without such a mechanism because of inheritance (*e.g.* LQT syndromes) or ion channel remodellings in different pathophysiological conditions (heart failure, acut myocardial infarction, diabetes mellitus, etc.), excessive APD lengthening might lead to enhanced repolarization prolongation and increase propensity for development of EAD associated with TdP induction. Accordingly, in situations where the "*repolarization reserve*" is impaired, even relatively weak inhibition of another potassium channel may lead to excessive APD prolongation which can result in increased risk of *proarrhythmia.*

In the past few years it became evident that several non-cardiac drugs can also moderately prolong repolarization by inhibition of one or more potassium currents. These noncardiac drugs such as psychotropic medication, antihistamines and antibiotics can induce TdP. The macrolide antibiotic erythromycin is a commonly prescribed antibiotic and is known to be associated with QT prolongation and TdP. In the present work a clinical case is reported in which erythromycin induced TdP ventricular tachycardia in a patient with hypokalemia. In our case, the life-threatening ventricular proarrhythmia disappeared in response to mexiletine.

Eliprodil, a newly developed NMDA (*n*-methyl-*d*-aspartate) receptor antagonist neuroprotective agent, has been at times observed to prolong the QT interval in patients, which may involve the risk of development of proarrhythmic complications. Therefore, the next purpose of the present study was to analyse the effect of eliprodil, a noncardiac drug, on the cardiac repolarization under *in vitro* circumstances, under normal conditions and after the attenuation of the "repolarization reserve" by blocking the I_{K1} current with $BaCl_2$.

1.1. Major experimental goals

(1) To carry out experimental studies to establish whether under *in vitro* conditions mexiletine is able to decrease the erythromycin-induced cardiac electrophysiological changes leading to a tendency to torsade de pointes ventricular tachycardia.
(2) To investigate and to compare the electrophysiological properties of the rapid and slow components of the delayed rectifier potassium current (I_{Kr} and I_{Ks}) in Langendorff-perfused hearts, in multicellular right ventricular papillary muscle preparations and in ventricular myocytes isolated from rabbit hearts.
(3) To evaluate the role of I_{Ks} current when cardiac repolarization is abnormally lengthened by pharmacological means.
(4) To analyse the effect of eliprodil, a noncardiac drug, on the cardiac repolarization under in vitro circumstances, under normal conditions and after the attenuation of the "repolarization reserve".

2. Case report: erythromycin induced torsade de pointes ventricular tachycardia

A 59-year-old woman was referred to our clinic because of palpitation, ventricular extrasystoles and a syncopal attack. She was regularly taking clopamid (10 mg/day) and potassium chloride (1000 mg/day) because of pedal edemea. In addition to these drugs, she had taken erythromycin (500 mg three times a day) and acetylcysteine (600 mg/day) for respiratory infection three days before the syncopal attack. There was no family history of long QT syndrome, sudden death, frequent syncope or seizure. Her physical examination was unremarkable other than a moderate bilateral lower extremity edema, minimal crackles at lung bases, quiet systolic murmur at the heart apex and extrasystolia. The blood pressure was in the normal range. Chest x-ray showed a moderate pulmonary congestion. Transthoracic echocardiography demonstrated an enlarged left atrium (50 mm), normal ventricular diameters and normal wall motion. The left ventricular ejection fraction was 54%.

The admission 12-lead electrocardiogram (ECG) showed a sinus rhythm at mean heart rate of 85 beats/min, prolonged ventricular repolarization (QT = 560 ms, QT_c = 663ms, corrected by Bazett formula), particular bigeminy and *torsade de pointes* ventricular tachycardias preceded by "short-long-short" RR interval sequence. The proarrhythmic ventricular tachycardia causing syncopal attacks was abolished by the discontinuation of erythromycin treatment, parenteral potassium chloride (3000 mg) and magnesium sulphate (1000 mg) supplemenation and oral mexiletine therapy (200 mg three times a day). Since then she has been free of ventricular tachycardia or ventricular ectopics. Holter monitoring for 24 hours before discharge revealed no premature beats or tachyarrhythmias. The QT interval at that time was normal (360 ms).

3. Methods of the experiments

3.1. Preparation of the rabbit and canine hearts

New Zealand rabbits were sacrificed by cervical dislocation after an intravenous injection of heparin. The chest was opened, the heart quickly removed and immediately immersed in oxygenated modified Locke's solution. Adult mongrel dogs were used in canine expeiments. Following sodium pentobarbital induced anaesthesia each heart was rapidly removed through a right thoracotomy and immediately rinsed in oxygenated modified Locke's solution.

3.2. ECG measurements in Langendorff-perfused rabbit hearts

The rabbit heart was mounted on a Langendorff column and perfused with oxygenated modified Locke's solution. After appropriate preparation, the heart was immersed in a tissue chamber filled with perfusion solution. Volume-conducted electrocardiograms (ECGs) were obtained as previously described by *Zabel et al*. ECG leads were acquired by an ECG signal processing system and data were analyzed off-line. After an equilibration period, baseline ECGs were obtained and a 40 min perfusion period was initiated with either investigated drug. ECG recordings were monitored continuously and compared to baseline measurements at the end of this period. QT intervals were always measured on lead II.

3.3. Conventional microelectrode measurements

Canine Purkinje strands obtained from both ventricle and rabbit or canine isolated right ventricular papillary muscle preparations were mounted individually in a tissue chamber continuously superfused with modified Locke's solution while stimulated at 1000 ms cycle length using rectangular constant current pulses 2 ms in duration. Transmembrane potentials were recorded using conventional microelectrodes connected to the input of a high impedance electrometer and continuously monitored on a dual beam storage oscilloscope. The maximum diastolic potential, action potential amplitude and action potential duration (APD) were automatically measured. In each experiment, baseline action potential characteristics were first determined during continuous pacing at 1 Hz, and then while pacing cycle length was sequentially varied between 300 and 5000 ms. Twenty-five action potential were evoked at each cycle length and the cycle length was then changed so that "quasi" steady-state frequency response relations could be rapidly generated. Each preparation was then superfused for 40 to 60 min with either investigated drug before repeating the pacing protocol.

3.4. Patch-clamp measurements

Single ventricular myocytes were obtained by enzymatic dissociation of isolated rabbit and canine hearts. After the isolation pocedure, one drop of cell suspension was placed in a transparent recording chamber mounted on the stage of an inverted microscope. Myocytes were used that were rod shaped with clear striations. HEPES buffered Tyrode solution served as the normal superfusate in all experiments. Patch-clamp micropipettes were fabricated from borosilicate glass capillaries using a micropipette puller. These electrodes had resistances between 1.5 and 2.5 MΩ when filled with pipette solution. The pH of this solution was adjusted to 7.2 by addition of KOH. Nisoldipine (1 μM) in the external solution eliminated inward Ca^{2+} current (I_{Ca}) while the sodium current (I_{Na}) was inactivated during experiments by applying a holding potential of -40 mV. At this holding potential, transient outward current (I_{to}) was also largely inactivated. An amplifier was used to record membrane current in the whole-cell configuration of the patch-clamp technique. Membrane currents were digitized using an analog-to-digital converter under software control. Analyses were performed using pClamp 6.0 software. All patch-clamp data were collected at 37 °C.

4. Results

4.1. Effect of erythromycin on the action potential in isolated canine Purkinje-fiber.

The isolated, free-running Purkinje fibers (n = 9) were individually mounted in a tissue chamber containing saline. After equilibration period, erythromycin was applied in a concentration of 200 mg/l, while the electrical stimulation cycle length was progressively increased from 1000 ms to 5000 ms. In three experiments, the EAD was facilitated by addition of the K^+-channel blocker cesium chloride (CsCl; 2 mM). Mexiletin was added to the organ bath in a concentration of 10 μM. Under control conditions, when cycle length was changed from 1000 ms to 5000 ms, although the APD increased considerably, EADs were never observed. CsCl (2 mM, n=3) lengthened APD further without eliciting EADs. Application of 200 mg/l erythromycin for 25-30 minutes at 1 Hz basic stimulation frequency did not significantly influence the maximal diastolic potential, the action potential ampitude and slightly decreased the maximal rate of depolarization (V_{max}). The APD, however, was markedly increased from 289.4 ± 20.6 ms and 387.9 ms to 360.1 ± 28.0 ms and 567.4 ± 47.7 ms, respectively ($p < 0.005$). Erythromycin evoked EADs after 30 minutes in all experiments when cycle length was gradually increased from 1000 ms.The average cycle length at which erythromycin-induced EADs developed was 2344 ± 310 ms (n = 9). In the continuous presence of 200 mg/l erythromycin, the addition of 10 μM/l mexiletine to the tissue bath, markedly shortened APD and, in most Purkinje fiber preparations (7/9), the abolition of EADs was observed.

4.2. Comparison of the effects of I_{Ks} and I_{Kr} block in rabbit hearts

4.2.1. The choice of drug concentrations

The concentrations of L-735,821 (100 nM) and chromanol 293B (10 μM) were comparable to those used by others and shown to block I_{Ks} in other species. We used 100 nM L-735,821 to assure completely block I_{Ks} during assessment of I_{Kr}, and 1-5 μM E-4031 to fully block I_{Kr} during assessment of I_{Ks}. E-4031 concentrations (100 nM) were also similar to those used previously by us and others.

4.2.2. Comparison of the effects of I_{Ks} and I_{Kr} block on QT_c interval in isolated Langendorff-perfused rabbit hearts

Neither I_{Ks} blocker, chromanol 293B (10 μM) nor L-735,821 (100 nM) significantly lengthened QT_c or increased RR interval in isolated, Langendorff-perfused rabbit hearts after 40 min of exposure. The I_{Kr} blocker E-4031 (100 nM), significantly increased QT_c under identical conditions. This E-4031 induced increase in QT_c was associated with a significant increase in RR interval (420.5 ± 17.5 ms at baseline *vs*. 463.5 ± 17.8 ms after E-4031, n = 8, $p < 0.05$).

4.2.3. Effects of I_{Ks} and I_{Kr} block on ventricular action potential duration in isolated rabbit papillary muscle

Concentrations of chromanol 293B (10 μM) and L-735,821 (100 nM) reported to block I_{Ks} in other species failed to significantly affect rabbit papillary muscle APD while pacing at a constant pacing cycle length of 1000 ms. On the other hand, E-4031 (100 nM) markedly and significantly increased rabbit papillary muscle APD under identical conditions. A similar difference in the effects of chromanol 293B (10 μM) and L-735,821 (100 nM) compared to E-4031 (100 nM) on APD was observed in rabbit ventricular muscle over a wide range of pacing cycle lengths. Chromanol 293B and L-735,821 produced only small changes in APD over this entire range of pacing rates while E-4031 markedly lengthened rabbit papillary muscle APD in a reverse frequency-dependent fashion so that the increase in APD was greater at long cycle lengths than at short ones.

4.2.4. Effect of I_{Ks} block in the presence of forskolin

Because I_{Ks} is modulated by changes in intracellular cAMP, we also examined the effect of I_{Ks} block on APD in the presence of 1 μM forskolin to activate adenylcyclase and thereby increase intracellular cAMP. Forskolin (1 μM) alone shortened APD in rabbit papillary muscle paced at cycle length of 1000 ms from 217.4±18.7 ms to 194.0±15.7 ms (n=5, $p<0.05$). Addition of 10 μM chromanol 293B in the continuous presence of forskolin had little effect on APD (194.0±15.7 ms versus 190.8±12.9 ms, n=5). Similar result was obtained with L-735,821 (100 nM). These results show that selective I_{Ks} block does not alter APD substantially even in the presence of elevated intracellular cAMP.

4.2.5. Effect of L-735,821 on I_{Ks} compared to that of E-4031 on I_{Kr} in isolated rabbit ventricular myocytes

L-735,821 (100 nM) completely abolished I_{Ks}. In comparison, a greater concentration of E-4031 (1 μM) than used in examining its effects on rabbit QT_c and APD was required to fully block I_{Kr} tail currents..

4.2.6. I_{Ks} and I_{Kr} activation and deactivation kinetics in rabbit ventricular myocytes

I_{Ks} kinetics were assessed in rabbit ventricular myocytes using an envelope of tails protocol in the presence of 5 μM E-4031 to eliminate I_{Kr}. Under these conditions, I_{Ks} activation was slow (τ = 888.1 ± 48.2 ms, n = 21, at +30 mV) and I_{Ks} deactivation was fast (τ = 157.1 ± 4.7 ms, n = 22, at –40 mV).

In the presence of 100 nM L-735,821 to block I_{Ks}, the activation time constant (τ) for I_{Kr} was 35.5 ± 3.1 ms (n = 26) and deactivation was slow and best fit as the sum of two exponentials; τ_1 = 641.5 ± 25.0 ms and τ_2 = 6531 ± 343 ms with amplitudes of A_1 = 32.8 ± 1.7 pA and A_2 = 42.4 ± 2.1 pA, respectively (n = 35).

The E-4031 sensitive current (I_{Kr}) amplitude at the end of the 150 ms long test pulse was 34.1 ± 4.2 pA (n = 14), or about 30% of the tail current amplitude measured after the voltage test pulse returned to -40 mV (85.8 ± 9.2 pA, n = 14). The L-735,821 sensitive current (I_{Ks}) during the test pulse to +30 mV was larger than its tail current on return to -40 mV. The magnitude of I_{Ks} during the test pulse was 13.27 ± 1.2 pA at +30 mV *vs.* 6.6 ± 0.8 pA at -40 mV, (n = 15), approximately an order of magnitude less than the I_{Kr} tail current.

4.3. Effect of I_{Ks} block in canine hearts

4.3.1. The effects of L-735,821 and chromanol 293B on action potential repolarization in dog ventricular muscle

Chromanol 293B and L-735,821 produced small changes in APD amounting to less than a 7% increase over baseline measurements, and these unremarkable effects of I_{Ks} demonstrated little frequency dependence in right ventricular papillary muscles. Selective I_{Ks} block in dog has little effect on normal cardiac APD in ventricular muscle fibres.

4.3.2. The effects of L-735,821 and chromanol 293B on pharmacologically lengthened action potentials

The effects of both L-735,821 and chromanol 293B were tested in dog ventricular papillary muscle action potentials, lengthened pharmacologically by exposure to 1 μM E-4031 (to block I_{Kr}) and 1 μg/ml veratrine (a recognized sodium channel agonist). L-735,821 markedly lengthened APD under these conditions from 383.5 ± 25.2 to 442.1 ± 32.3 ms ($p < 0.01$, n = 7). This effect was in

sharp contrast to the negligible effect of L-735,821 on normal APD. Comparable effects on APD were obtained with chromanol 293B in the continuous presence of E-4031 and veratrine (APD was 366.1 ± 13.1 ms before chromanol 293B versus 429.5 ± 23.5 ms after its addition, $p < 0.01$, n = 8).

4.4. Effect of eliprodil on ventricular repolarization

4.4.1. Effect of eliprodil on ventricular action potential duration in isolated canine ventricular papillary muscle under normal condition

Eliprodil (1 μM) lengthened APD moderately (<10%) from 235.3±5.9 ms to 257.3±9.0 ms (1Hz, n = 9, $p < 0.05$) without causing significant change in the resting membrane potential, the action potential amplitude, and the V_{max}. Under normal condition, the drug produced a moderate reverse rate-dependent APD prolongation (7.4 ± 1.5%, 8.9 ± 2.1% and 9.9 ± 1.8% at cycle lengths of 300, 1000 and 5000 ms, respectively; n = 9).

4.4.2. Effect of eliprodil on ventricular action potential duration in isolated canine ventricular papillary muscle after I_{K1} inhibition

Partial block of I_{K1} by 10 μM $BaCl_2$ lengthened APD in a reverse frequency dependent manner (7.0 ± 1.3%, 14.2 ± 1.6% and 28.1 ± 2.1% at cycle lengths of 300, 1000 and 5000 ms, respectively; n = 8). In the presence of $BaCl_2$, 1 μM eliprodil induced a marked further lengthening relative to the APD values measured after the administration of $BaCl_2$ (12.5 ± 1.0%, 17.6 ± 1.5% and 20.5 ± 0.9% at cycle lengths of 300, 1000 and 5000 ms, respectively; n = 8), ie. the APD lengthening effect of eliprodil was significantly augmented in preparations where the "repolarization reserve" was attenuated by previous application and presence of $BaCl_2$.

4.4.3. Effect of eliprodil on QT_c interval in isolated Langendorff-perfused rabbit hearts in the absence and presence of I_{K1} block

In the normal Langendorff-perfused rabbit heart, eliprodil (1 μM) produced a significant QT_c prolongation (12.7 ± 1.8%, n = 9). After the attenuation of the "repolarization reserve" by the I_{K1} blocker $BaCl_2$ (10 μM), this eliprodil evoked QT_c prolongation was greatly enhanced (28.5 ± 7.9%, n = 6). In 2 out of 6 Langendorff preparations the QT_c lengthening degenerated into *torsade de pointes (TdP)* ventricular tachycardia.

4.4.4. The effect of eliprodil on the transmembrane potassium currents in canine ventricular myocytes

Eliprodil (1 μM) does not considerably influence I_{K1} or I_{to} in canine ventricular myocytes (I_{K1} current values at -60 mV: 365.7±29.2 pA as control and 321.5±30.5 pA in the presence of 1 μM eliprodil, n=5; I_{to} current values at 50 mV: 6017.2±963.0 pA as control and 5617.5±1025.0 pA in the presence of 1 μM eliprodil, n=5). The drug does not significantly affect I_{Ks} in canine ventricular myocytes (I_{Ks} tail current was 261.6±53.0 pA under control conditions and 202.4±40.0 pA after application of 1 μM eliprodil, at 50 mV of potential of activation, n=6). 1 μM eliprodil, however, abolished I_{Kr} tail current completely.

5. Discussion

5.1. Suppression of erythromycin-induced early afterdepolarizations and torsade de pointes ventricular tachycardia by mexiletine

A recent electrophysiological analysis of erythromycin at a cellular and ion channel level revealed that, in clinically relevant concentrations (10-200 mg/l), the macrolide antibiotic selectively blocks the I_{Kr}. Following single iv. injection of 1 g erythromycin, an average serum level of 30 mg/l may be measured. This exceeds the threshold concentration of 10-20 mg/l which induces a significant APD prolongation in the Purkinje and M cells. In the presence of predisposing pathogenic factors (bradycardia, hypokalemia, congenital LQTS, etc.), even smaller oral doses of erythromycin may induce proarrhythmia. A relatively frequent side effect of erythromycin treatment is diarrhoea, due to the prokinetic effect of the drug. This can give rise to clinically considerable myocardial potassium loss. In our case report, however, the hypokalemia was induced by concomitant diuretic therapy.

Our experiments demonstrated that mexiletin, an inhibitor of slowly inactivating window sodium current, may prevent I_{Kr}-blocking drug induced TdP ventricular tachycardia by abolishing APD prolongation and EADs. *In vitro*, mexiletin is capable of limiting the APD prolongation and EAD-inducing effects not only of erythromycin, but also of other I_{Kr}-blocking drugs. In accordance with this, mexiletin is also suitable for *in vivo* elimination of the TdP induced by antiarrhythmic agents with Class IA and III actions. Shortening of the plateau phase of the action potentials is accompanied by decreases in the transsarcolemmal calcium inflow and in the intracellular calcium loading of the heart cells. This is clearly a beneficial effect, if it is taken into consideration that cytosolic calcium overload is a fundamental pathogenetic factor of EAD formation.

5.2. Comparison of the electrophysiological properties of the I_{Kr} and I_{Ks} in isolated rabbit heart preparations

Because the surface electrocardiogram remains the best clinical means of assessing antiarrhythmic drug therapy and monitoring development of proarrhythmic side effects, we determined the effects of two potentially beneficial antiarrhythmic agents, chromanol 293B and L-735,821, on QT_c in isolated, Langendorff-perfused rabbit hearts. This experimental preparation allowed us to also determine the effect of the exactly the same drug concentrations on rabbit ventricular papillary muscle action potential configuration as well as the underlying membrane currents in isolated rabbit ventricular myocytes. We compared the effects of these two reportedly selective I_{Ks} blockers to those of a recognized selective I_{Kr} blocker, E-4031. This comparison allowed direct assessment of the degree of QT_c and action potential lengthening produced by complete, selective block of I_{Ks} versus I_{Kr} block in rabbit ventricular tissue. We found that chromanol 293B and L-735,821 did not substantially increase QT_c in Langendorff-perfused rabbit hearts, nor did they increase isolated rabbit ventricular papillary muscle APD. L-735,821, however, did completely block I_{Ks} in isolated rabbit ventricular myocytes. In contrast, a concentration of E-4031 an order of magnitude less than that which totally blocked I_{Kr}, markedly increased QT_c and rabbit ventricular muscle APD. Thus, if the basis of the ventricular antiarrhythmic effectiveness of I_{Kr} block by agents like E-4031 is cardiac APD prolongation reflected as an increase in QT_c, selective I_{Ks} block is unlikely to prove to be of antiarrhythmic benefit.

Based on the earlier results in guinea pig ventricular myocytes, where I_{Ks} activates and deactivates slowly, selective I_{Ks} block was expected to increase APD without inducing reverse use-dependent lengthening as associated with I_{Kr} block. In rabbit, I_{Ks} is usually recorded as a large membrane current relative to other species. We found in patch clamp experiments that in rabbit ventricular myocytes I_{Ks} activated slowly and deactivated rapidly in relation to the time of normal electrical diastole. We also found that I_{Kr} activated rapidly as expected, but deactivated slowly. Former report that I_{Ks} deactivates rapidly in human myocytes while I_{Kr} in human myocytes

deactivates slowly strongly suggests that rabbit would serve as better preclinical models for examining the effects of new antiarrhythmic agents than guinea pig.

5.3. Evaluation of the role of I_{Ks} current when cardiac repolarization is abnormally lengthened by pharmacological means

Our results indicate that both chromanol 293B and L-735,821, purportedly selective I_{Ks} blockers did not substantially lengthen APD in dog right ventricular papillary muscle preparations. These drugs produced small changes in APD amounting to less than a 7% increase over baseline measurements, and these unremarkable effects of I_{Ks} demonstrated little frequency dependence in right ventricular papillary muscles. Selective I_{Ks} block in dog has little effect on *normal* cardiac APD in ventricular muscle fibres. This observation is in good agreement with our above-mentioned findings in rabbit ventricle.

However, in papillary muscle preparations where APD was extremely prolonged by the I_{Kr} blocker E-4031 and the I_{Na} activating veratrine, both chromanol 293B and L-735,821 increased repolarization considerably. Our finding suggests that I_{Ks}, unlike I_{Kr}, plays little role during normal action potential repolarization. Such a conclusion is well supported by the negligible effect of I_{Ks} block on isolated ventricular muscle APD. If repolarization is excessively lengthened due to drug induced I_{Kr} block, hypokalaemia, genetic abnormality, or bradycardia, the subsequent increase in APD would favour I_{Ks} activation and provide a negative feedback mechanism to limit further APD lengthening. Without such a mechanism, excessive APD lengthening might lead to enhanced regional repolarization dispersion and increase propensity for development of EAD associated with TdP induction.

5.4. Analysis of the effect of eliprodil, a non-cardiac drug, on the cardiac repolarization under normal conditions and after the attenuation of the "repolarization reserve".

It has become apparent that not only antiarrhythmic drugs but a variety of non-antiarrhythmic agents may provoke TdP tachycardia. The number of non-cardiac drugs reported to induce QT interval prolongation with or without TdP continues to increase. A number of clinically available or still investigational non-cardiovascular agents have been implicated. Therefore, there is a great importance of the preclinical detection of torsadogenic propensity of the newly developed agents to decrease the proarrhythmic risk. The most important finding of this part of the present work was that eliprodil which blocks I_{Kr} current without considerably interfering with I_{K1}, I_{Ks} and I_{to}, caused moderate APD and QT_c lengthening when it was applied alone, but when the "repolarization reserve" was attenuated by $BaCl_2$, it evoked augmented prolongation of repolarization, occasionally resulting in torsade de pointes ventricular tachycardia.

The present experiments may have important therapeutical and practical implications. Some non-cardiac drugs exhibit weak inhibition of one or more potassium, most frequently the I_{Kr} (HERG/MiRP) channel. Since this effect does not markedly influence repolarization in normal situation, their effect on QT is often unmasked. Therefore the potential proarrhythmic danger can be easily underestimated in individuals who have decreased "repolarization reserve" in spite of their baseline QT_c falls within the normal range. Accordingly, eliprodil or any drug which is known to inhibit potassium current and exert only moderate or not even consistent repolarization lengthening, should be administered under repeated or continuous ECG control, and if QT_c prolongation longer than expected is noticed, the therapy with such a drug should be discontinued. Also, the concept of attenuated "repolarization reserve" should be considered during safety pharmacology studies, since the rabbit and guinea pig possessing fast heart rate or even the dog, all of which probably have relatively strong repolarization reserve, can not be expected to respond with significant QT lengthening when drugs partially block only one type of cardiac potassium channels. Instead of studying drug effects on the cardiac repolarization and proarrhythmic risk in the *normal* heart, it would certainly be more useful to develop and apply screening tests where repolarization reserve is *attenuated*.

6. Summary: conclusions and potential significance

1. Erythromycin is a selective I_{Kr}-blocking, APD-prolonging antibiotic drug, which may induce *in patients* QT interval prolongation and in particular cases TdP ventricular tachycardia. Under *in vitro* circumstances, at therapeutic concentration (200 mg/l), erythromycin was able to lengthen APD and induce EADs in isolated Purkinje fibers. After the addition of mexiletin (10 μM), a marked shortening of APD and the disappearance of EADs (7/9) were observed. Our experiments demonstrated that mexiletin, an inhibitor of slowly inactivating sodium current, may prevent I_{Kr}-blocking drug induced TdP ventricular tachycardia by abolishing APD prolongation and EADs.

2. In rabbit ventricular myocytes, chromanol 293B (10 μM) and L-735,821 (100 nM) markedly or totally blocked I_{Ks}, and E-4031 (1 μM) completly inhibited I_{Kr}. The same concentration of chromanol 293B and L-735,821 had no significant effect on QT_c interval in Langendorff-perfused rabbit hearts, whilst E-4031, even at lower concentration (100 nM), significantly increased QT_c interval (~36%). Similarly both chromanol 293B (10 μM) and L-735,821 (100 nM) produced little increase in papillary muscle APD (less than 7 %) while pacing at cycle lengths between 300 and 5000 ms. In contrast, E-4031 (100 nM) markedly increased APD (30-60 %) in a reverse frequency-dependent manner. In rabbit ventricular myocytes, I_{Ks} tail currents activated slowly and deactivated rapidly, while I_{Kr} tail currents activated rapidly and deactivated slowly. I_{Kr} was estimated to contribute substantially more to total current density during normal ventricular muscle action potentials than does I_{Ks}. The kinetics of I_{Ks} and I_{Kr} activation and deactivation in rabbit ventricular myocytes are similar to those reported in dog and man. These new findings suggest that rabbit is a good species for preclinical evaluation of new drugs believed to affect cardiac action potential repolarization. In addition, these results indicate that block of I_{Ks} is not likely to provide antiarrhythmic benefit by lengthening normal ventricular muscle QTc, APD, and refractoriness over a wide range of frequencies.

3. Similarly to the outcome of the rabbit experiments, our results indicate that neither chromanol 293B (10 μM) nor L-735,821 (100 nM) did substantially increase APD in dog papillary muscle. However, these compounds lengthened repolarization markedly, when APD was pharmacologically prolonged by E-4031 (1 μM) and veratrine (1μg/ml). We conclude that I_{Ks} plays little role in normal dog ventricular muscle action potential repolarization. In pathological situation, when APD is abnormally increased, the role of I_{Ks} in final repolarization increases to provide an important safety mechanism that reduces arrhythmia risk.

4. Eliprodil (1 μM), a non-cardiac drug with neuroprotective properties, significantly decreased the amplitude of I_{Kr}, but I_{Ks}, I_{to} and I_{K1} were not considerably affected by the drug when measured in dog ventricular myocytes by applying the patch clamp technique. In canine right ventricular papillary muscle by applying the conventional microelectrode technique, under normal conditions, eliprodil produced a moderate reverse rate-dependent prolongation of the action potential duration. This effect was augmented in preparations where I_{K1} was previously blocked by $BaCl_2$ (10 μM). In the normal Langendorff-perfused rabbit heart, eliprodil produced a significant QT_c prolongation (~13%). After the attenuation of the "repolarization reserve" by the I_{K1} blocker $BaCl_2$, the eliprodil evoked QT_c prolongation was greatly enhanced (~29%) In 2 out of 6 Langendorff preparations this QT_c lengthening degenerated into TdP ventricular tachycardia. The results indicate that eliprodil, under normal conditions, only moderately lengthens cardiac repolarization by inhibition of I_{Kr}. However, after the attenuation of the normal "repolarization reserve", this drug can induce marked QT interval prolongation, which may result in proarrhythmic action.

The thesis is based on the following publications

Full length papers

I. Lengyel, Cs., Várkonyi, T.T., Tazekas, T.: Erythromycin által előidézett "Torsade de Pointes" kamarai tachycardia [Erythromycin-induced "torsade de pointes" ventricular tachycardia]. *Orv. Hetil.*, 1997, *138*, 1003-1006.

II. Fazekas, T., Krassói, I., Lengyel, Cs., Varró, A., Papp, J. Gy.: Suppression of erythromycin-induced early afterdepolarizations and *torsade de pointes* ventricular tachycardia by mexiletine. *PACE*, 1998, *21*, 147-150. (IF: 1.132)

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V. Lengyel, Cs., Iost, N., Virág, L., Varró, A., Lathorp, D. A., Papp, J., Gy.: Pharmacological block of the slow component of the outward delayed rectifier current (I_{Ks}) fails to lengthen rabbit ventricular muscle QT_c and action potential duration. *Br. J. Pharmacol.,* 2001, *132*, 101-110. (IF: 3.611)

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