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Atrial-selective sodium channel block as a novel strategy for the management of atrial fibrillation

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Abstract

Safe and effective pharmacologic management of atrial fibrillation (AF) is one of the greatest challenges facing an aging society. Currently available pharmacologic strategies for rhythm control of AF are associated with ventricular arrhythmias and in some cases multi-organ toxicity. Consequently, drug development has focused on atrial-selective agents such as I_{Kur} blockers. Recent studies suggest that I_{Kur} block alone may be ineffective for suppression of AF and may promote AF in healthy hearts. Recent experimental studies have demonstrated other important electrophysiologic differences between atrial and ventricular cells, particularly with respect to sodium channel function, and have identified sodium channel blockers that exploit these electrophysiologic distinctions. Atrial-selective sodium channel blockers, such as ranolazine and amiodarone, effectively suppress and/or prevent the induction of AF in experimental models, while producing little to no effect on ventricular myocardium. These findings suggest that atrial-selective sodium channel block may be a fruitful new strategy for the management of AF.

Keywords

antiarrhythmic drugs; arrhythmias; pharmacology; electrophysiology

Introduction

Effective and safe treatment of atrial fibrillation (AF) remains a major unmet medical need in our society and the problem is growing as the prevalence of AF continues to increase with the aging of the baby boomgeneration. AF is the most prevalent sustained clinical arrhythmia associated with increased morbidity and mortality. Its prevalence is 0.4–1% in the general population and greater than 8% in individuals >80 years of age. An estimated 2.5 million individuals in North America and 4.5 million in Europe are affected by AF.[1] These numbers are projected to increase to 15 million in North America alone by 2050, largely due to aging of the population.

Despite significant progress in ablation therapy, antiarrhythmic drugs (AADs) remain first-line therapy for rhythm control of AF.[1,2] However, the effectiveness and/or safety of agents available for the treatment of AF are not optimal. Currently available pharmacologic strategies for the rhythm control of AF include: (1) sodium channel blockers, such as propafenone and flecainide; (2) potassium channel blockers (largely I_{Kr}), such as sotalol and dofetilide; and (3) mixed ion channel blockers, such as amiodarone and dronedarone.

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Electrophysiologic distinctions between atrial and ventricular cells

Because of the proclivity of currently available drugs to induce ventricular arrhythmias, new drug development has focused atrial-selective drugs, with the goal of avoiding the ventricular proarrhythmic effects of currently available agents. In order to fully appreciate the basis for atrial-selective actions of these agents, it would be helpful to review the electrophysiologic differences between atrial and ventricular cells under normal and pathophysiologic conditions.

The normal action potential in atria differs from that of the ventricle with respect to ion channel currents that contribute to resting membrane potential (RMP), phase 1, and phase 3 of the action potential (Fig. 1).[3,4]

RMP in atria is more depolarized than in the ventricle, in large part because of a smaller inward rectifier potassium current, I_{K1}. Phase 1 is more prominent in atria because of the presence of a prominent transient outward current (I_{to}) and a current that is exclusive to atria, known as the ultra-rapid delayed rectifier potassium current, I_{Kur}. Another current that is exclusive to atria is the acetylcholine-activated potassium current, $I_{K–ACh}$. Phase 3 of the action potential is much slower to repolarize in atria because of weaker repolarizing currents, including the rapidly and slowly activating delayed rectifier currents (I_{Kr} and I_{Ks}) and I_{K1}.

Initiation of AF involves the development of both a substrate and a trigger. The electrical substrate develops as a consequence of a reduction in wavelength largely due to an abbreviation of the effective refractory period (ERP). The maintenance of AF often is facilitated by electrical and structural remodeling that is the result of the rapid activation of the atria (AF begets AF).[5] The electrical remodeling further abbreviates ERP by abbreviating the atrial action potential (Fig. 2).

Rapid activation of the atria during AF results in a decrease in I_{Ca}, I_{Kur}, and I_{to}, but to an increase in I_{K1} and constitutively active $I_{K–ACh}$. The abbreviation of action potential duration (APD) is principally due to the decrease in I_{Ca} and the increase in I_{K1} and constitutively active -$I_{K–ACh}$.[6]

Atrial-selective drugs

One of the principal goals of rhythm control therapy is to prolong the ERP, thus eliminating the substrate for development of AF. Sodium channel blockers accomplish this by reducing excitability and promoting post-repolarization refractoriness (PRR). Potassium channel blockers do this by prolonging the atrial APD, and mixed ion channel blockers achieve this through a combination of both actions. Because all three classes of drug have an inclination to induce ventricular arrhythmias, recent drug development for the management of AF has focused on agents that selectively affect the atria, but not the ventricles of the heart.

Inhibition of I_{Kur}, present in atria, but not ventricles, is an example of an atrial-selective approach.[7,8] Design of selective I_{Kur} blockers has been a great challenge because these agents often block other currents (e.g., I_{Na} by vernakalant and AZD7009 and I_{to}/I_{KACh}/CA-I_{KACh} by AVE0118).[9–12] A number of studies indicate that the relative contribution of I_{Kur} to atrial repolarization in remodeled hearts maybe relatively low. I_{Kur} density is known to be progressively reduced with acceleration of activation rates[13] and I_{Kur} density is decreased in cells isolated from chronic AF atria.[12,14] Selective I_{Kur} reduction produces only minor APD_{90} prolongation in human remodeled atria or canine acetylcholine-treated atria (both showing a triangular action potential morphology and proneness to develop AF).[15,16] Although I_{Kur} block may contribute to the antiarrhythmic efficacy of the I_{Kur} blockers, I_{Kur} block alone may be insufficient to effectively suppress AF, and inhibition of additional currents maybe required (e.g., I_{Na}, I_{kr}, I_{to}, $I_{K–ACh}$, CA-$I_{K–ACh}$).[17,18]

Interestingly, recent studies have shown that loss-of-function mutations in *KCNA5*, the gene that encodes the α subunit of the I_{Kur} channel is associated with the development of AF, suggesting that a reduction in I_{Kur} may promote the development of AF in humans.[19] Indeed, inhibition of I_{Kur} has been shown to be capable of permitting the induction of AF in experimental models consisting of coronary-perfused canine right atrial preparations.[16]

Atrial-selective sodium channel block

We recently introduced the concept of atrial-selective sodium channel block as a novel strategy for the management of AF.[20–23] Two agents identified as atrial-selective sodium channel blockers are ranolazine and amiodarone. Ranolazine produces a much greater depression of atrial versus ventricular sodium channel-dependent parameters and suppresses AF at concentrations that produce little to no effect in the ventricles.[20]

Chronic amiodarone likewise exerts atrial-selective depression of I_{Na}-dependent parameters, which prevent the induction of AF in experimental models.[21] Ranolazine and chronic amiodarone reduce maximum rate of rise of the action potential upstroke (V_{max}), prolong conduction time (CT), increase diastolic threshold of excitation (DTE), and induce PRR specifically or predominantly in the canine isolated atrial versus ventricular coronary-perfused preparations (Figs. 3 and 4).[20,21] Induction of PRR is a unique feature of I_{Na} blockers, occurring when ERP is prolonged beyond the end of repolarization of the action potential. In contrast, propafenone depresses V_{max} and CT, decreases DTE, and induces PRR in a chamber-independent manner at a pacing cycle length of 500 ms, but becomes slightly more atrial-selective at a BCL of 300 ms.[24]

Ranolazine, first recognized as an antianginal and then as an antiarrhythmic agent, blocks early I_{Na}, late I_{Na}, I_{Kr}, and late I_{Ca} at concentration within the therapeutic range (2–8 μM)[20,25] Amiodarone has likewise been shown to inhibit multiple cardiac ion channel currents (I_{Kr}, I_{Ks}, I_{Na}, late I_{Na}, I_{to}, $I_{Ca–L}$, $I_{Ca–T}$, I_{K1}) as well as to block α- and β-adrenoceptors.[26,27]

Although AZD7009 is considered to be an atrial-selective agent on account of inhibition of I_{Kur}, its IC_{50} to block this current is many times greater than its IC_{50} to inhibit I_{Kr} and I_{Na} (27,0.6, and 4.2 μM, respectively).[28,29] AZD7009 decreases excitability (i.e., DTE) and conduction velocity preferentially in atria of dogs *in vivo*,[30] indicating that its atrial selectivity is due in part to its inhibition of I_{Na} giving rise to an atrial-selective prolongation of ERP.[10,30] Vernakalant, another I_{Kur} blocker, also potently blocks I_{Na}.[9] ISQ-1 and TAEA, two more I_{Kur} blockers, slow conduction velocity in atria, suggesting an ability to block I_{Na}.[31] Interestingly, in non-remodeled atria, I_{Kur} blockers abbreviate or produce no change in $APD_{70–90}$,[15,16,32,33] but apparently always prolongs ERP in both non-remodeled and remodeled atria,[8] which can be explained by the induction of sodium-channel dependent PRR. Differences in the response of atrial and ventricular cells to I_{Na} blockers are not well defined and relatively poorly investigated. A semi-quantitative appraisal of atrial selectivity of I_{Na} blockers is presented in Figure 5.

The "atrial-selective" properties of sodium channel blockers are due to atrioventricular differences in the biophysical properties of the sodium channel and differences in the morphology of atrial and ventricular action potentials.[20,21,23] As previously discussed, RMP is intrinsically more depolarized in atrial versus ventricular myocytes.[34] Steady-state inactivation of I_{Na} is more negative in atrial cells; half-inactivation voltage ($V_{0.5}$) in atrial cells is 9–14 mV more negative than in ventricular myocytes.[20,35,36] As a consequence of the more depolarized RMP and more negative $V_{0.5}$, a large fraction of sodium channels are inactivated at the normal resting membrane potential in atrial cells. The fraction of resting channels is therefore smaller in atrial versus ventricular cells at RMP. As much of the recovery from sodium channel block commonly occurs during the resting state of the channel,[37,38] atrial cells

show a greater accumulation of use-dependent sodium channel block. Atrial-selective APD prolongation (due to I_{Kr} block) may also importantly promote atrial-selective depression of sodium channel-dependent parameters.

Atrial selectivity of sodium channel block at rapid activation rates is believed to be due to several factors working in concert: (1) The fraction of inactivated sodium channels is greater in atrial cells because of the more negative half-inactivation voltage; (2) RMP is more depolarized in atrial cells, thus further reducing the availability of sodium channel and potentiating the effect of sodium channel blockers; (3) Drug-induced atrial selective slowing of the already slow phase 3 in atria (due to I_{Kr} block) results in failure of the action potential to achieve maximum resting potential at rapid rates, thus leading to a depolarized take-off potential, further reducing the availability of sodium channels (Fig. 3); (4) The slower phase 3 also leads to elimination of the diastolic interval in atria, but not ventricles, thus reducing the rate of dissociation of sodium blockers from the channel; and (5) Recovery from inactivation of the sodium channel is slower in atrial cells.[36]

It is noteworthy that I_{Na} density is much greater in atrial versus ventricular cells.[20,36] The higher density of I_{Na} in atrial cells[20,36] may offset the lower availability of sodium channels in atrial versus ventricular cells. Time constants for sodium channel activation and inactivation are also twice as rapid in atrial as in ventricular myocytes,[36] indicating that the total open time of the sodium channels during each action potential should be shorter in atrial cells.

The promise of selective ion channel block for the management of AF is attractive in theory; however, clinical experience and experimental evidence suggest that mixed ion channel blockers, such as amiodarone, are generally more effective. Clinical data indicate that relatively pure I_{Na} blockers, such as lidocaine or mexiletine (Class IB agents), which have rapid binding/unbinding kinetics, are not very effective in suppressing AF.[1] All clinically effective anti-AF Class I agents inhibit multiple currents (such as I_{Kr}, I_{Ks}, I_{to}, etc.) and have relatively slow binding/unbinding kinetics from the sodium channel (e.g., flecainide or propafenone, Class IC; and quinidine, Class IA).

Ranolazine, propafenone, and chronic amiodarone are effective in suppression of acetylcholine (ACh)-mediated canine isolated coronary-perfused right atria.[20,21,24] Figure 6 shows an example of the effect of ranolazine to suppress AF in two experimental models. A major difference between ranolazine and propafenone is that at clinically relevant concentrations, which effectively suppress AF (10.0 and 1.5 μM, respectively), ventricular electrophysiologic parameters are strongly affected by propafenone, but not ranolazine. Ranolazine has been also shown to potently suppress isoproterenol-mediated AF associated with ischemia and reperfusion in canine isolated right atria.[20] Chronic amiodarone (40 mg/kg/day for 6 weeks) prevents ACh-mediated AF, while causing moderate electrophysiologic changes in canine isolated coronary-perfused left ventricular preparations.[21] The antiarrhythmic efficacy of lidocaine (at 21 μM, also a clinically relevant concentration) in this ACh-mediated AF model is relatively poor and its electrophysiologic effects in the ventricles are much greater than those of ranolazine.[20]

The actions of ranolazine to suppress AF in experimental models is consistent with the results of the MERLIN-TIMI 36 clinical study, in which ranolazine treatment was associated with reduced incidence of supraventricular arrhythmias and a 30% reduction in new onset AF in patients with non-ST segment elevation acute coronary syndrome.[39] In a recent single-center study, ranolazine was effective in maintaining sinus rhythm in a cohort of AF patients (most of them with structural heart diseases) in whom more established AADs had failed.[40]

Ranolazine and amiodarone both demonstrate antiarrhythmic efficacy and have a low proarrhythmic potential in the ventricles, likely due to their ability to significantly block late I_{Na}.[41,42]

Conclusion

Experimental and clinical evidence suggests that atrial-selective sodium channel blockers may offer a safe and effective strategy for the management of AF. These agents, including ranolazine and amiodarone, are effective in suppressing AF and preventing its reinduction, without the risk of VT/VF or TdP. Two principal factors contributing to atrial selectivity appear to be (1) rapid dissociation of the drug from the sodium channels and (2) atrial APD prolongation secondary to inhibition of I_{Kr}, I_{Kur}, and/or Ito. These data suggest that additional studies specifically designed to evaluate atrial-selective sodium channel blockers for the management of AF are warranted.

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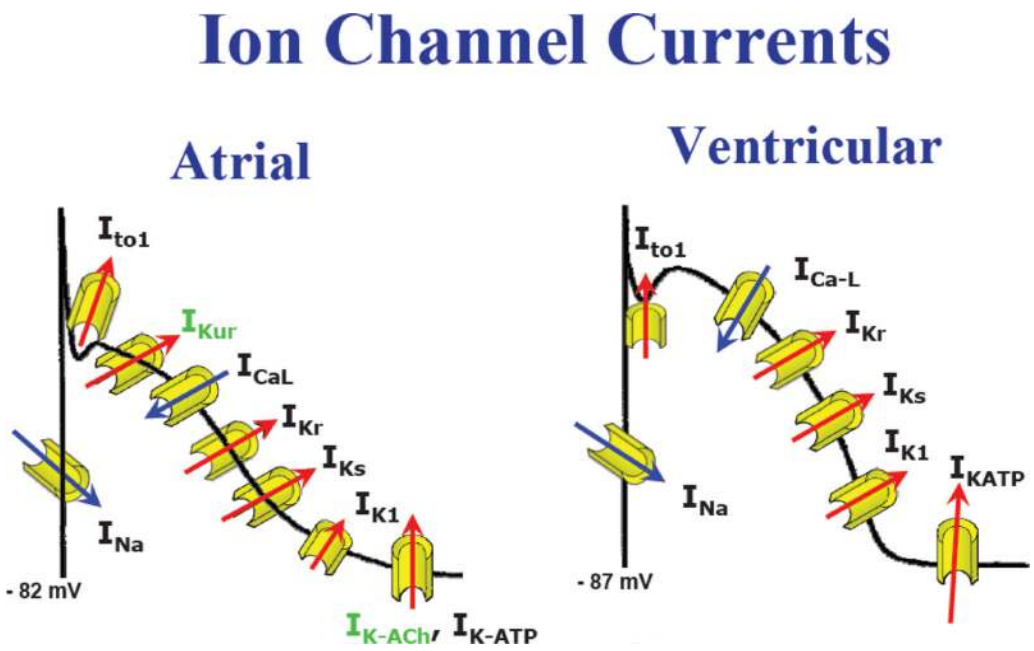

Figure 1.

Ion channel differences between atrial and ventricular action potentials. The normal action potential in atria differs from that of the ventricle with respect to ion channel currents that contribute to resting membrane potential (RMP), phase 1, and phase 3 of the action potential. RMP in atria is more depolarized than in the atrial on account of a smaller I_{K1}. Phase 1 is more prominent in atria due to the presence of a prominent I_{to} and I_{Kur}. Both I_{Kur} and $I_{K–ACh}$ are exclusive to atria. Phase 3 of the action potential is much slower to repolarize in atria because of weaker repolarizing currents I_{Kr}, I_{Ks}, and I_{K1}.

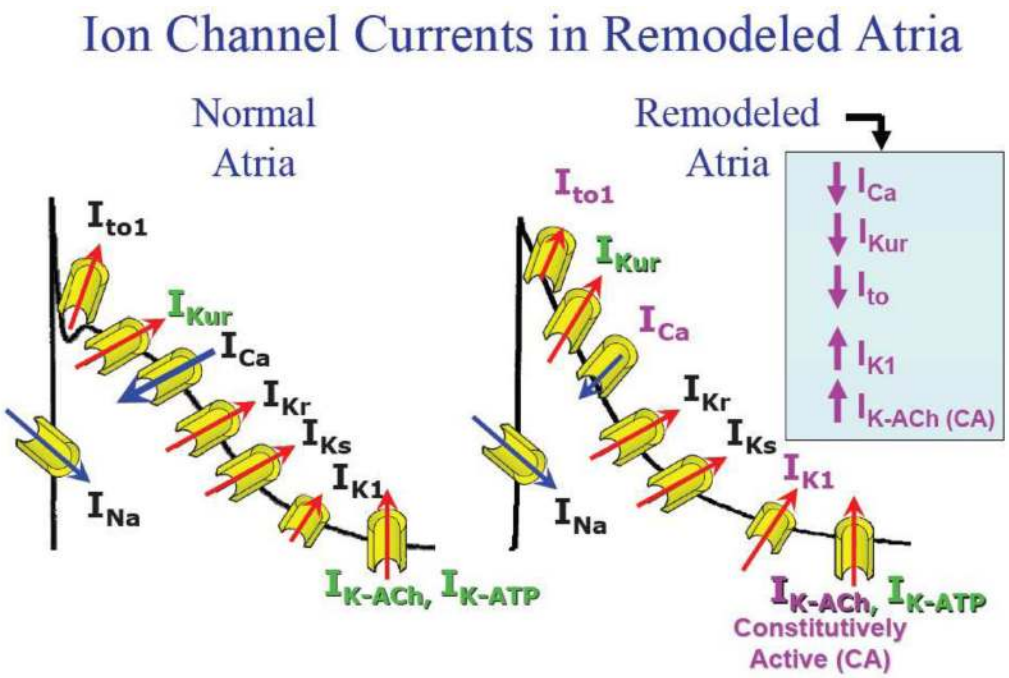

Figure 2.

Ion channel currents in remodeled atria. Electrical remodeling of the atrial action potential. Rapid activation of the atria during AF results in a decrease in I_{Ca}, I_{Kur}, and I_{to}, but to an increase in I_{K1} and constitutively active $I_{K–ACh}$. The abbreviation of action potential duration is due principally to the decrease in I_{Ca} and the increase in I_{K1} and constitutively active - $I_{K–ACh}$.

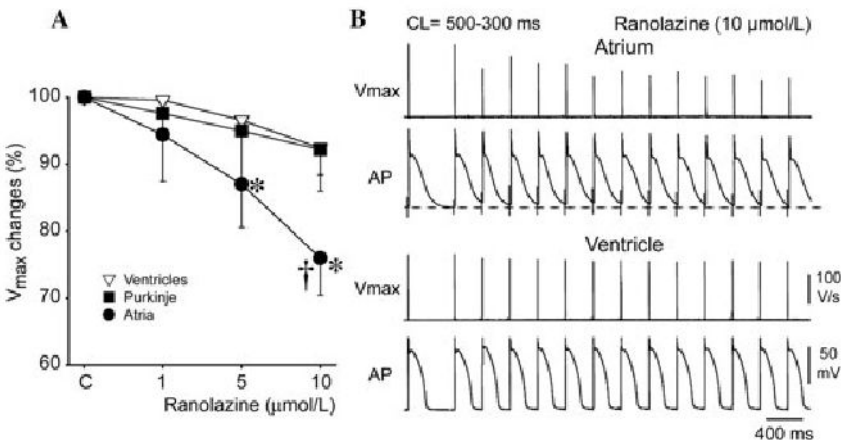

Figure 3.

Atrial-selective depression of maximal action potential upstroke velocity (V_{max}) by ranolazine. Ranolazine produces a much greater rate-dependent inhibition of the maximal V_{max} in atria than in ventricles. (A) Normalized changes in V_{max} of atrial and ventricular cardiac preparations paced at a cycle length (CL) of 500 ms. (C) Ranolazine prolongs late repolarization in atria, but not ventricles and acceleration of rate leads to elimination of the diastolic interval, resulting in a more positive take-off potential in atrium and contributing to atrial selectivity of ranolazine. The diastolic interval remains relatively long in ventricles. *$P < 0.05$ versus control. † $P < 0.05$ from respective values of M cell and Purkinje ($n = 7–21$). (From Burashnikov *et al.* [20] Reproduced by permission.)

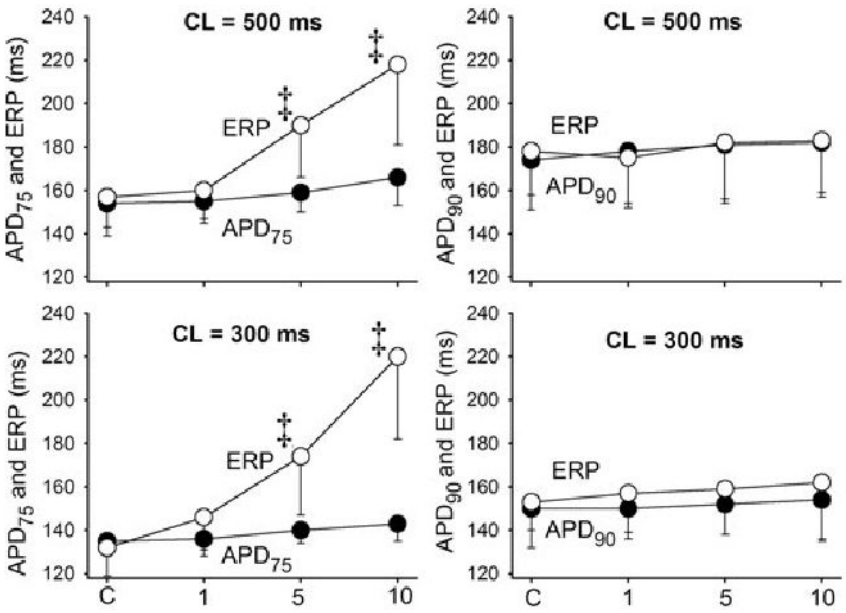

Figure 4.

Atrial-selective development of post-repolarization refractoriness after exposure to ranolazine. Ranolazine-induced prolongation of effective refractory period (ERP) is much greater than prolongation of action potential duration (APD), resulting in the development of post-repolarization refractoriness in atria (PRR) but not ventricles. PRR is defined as the difference between ERP and APD_{75} in atria and between ERP and APD_{90} in the ventricles; ERP corresponds to APD_{75} in atria and APD_{90} in ventricles). *$P < 0.05$ versus control. ‡ = $P < 0.05$ versus APD_{75} values in atria and APD_{90} in ventricles; ($n = 5–18$). (From Burashnikov *et al.* [20] Reproduced by permission.)

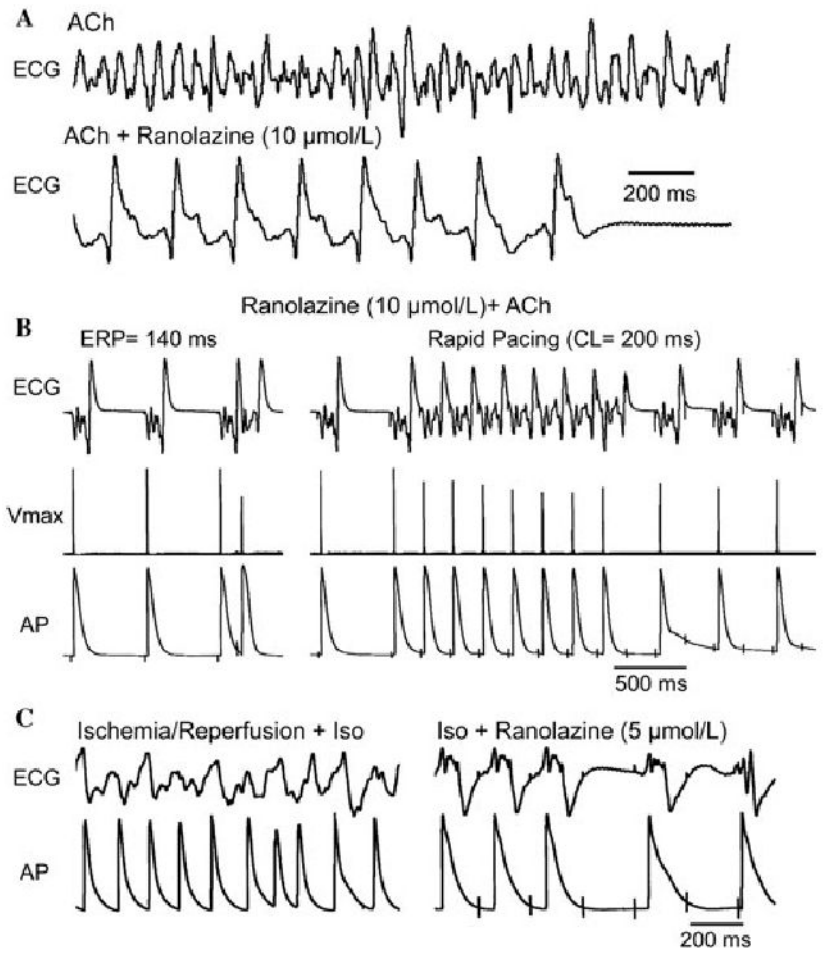

Figure 5.

Ranolazine suppresses AF and/or prevents its induction in two experimental models involving isolated arterially perfused right atria at concentrations producing little to no effects in ventricles. Persistent acetylcholine (ACh)-mediated AF (A) and isoproterenol (Iso)- induced AF (C) are suppressed by ranolazine. In both models, ranolazine causes prominent use-dependent reduction of excitability and induction of PRR. (From Burashnikov *et al.*[20] Reproduced by permission.)

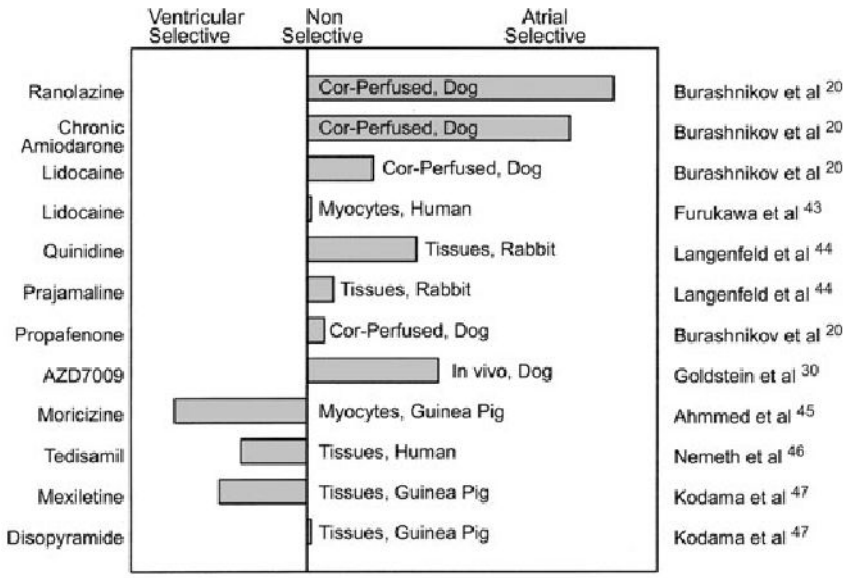

Figure 6.

Sodium channel block. A semi-quantitative assessment of atrial selectivity of I_{Na} blockers based on studies conducted in atrial and ventricular coronary-perfused (Cor-perfused) and superfused (Tissues) preparations, isolated myocytes, and *in vivo*. (From Burashnikov and Antzelevitch.[23] Reproduced by permission.)