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Mini-Review

Problems with class 3 antiarrhythmic agents: Conclusions of the past - perspectives of the future

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ABSTRACT

The majority of the currently used antiarrhythmic drugs carry serious proarrhythmic risk at the same time. Regarding class 3 agents, their torsadogenic action, which is associated with the reverse rate-dependent mode of action of these drugs, is the most serious side-effect. This mini-review provides a mass of evidence suggesting that the reverse rate-dependent nature of class 3 antiarrhythmic drug-effects is a common feature of all cardioactive agents in human cardiac tissues, consequently, development of selective blockers of the rapid delayed rectifier K^+ current (I_{Kr}) without reverse rate-dependent properties has little chance to succeed. A more promising approach might be to combine prolongation of action potential duration with interventions suitable to minimize arrhythmogenesis at slow heart rates. This can likely be achieved by combining K^+ channel blocking drugs with blockers of plateau inward currents, such as L-type Ca^{2+} current and window Na^+ current. This view is supported by the results obtained by either combining two distinct molecules, or by applying single drugs having intrinsically combined modes of action.

KEYWORDS: action potential duration, class 3 antiarrhythmic drugs, combination therapy, human myocardium, membrane current, reverse rate-dependency, ventricular repolarization

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INTRODUCTION

Development of more and more effective antiarrhythmic agents has been in the focus of interest of drug research during the last four decades. The ideal omnipotent compound, however, has not been shown up so far. The currently applied antiarrhythmic strategies largely follow the classic scheme of Vaughan Williams [1], which has been modified several times since its first publication [2, 3]. According to this classification, class 1 drugs suppress action potential upstroke and intraventricular conduction velocity due to inhibition of fast Na^+ channels in a use-dependent manner. Class 2 agents block beta-adrenergic receptors, resulting in reduction of intracellular cAMP level, and consequently, the activity of cAMP-activated ion channels. Class 3 compounds prolong action potential duration, and consequently, the refractory period, decreasing this way the probability of formation of re-entrant circuits. Class 4 drugs are Ca^{2+} channel antagonists reducing Ca^{2+} entry into cardiac cells, which, in turn, improves impulse propagation and helps to prevent the development of triggered activity in Ca^{2+}-loaded myocardium. Each of these antiarrhythmic mechanisms, however, may also carry serious proarrhythmic risks [4]. In the case of class 3 agent, prolongation of action potentials due to K^+ channel blockade may facilitate reactivation of I_{Ca}, and increase Ca^{2+} content of cardiac cells, which mechanisms are responsible for generation of early and late afterdepolarizations, respectively [5, 6]. Unfortunately, these theoretical considerations are supported by results of some clinical trials, like the SWORD study, in which

the class 3 drug d-sotalol has been shown to increase mortality in patients with acute myocardial infarction [7]. The increased mortality observed after application of class 3 agents was clearly due to the reverse rate-dependent torsadogenic action of the compounds. It was, therefore, be concluded that, in spite of the relative efficacy of class 3 drugs a new group of selective class 3 agents, which is devoid of reverse rate-dependence, should be developed [8]. Before discussing why this concept is not feasible, our current knowledge on the reverse rate-dependent nature of class 3 antiarrhythmic drug-effects has to be overviewed.

Reverse rate-dependency

Dofetilide, d-sotalol, E-4031 and several other compounds, which are considered more or less selective blockers of the rapid delayed rectifier K^+ current, are prominent representatives of class 3 antiarrhythmic agents. These drugs display a reverse rate-dependent prolongation of action potential duration (APD), i.e. the drug-induced lengthening of APD is greater at longer than at shorter cycle lengths [9]. This reverse rate-dependent nature of the APD lengthening is undesirable because it minimizes drug effects on repolarization during tachyarrhythmias, while enhances their proarrhythmic potential at normal and even more at slow heart rates [5, 8, 10]. Several hypotheses have been developed so far to explain the mechanism responsible for the reverse rate-dependent action of class 3 antiarrhythmics. Based on results obtained in guinea pig ventricular myocytes, it was first suggested that significant accumulation of I_{Ks} may occur due to the incomplete deactivation of the current at fast heart rates, which would greatly attenuate the APD lengthening effect of I_{Kr} blockade [9]. This theory is strongly opposed by the finding that reverse rate-dependency was evident after full suppression of I_{Ks} as well [11]. Another hypothesis, the modulated receptor theory, was based on the rate-dependent nature of the drug-channel interaction. Drug access to the channel, as well as its binding and unbinding rate constants may depend on the actual channel state [12, 13], which dynamically changes during the cardiac cycle. For instance, reverse rate-dependent prolongation of APD could be expected when drug-binding, and consequently the channel block, develops preferentially during the diastole and dissipation of the drug during the action potential plateau. According to a third hypothesis the effect of I_{Kr} blockers is reduced, and consequently the drug-induced prolongation of APD becomes diminished, at fast heart rates due to the potassium accumulation in the sarcolemmal clefts. This theory was based on observations showing that I_{Kr} blockade by quinidine and dofetilide was attenuated when extracellular potassium concentration was elevated [14]. Finally, rate-dependent changes in action potential morphology were also claimed to contribute to the reverse rate-dependency in various mammalian preparations by controlling the kinetic properties of I_{Kr} and I_{K1} during ventricular repolarization in a way potentially contributing to reverse rate-dependency [15, 16]. The multitude of theories developed in the past to explain reverse rate-dependency indicates that its exact mechanism has not been fully elucidated.

Reverse rate-dependency is not restricted to class 3 antiarrhythmic agents

In recent studies, performed in multicellular and single-cell cardiac preparations obtained from human, canine, and guinea-pig hearts, it has been clearly demonstrated that many drugs that are known to lengthen APD independently of I_{Kr} blockade, like the I_{to} blocker 4-aminopyridine [17], the I_{Ks} inhibitor chromanol 293B [18], the non-selective K^+ channel blocker tetra-ethylammonium [17], the I_{Ca} activator BAY K 8644 [19], or the I_{Na} activator veratridine [19], also exert reverse rate-dependent actions on APD. In other words, the phenomenon of reverse rate-dependency is not restricted to I_{Kr} blockade, but can be observed with several drugs that lengthen APD independently of the underlying ionic mechanism. Due to the wide diversity of these agents, the modulated receptor theory is not likely to explain the phenomenon of reverse rate-dependency. More importantly, it has turned out also that not only the lengthening, but also the drug-induced shortening of APD is reversely rate-dependent, as it was shown with the I_{Na} blocker lidocaine [19], mexiletine [20], articaine [21], ropivacaine [22], tetrodotoxin [20], as well as with the ATP-sensitive K^+ channel opener nicorandil [19] and lemakalim [20]. Here again, another group of

agents with very diverse chemical structures and targets were shown to display actions of reverse rate-dependent nature. In these experiments the lengthening or shortening of APD increased monotonically with increasing the cycle length of stimulation, independently of the drug applied and the ion channel activated or blocked. This reversely rate-dependent modulation of APD was equally observed if the change in APD was expressed in absolute values or in a percentage form [19]. At this point one might conclude that the reverse rate-dependent nature of drug-action in the heart is a general property of mammalian cardiac tissues, independent of the species or preparation used, of the ion channel modified, or the direction of the resultant change in APD. In the followings we examine whether really is that the case.

Magnitude of drug-induced APD changes depends on the initial value of APD

Human, canine and guinea pig cardiac preparations display a monotonic APD-frequency relationship, i.e. APD monotonically increases with increasing the cycle length of stimulation. In contrast, APD displays a non-monotonic dependency on the cycle length in rabbits: the maximal value of APD is achieved at an intermediate cycle length between 0.5 and 0.7 s [23]. This provides a unique opportunity to discriminate between rate-dependency and APD-dependency of drug-induced APD changes. In this case, sotalol and lemakalim were used to prolong and shorten APD, respectively [20]. As expected, sotalol lengthened and lemakalim shortened APD in rabbit papillary muscles at all frequencies. However, in contrast to results obtained in canine, human, and guinea pig preparations, where the APD lengthening and shortening effects displayed monotonic reverse rate-dependency, the maximal drug-induced APD changes in rabbit preparations occurred at the intermediate cycle length of 0.5-0.7 s, at which the baseline APD was the longest [20]. According to this result, the magnitude of a drug-effect seems to depend on the duration of the baseline (pre-drug) action potential, rather than on the pacing rate, suggesting that longer action potentials are more sensitive to modulation than shorter ones, irrespective of the actual pacing rate. This hypothesis was examined by studying the frequency-dependent properties of actions of various K^+ and Ca^{2+} channel inhibitors on APD during the electrical restitution process of rat ventricular muscle. This preparation has a set of ion currents markedly different from those of all other species, and consequently, its APD is shorter by one order of magnitude than that of the plateau-forming larger mammals [24, 25]. Most importantly, rat ventricular APD increases at higher heart rates, displaying negative APD-cycle length relationship, opposite to many other species [26, 27]. The APD lengthening effect of the K^+ channel blocker 4-aminopyridine and tetraethylammonium, as well as the APD shortening effect of the Ca^{2+} channel blocker nifedipine and $MnCl_2$ [28] were studied in rat as a function of the diastolic interval, a parameter indicating the proximity of two consecutive action potentials. As could be expected from the negative APD-cycle length relationship, all drug-induced APD changes were largely inversely proportional with the diastolic interval in rat [17]. This result is very different from that previously seen in canine, guinea pig, and human preparations, where the drug-induced changes were directly related to cycle length. However, when these drug-induced APD changes were studied as a function of the baseline APD, the larger drug effect was observed with the longer baseline action potential in all mammalian species. This indicates that dependency of APD on cycle length or diastolic interval and modulation of APD by drugs are tightly coupled, since cycle length and diastolic interval act as the modulator of APD itself, while this latter may directly determine the magnitude of drug-induced changes independently of the pacing cycle length or diastolic interval applied.

Reverse rate-dependent APD changes induced by current injection

When studying the effect of an ion channel activator or blocker agent on action potential configuration, it can be considered as if we have added or removed an inward or outward current to/from the net membrane current flowing during the action potential plateau. In experiments performed in enzymatically isolated canine ventricular myocytes, impaled with sharp microelectrodes, inward and outward current pulses were injected into the myocytes in order to lengthen or shorten APD,

respectively [19, 20]. These measurements were performed at various pacing cycle lengths changing between 0.3 and 5 s. The effect of a current injection on APD was reversely rate-dependent in both cases. Furthermore, the changes in APD induced by the inward and outward current pulses were linearly proportional to baseline APD values, measured prior to current injection [19, 20]. Plots generated this way were almost indistinguishable from those obtained with some ion channel agonist or antagonist, indicating that the magnitude of APD modification is exclusively a function of the baseline APD, and independent of the source of current, the gating kinetics and profiles of the ion current involved, or properties of the drug applied [19, 20]. This point was further demonstrated in another set of experiments by showing the reversal of the $BaCl_2$-induced prolongation of APD by applying an injection of an outward current pulse as a function of the stimulation frequency. The $BaCl_2$-induced prolongation of APD was completely offset at all cycle lengths by the concomitant injection of the same amount of current [19]. APD lengthening by $BaCl_2$ is the consequence of I_{K1} blockade. Since, neither I_{K1}, nor its inhibition by $BaCl_2$ are significantly rate-dependent, the resulting APD prolongation could be exclusively influenced by the baseline value of APD, which, in turn, was determined by the pacing cycle length. Similarly, APD modifications induced by abrupt changes in the cycle length could be fully compensated by injections of current pulses having appropriate amplitude [19].

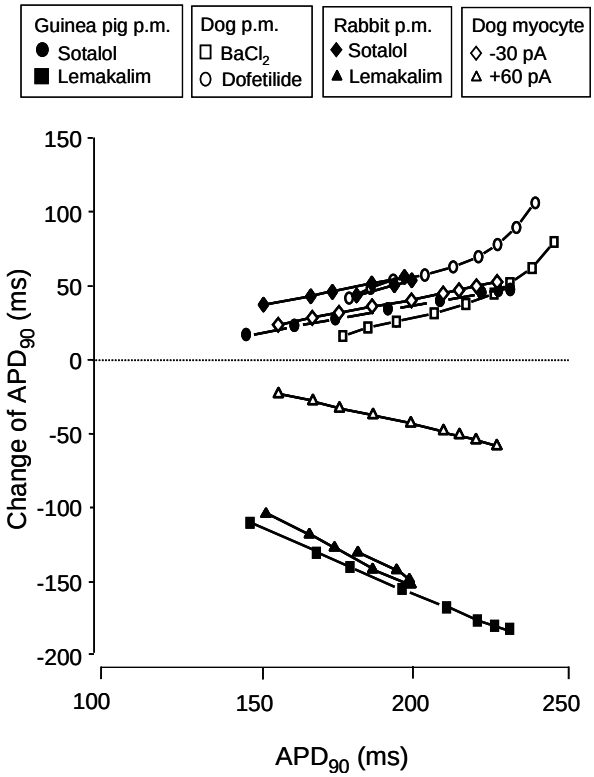

Fig. 1. Drug-induced and current-induced changes in action potential duration, plotted against baseline (pre-drug) APD values. Pharmacological experiments were performed in papillary muscle preparations of dogs, rabbits and guinea pigs, current pulses were injected into single canine ventricular myocytes. Error bars are ignored for the sake of clarity.

Mechanism of the reverse rate-dependency

If the magnitude of an APD change of any kind of origin is in fact proportional to the baseline value of APD, as it is shown in Fig. 1, it must somehow be related to the change in the net membrane current (I_{net}) flowing during the action potential plateau. I_{net} can be determined from the slope of the membrane potential change at any point of the action potential. The assumption that APD modulation reflects a change in I_{net}, independently of the specific current affected, was verified by plotting I_{net} against baseline APD under a variety of experimental conditions: at various pacing cycle lengths, before and after applying ion channel blockers or activators, and in the presence or absence of inward or outward current pulses [19, 20]. Two examples to constancy of the I_{net}-APD relationship are demonstrated in Fig. 2, where the results of two distinct experiments are summarized. Both were performed in isolated canine ventricular myocytes paced at a variety of cycle length ranging between 0.3 and 5 s. In one experiment the cells were exposed to $BaCl_2$, while in the other one constant inward and outward current pulses were delivered during the action potential to lengthen or shorten APD. The I_{net}-APD relationship followed a hyperbolic function in both cases. The overlap of data points obtained from the two different experiments strongly suggest a common origin, which was supported by fitting all data to one single hyperbolic curve. In conclusion, the reverse rate-dependency of drug-effects may be a pure consequence of the reverse

rate-dependent behavior of APD itself, namely because APD is greater at longer than at shorter cycle lengths in the majority of larger mammals including human ventricular myocardium. In this case the explanation for the reverse rate-dependency seems to be quite mechanistic. Since I_{net} flowing during the plateau is smaller in the case of a longer than a shorter action potential, any given current added to or removed from the system (either as a current pulse, or due to a pharmacological intervention) is expected to cause a relatively larger displacement of I_{net} when the magnitude of I_{net} is originally smaller. Consequently, a greater change in APD can be observed in the case of a longer baseline action potential. It appears, therefore, that the reverse rate-dependent nature of drug-action is a genuine intrinsic property of human cardiac tissues.

Then what to do with class 3 agents?

A crucially important implication of the above results is that further development of selective I_{Kr} blocker drugs, as potential class 3 antiarrhytmic agents, are not likely to be successful. Development of I_{Kr} blockers with suitable features may at best reduce reverse rate-dependency of APD modulation, because intrinsic reverse rate-dependency needs to be offset or at least minimized. Thus, prolongation of APD with direct rate-dependency, although clinically desirable as an antiarrhythmic intervention, may be difficult to attain with any of the currently used selective I_{Kr} blocker compound. Another implication of the above results is that not only drug-induced APD lengthening, but also the shortening of APD displays a reverse rate-dependent character. As a consequence, the reverse rate-dependent APD lengthening effect of class 3 antiarrhythmics can be compensated by concomitant blockade of plateau inward currents, such as I_{Ca} or window I_{Na} [29, 30]. According to the results discussed below this may be a promising approach to minimize the proarrhythmic potential of I_{Kr} blockers being more evident at slow heart rates.

Class 3+1 combination

Since several years ago efforts have been made to attenuate or at least minimize the proarrhythmic potential of class 3 agents by co-administration of class 1.B antiarrhythmics. Sotalol was combined

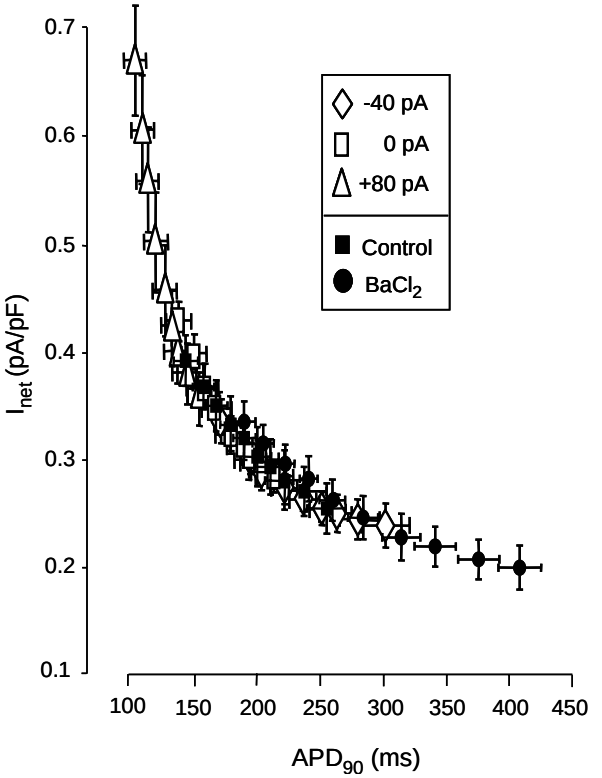

Fig. 2. Reciprocal relationship between action potential duration (APD_{90}) and the magnitude of net membrane current (I_{net}) determined from the slope of repolarization at half-duration of APD. Data were obtained in enzymatically isolated canine ventricular cells.

with lidocaine [31], mexiletine [32, 33, 34], and tocainide [35] in a variety of mammalian cardiac tissues. As could be expected, sotalol lengthened while class 1.B agents alone shortened APD - both in a reverse rate-dependent manner. When the two drugs were properly combined, the APD-cycle length relationship remained largely unchanged, i.e. the reverse rate-dependent APD prolongation could be prevented, while a markedly increased refractoriness was preserved. In addition, these combinations attenuated early premature beats and decreased the risk of complex ventricular arrhythmias very effectively and selectively due to the fast offset kinetics of the 1.B drugs applied. Most importantly, the duration of these early prematures was lengthened by the combination to values close to obtained with sotalol alone. At longer diastolic intervals (above 100 ms in the case of lidocaine) the APD lengthening effect was not any more evident [31]. Of course, the net

effect on APD depends on the relative concentrations of the ingredients, but at any rate, the observed APD changes display less reverse rate-dependency, or the phenomenon may be even be fully eliminated. These results lead to development of chemical structures intrinsically combining class 1 and class 3 effects, such as the compound GYKI 16638 [36, 37]. This molecule was shown to lengthen APD without reverse rate-dependency and suppress maximal velocity of depolarization with fast offset kinetics [36]. Interestingly, its chemical structure is largely different from that of amiodarone, which also shares class 1 and class 3 properties in case of chronic administration [38].

Class 3+4 combination

Another inward current contributing to the EAD-based torsadogenic effects of pure I_{Kr} blockers (such as dofetilide, E-4031, or d-sotalol) is the L-type Ca^{2+} current. Ca^{2+} channels were shown to reopen during EADs [39, 40] thus Ca^{2+} as a charge carrier plays an important role in generation of EADs. Accordingly, enhanced activation of I_{Ca} lengthens, while calcium channel blockers shorten APD and depress the plateau. Combination of verapamil or nitrendipine with E-4031 significantly reduced the reverse rate-dependent nature of APD prolongation in isolated guinea pig papillary muscles [41]. Furthermore, the reverse rate-dependency was also reduced by co-application of ryanodine with E-4031 [41]. Since ryanodine suppress sarcoplasmic reticular Ca^{2+} release without decreasing the transmembrane Ca^{2+} entry, it was concluded that elevation of cytosolic Ca^{2+} may also be involved in the torsadogenic action of class 3 antiarrhythmics. Indeed, combination of E-4031 with verapamil decreased the proarrhythmic risk of E-4031 significantly in canine and rabbit *in vivo* experiments [42]. It appears that limitation of both transmembrane Ca^{2+} entry as well as the magnitude of cytosolic Ca^{2+} transients are important components of the anti-torsadogenic action of Ca^{2+} channel blockers. Based on these theoretical backgrounds, novel compounds displaying combined class 3 and class 4 activities have been developed. The classical lead molecule was BRL-32872 [42, 43, 44], which was followed by several substituted derivatives [45]. BRL-32872 displays a biphasic concentration-dependent effect on APD: action potentials are lengthened by low, while shortened by higher concentrations of the drug [43, 44, 45]. This is in line with IC_{50} values of 28 nM and 2.8 μM, obtained in voltage clamp experiments for I_{Kr} and I_{Ca}, respectively [43].

Class 3+4+1 combination

Another compound, EGIS-7229 was also shown to exert combined antiarrhythmic activity. EGIS-7229 blocked I_{Kr} at micromolar and I_{Ca} at somewhat higher concentrations in canine ventricular cardiomyocytes [46]. Similarly to BRL-32872, EGIS-7229 displayed a bell-shaped dose-response curve when its effect on APD was studied [47]. Since the maximal velocity of depolarization was markedly suppressed by EGIS-7229, combined class 3+4+1 effects within one molecule were claimed [47, 48]. This is congruent with results of *in vitro* and *in vivo* experiments demonstrating that the enhancement of refractoriness was greater with EGIS-7229 than with sotalol in the case of identical APD lengthening [49]. As a result, the torsadogenic effect of EGIS-7229 was apparently absent - in contrast, the drug was capable of effectively suppressing cesium-induced EADs in rabbit papillary muscle preparations [50].

FURTHER POSSIBILITIES

Class 3 antiarrhythmic effects - at least theoretically - are not restricted to I_{Kr} blockade. In contrast, action potential can be lengthened by suppression of other K^+ currents, like the slow delayed rectifier K^+ current (I_{Ks}), transient outward K^+ current (I_{to}), inward rectifier K^+ current (I_{K1}), and the ATP-sensitive K^+ current ($I_{K\text{-}ATP}$) [51]. Pharmacological blockade of I_{Ks} was shown to be harmful, since this current may be an important constituent of the repolarization reserve [52, 53, 54]. Regarding the other K^+ currents, no selective inhibitor has been recognized so far [51]. In addition, their class 3 effects are likely to be complicated by reverse rate-dependent properties, similarly to those of the conventional I_{Kr} blocker class 3 drugs. There is, however, another potential direction of application of certain K^+ channel blockers: they can effectively be used against atrial fibrillation [51]. This possibility arises because some atrial K^+ currents, such as the ultra rapid delayed rectifier K^+ current (I_{Kur}) and the acetylcholine-activated K^+ current

($I_{K\text{-}Ach}$) are abundantly present in atrial - but not in ventricular myocardium. Although absolute selective blockers of these currents are not available at present, I_{Kur} is believed to be quite sensitive to 4-aminopyridine [55, 56] and quinidine [57]. Similarly, $I_{K\text{-}Ach}$ can be suppressed - although not selectively - by some amidarone-derivatives as well as quinidine [58, 59]. Although these results are promising, further research is necessary to develop selective blockers of atrial K^+ currents.

ABBREVIATIONS

APD : action potential duration
EAD : early afterdepolarization
I_{net} : net membrane current
I_{Kr} : rapid delayed rectifier K^+ current
I_{Kur} : ultra rapid delayed rectifier K^+ current
I_{Ks} : slow delayed rectifier K^+ current
I_{K1} : inward rectifier K^+ current
I_{to} : transient outward K^+ current
$I_{K\text{-}ATP}$: ATP-sensitive K^+ current
$I_{K\text{-}Ach}$: acetylcholine-activated K^+ current
I_{Ca} : L-type Ca^{2+} current
I_{Na} : Na^+ current

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