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COMMENTARY

Is there a functional correlate of Kv1.5 in the ventricle of canine heart and what would it mean for the use of I_{Kur} blockers?

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The cardiac ultrarapid outward current I_{Kur}, encoded by KCNA5, is of special pharmacological interest, because it is considered to be atrium-specific. I_{Kur} has therefore become a target in the therapy of atrial tachyarrhythmias. However, the concept of atrium specificity is only valid if a functional I_{Kur} current is in fact absent from the ventricle. However, new work has detected a I_{Kur}-like current in canine ventricular myocytes, sensitive to 4-aminopyridine and suppressed by the I_{Kur} blocker DPO-1, findings that support the existence of a functional ventricular I_{Kur}. These indications are, however, indirect and more effort is needed to clarify unequivocally the putative role of an expectedly small I_{Kur} component in the ventricle.
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Abbreviations: AVE0118, I_{Kur}-blocker (2′-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide); DPO-1, I_{Kur}-blocker 2-isopropyl-5-methylcyclohexyl) diphenylphosphine oxide

The cardiac ultrarapid potassium outward current I_{Kur} encoded by Kv1.5 (KCNA5), which is the gene for the pore-forming α-subunit of I_{Kur}, has gained considerable interest during the last years. Since I_{Kur} is a prominent current in atrial myocytes of the mammalian heart including man, but not in ventricular tissue, it was regarded as a putative 'atrial selective' target for treatment of atrial fibrillation (Ehrlich *et al*., 2007) and several I_{Kur} blockers have been synthesized during the past 10 years (Lagrutta *et al*., 2006). The idea was that block of I_{Kur} should prolong atrial action potential duration and effective refractory period without pro-arrhythmic effects on the ventricle. Several of these drugs, for instance AVE0118 (I_{Kur}-blocker(2′-{[2-(4-methoxy-phenyl)-acetylamino]-methyl}-biphenyl-2-carboxylic acid (2-pyridin-3-yl-ethyl)-amide) (Blaauw *et al*., 2004) and DPO-1 (I_{Kur}-blocker 2-isopropyl-5-methylcyclohexyl)diphenylphosphine oxide) (Stump *et al*., 2005), have been shown to inhibit effectively I_{Kur}, to prolong action potential duration and to convert atrial fibrillation (goat, pig) or flutter (dog). This concept of regional drug specificity is only valid if I_{Kur} is definitely absent in ventricle. In most mammals I_{Kur}-like outward currents have not been detected in ventricular myocytes with exception of small rodents that exhibit a well-defined current component attributed to I_{Kur} (Nerbonne, 2000). More than 15 years ago, Tamkun *et al*. (1991) and Mays *et al*. (1995) detected the Kv1.5 both as messenger RNA and protein, although at much lower level than in atrial tissue; these findings have been confirmed in healthy human (Gaborit *et al*., 2007) and dog heart (Fedida *et al*., 2003). However, no functional correlate has been identified until now, and Fedida *et al*. (2003) commented that 'the electrophysiological role of Kv1.5 expressed in the ventricle remains to be clarified'. Therefore, the question arises whether any non-identified functional I_{Kur} channels exist in the human ventricle. If so, do we have to revise the concept of an atrium-specific pharmacotherapy based on I_{Kur} blockade?

It is difficult unequivocally to separate I_{Kur} from total membrane outward currents even in myocytes with a large I_{Kur} as in human atrial myocytes (Amos *et al*., 1996). Because of its ultrarapid activation, I_{Kur} contributes during the very early phase of atrial repolarization, where the other major player, the transient outward current I_{to}, is also active. In addition, I_{Kur} is not the 'sustained' outward current it was initially taken for (Amos *et al*., 1996; Wettwer *et al*., 2004), since, especially at physiological temperature, I_{Kur} displays extensive inactivation. In addition, there are no truly specific drugs available. 4-Aminopyridine, in low concentrations, discriminates fairly well between I_{Kur} ($IC_{50} \sim 10\,\mu M$) and I_{to} ($IC_{50} \sim 1\,mM$) (Amos *et al*., 1996). Further complications arise from interactions of the Kv1.5

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channel with Kvβ subunits that modulate current kinetics from slow to fast inactivation (Uebele *et al.*, 1998). Two current components that activate and inactivate with overlapping time courses can be separated by several methods. Specific knock-out with siRNA would be ideal but is yet not feasible in human native myocytes. Another approach utilizes the 4-aminopyridine selectivity of I_{Kur} as reported by Sridhar *et al.* (2007, this issue). With low concentrations of 4-aminopyridine (50 and 100 μM), the authors demonstrate a reversible prolongation of action potential duration in isolated canine ventricular myocytes without effects on the rapid potassium outward current (I_{Kr}) and I_{to}. In addition, action potential prolonging effects can also be elicited with DPO-1, a selective I_{Kur} blocker (Stump *et al.*, 2005). The 4-aminopyridine sensitive current ($IC_{50} = 24\ \mu M$) was, however, very small, the current density at $+50$ mV was 0.5 pA pF^{-1} compared to 10 pA pF^{-1} of total outward current in human atrial myocytes (Amos *et al.*, 1996). It should be kept in mind, however, that it is the *relative* magnitude of I_{Kur} current with respect to other components that determines the influence on the action potential plateau and action potential duration. In his pioneering cardiac electrophysiological experiments, Weidmann (1951) described the very low conductance during the plateau of the action potential and therefore only small currents are necessary for regulation of plateau duration. Model simulations performed by Sridhar *et al.* (2007) support the action potential prolonging effects by blocking the small 4-aminopyridine sensitive current component denoted 'I_{Kur}-like'. These results could have implications for the therapeutic use of I_{Kur} blockers and may require more caution concerning possible arrhythmogenic effects of I_{Kur} blockers in the ventricle. Action potential- and QT-prolonging effects have not been detected so far for AVE0118 (Schotten *et al.*, 2007) or DPO-1 (Lagrutta *et al.*, 2006). Knock-down experiments with antisense oligonucleotides directed against Kv1.5 did not uncover any sensitive current component in human ventricular myocytes (Feng *et al.*, 1997). Nevertheless, there are indications that I_{Kur} may indeed contribute to the ventricular action potential plateau. Lagrutta *et al.*, 2006 (figure 8) show elevation of the action potential plateau in the presence of DPO-1. In addition, it is possible that the I_{Kur} channels, largely localized in the intercalated disk (Mays *et al.*, 1995), are redistributed under pathological conditions due to highly dynamic trafficking (McEwen *et al.*, 2007). This could result in an increased surface expression and function. In a recent study (Oros *et al.*, 2006) of the pro- and anti-arrhythmic effects of AVE0118 in anaesthetized dogs, 3 out of 5 animals died unexpectedly within 24 h after slow infusion with AVE0118 followed by a challenge with dofetilide to provoke torsade de pointe arrhythmias. It is quite possible that torsade de pointe arrhythmias was promoted due to block of ventricular I_{Kur}. In addition, under conditions of increased sympathetic tone, I_{Kur} could have an larger impact on ventricular repolarization (Yue *et al.*, 1999). In conclusion, the presence or absence of I_{Kur} in ventricular tissue needs further experimental investigation, especially in human myocardium. Irrespective of the results, they will have major implications for the development of new anti-arrhythmic drugs.

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Conflict of interest

The author states no conflict of interest.

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