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Molecular Cloning and Characterization of Potassium Channels (cKv1.2, cKv1.4, CERG and cKVLQT1) from Canine Myocardium

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Cardiac arrhythmias are a common cause of morbidity and mortality, accounting for approximately 11% of all natural deaths. In general, presymptomatic diagnosis and treatment of individuals with life-threatening ventricular tachyarrhythmias is poor, and in some cases medical management actually increases the risk of arrhythmias and death. These factors make early detection of individuals at risk for cardiac arrhythmias and arrhythmia prevention high priorities. Most recently, it is shown that both genetic and acquired factors contribute to the risk of developing cardiac arrhythmias. The application of techniques of contemporary human molecular genetics has resulted in the cloning of new potassium channel genes and finding mutations in these genes, which further increases the understanding of the genesis of normal and abnormal cardiac rhythms. Only a few data are published about alterations of ion channel expression and function in myocardium with diseases like heart failure or hypertrophy.

In this work here, four dinstinct potassium channel cDNAs were isolated, cloned and characterized from canine myocardium to obtain information about these canine specific ion channel sequences. Two of these channel sequences (cKv1.2 and CERG) are full-length cDNAs including the start- and stop-codons for the protein coding region. The cKv1.2-cDNA (1,612 kb) and CERG-cDNA (3,740 kb) encode proteins of 499 and 1159 amino acids, respectively. The two other isolated cDNAs are partial clones missing the start-codon in the cKv1.4-channel and the stop-codon in the cKVLQT1 channel, but both encompass the membrane spanning segments S1 to S6 including the pore region. The cKv1.4-cDNA (1.5 kb) and the cKVLQT1-cDNA (1.2 kb) encode protein of 510 and 345 amino acids, respectively. The protein sequences of each isolated channel display a high level of identity among the same gene family in different species (cKv1.2: 98%-99%, cKv1.4: 98%-99%, CERG 95-97%, cKVLQT1: 93%). The highest identity of each channel to its own class is found in

the central regions containing the six putative membrane-spanning domains, while less-conserved domains are present in the NH_2- and COOH- terminal regions. However, at the NH_2-end of cKVLQT1 protein sequence, five amino acids are absent in comparison to the published human sequence. This possibly is a result of a new form of alternative splicing in the KVLQT1 gene, which shows a rich variation in splicing mechanisms. So the cKVLQT1 cDNA presented here is

probably a new isoform, whose functiuonal characteristics must be proven in further expression studies.

The new available sequences from these four isolated potassium channels can be used for creating specific PCR-primers and fragments for expression analysis of these channels in two dog models with different heart diseases. At first, the CERG-RNA expression was investigated with a new modified RT-PCR method. With this technique, it is possible to compare the relative RNA expression of the chosen ”target molecule” (CERG) with an internal standard (S26 ribosomal protein) out of the same RNA sample in one reaction tube. CERG-RNA expression is only found in the heart and brain, but not in lung, liver, pancreas, spleen and skeletal muscle. First results of the CERG expression analysis in canine hearts three weeks after myocardical infarction showed no detectable levels of specific CERG-RNA either in left ventricle of infarcted or in non-infarcted myocardium, interestingly. A remarkably expression gradient of CERG-RNA (midmyocardium > endocardium > epicardium) is found across the left ventricular wall in the second dog heart model with a distinct biventricular hypertrophy six weeks after ablation of the atrioventricular node. These first data about CERG expression in two different pathophysiological canine heart models present possibly new molecular aspects for the up- and down-regulation of gene expression of ion channels in heart deseases. It is conceivable that a changed context of ion channel gene expression contribute finally to the complex origin of cardiac arrhythmias.