Electrophysiological properties of the *hERG* mutation E444K, found in familial atrial fibrillation

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Atrial fibrillation (AF) is a cardiac arrhythmia characterized by rapid and irregular activation of the atria. Until recently, AF was regarded as a sporadic, non-genetic disorder. Although there is now accumulating evidence that familial aggregation of AF occurs in a significant proportion of cases, the extent to which genetic factors are responsible for this familial aggregation is unknown. Identification of single gene mutations in families will provide a framework for elucidation of key molecular and cellular pathways that underlie the more commonly-occurring complex forms of AF. Here we present a novel mutation in hERG (E444K), found in a case of familial AF, and the electrophysiological changes of the mutant channels compared to wildtype (WT) channels. Mutant channels were expressed in transiently transfected Chinese hamster ovary (CHO) cells. Whole-cell voltage-clamp recordings were performed in physiological solutions at room temperature. Under these baseline conditions the steady state half activation voltage of E444K channels was not significantly shifted compared to WT channels, whereas the steady state half inactivation voltage was shifted 10 mV in a hyperpolarizing direction compared to WT channels. Rates of activation, deactivation, and inactivation were not significantly altered compared to WT channels. Due to the left shifted steady state inactivation curve, at a given membrane potential the fraction of inactivated mutant channels will be greater than the fraction of inactivated WT channels at the same potential, ultimately leading to a smaller potassium current through hERG channels at the end of the cardiac action potential. To further assess the effects of the mutated channel on cardiac action potential, E444K transfected CHO cells were voltage-clamped to prerecorded human atrial action potential waveforms for both a normal sinus rhythm as well as an episode of atrial fibrillation. During the AF episode an increase in potassium current was observed in E444K experiments as well as in WT control experiments, with no significant difference between mutant and WT channels. We conclude that at baseline conditions the effect of the E444K mutation is not sufficient to change atrial action potential shapes sufficiently to promote AF.