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Influence of Arg176Trp Missense Mutation onto Cardiac hERG K+ Channel

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The signal transmission between cardiomyocytes is a very strictly regulated system. The mutations on ion channels involved in this system can lead to electrical changes [2]. Among them, long QT syndrome (LQTS) is a serious inherited cardiac disease caused by functional defects of cardiac ion channels. It is characterized by prolonged cardiac repolarization phase, resulting in prolonged QT interval in surface electrocardiogram (ECG). Clinical symptoms include palpitation, syncope, convulsion and even sudden cardiac death [4]. Interestingly, many mutation carriers have no symptoms. LQTS type 2 (LQT2), one of the congenital LQTS subtypes, is caused by a functional defect in the α-subunit of the rapid delayed potassium channel (I_{Kr}), which is encoded by KCNH2 [also known as human ether-a-go-go-related gene (hERG)] [1]. When screening the mutations in the coding region of hERG gene in some LQTS probands in Finland, it was found for the first time that a point mutation (526C>T) caused the N-terminal tryptophan in exon 4 to be replaced by arginine (R176W) [3]. The corresponding amino acid substitution was introduced into the plasmid encoding hERG channel, and the mutant gene was expressed in Chinese hamster ovary cell (CHO-K1) to evaluate the effect of the mutation on I_{Kr} current parameters. The integrated I_{Kr} current was studied using the whole-cell patch clamp technique in voltage clamp mode. The results showed that the c.526C>T (p.Arg176Trp) mutation is implemented according to the loss of function, and significantly changes the function of hERG channel.

References

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