Research on Voltage-Gated Potassium Ion Channels Related to Long QT Syndrome

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Hereditary long QT syndrome (LQTS), with an estimated prevalence of 1:2,000, is among the most prevalent inherited cardiac arrhythmias [1]. LQTS type 1 (LQTS1), the most common subtype, arises from loss-of-function mutations in the KCNQ1 gene, which encodes the pore-forming α-subunit of the slow delayed rectifier potassium channel Kv7.1 [2]. This study functionally characterizes a novel pathogenic missense variant, p.Arg583His (R583H), identified in unrelated LQTS1 patients. The mutation maps to the intracellular C-terminal linker connecting the HC and HD helices-a well-defined structural module essential for high-fidelity recruitment of the scaffolding protein Yotiao (AKAP9)[3,4].

Using whole-cell patch-clamp electrophysiology in CHO-K1 cells co-expressing Kv7.1 (wild-type or R583H), KCNE1, and Yotiao, we demonstrate that R583H induces a robust rightward shift (17–21 mV) in the voltage dependence of I_{Ks} activation, significantly impairing channel opening even under heterozygous expression conditions. Structural modeling confirms that Arg583 resides on the solvent-accessible outer surface of the HC–HD superhelix, positioning it to mediate critical intermolecular contacts with Yotiao. Critically, forskolin-a direct activator of adenylate cyclase-fails to augment I_{Ks} amplitude in R583H-expressing cells to the extent observed in wild-type controls, indicating defective assembly or functional coupling of the Yotiao–PKA signaling complex. Consequently, β-adrenergic stimulation cannot adequately enhance I_{Ks} during sympathetic activation, resulting in impaired repolarization reserve and unopposed action potential prolongation. This molecular mechanism directly accounts for the exercise-triggered QTc prolongation and life-threatening ventricular arrhythmias-including bidirectional ventricular tachycardia and torsades de pointes-observed in R583H carriers.

References

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