

An NMR study of the hERG potassium channel — towards writing the tale of a (bad) drug target

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The long QT syndrome (LQTS) is a cardiac muscle malfunction that prolongs the repolarization interval between Q and T waves on the electrocardiogram. This can lead to ventricular arrhythmia often responsible for heart failure. This syndrome is often caused by drug-induced disorders of the heart human ether-à-go-go-related-gene (hERG) potassium channels located in the myocardium cell membranes. A(cquired)LQTS is the most common form of the syndrome and occurs when drugs block hERG channels. It is the first cause of delayed drug approval by the FDA and the second most frequent cause of drug withdrawal from the market. Although similar to most voltage-gated potassium channels, the hERG channel is a unique member of this family because of its long extracellular loop connecting the transmembrane S5 helix to the pore helix in the pore domain. Because of its importance for the channel function and location in the membrane vicinity, we have investigated the interaction of the central loop segment I583-Y597 with bicelles using liquid- and solid-state nuclear magnetic resonance (NMR) spectroscopy. In addition, these techniques allowed exploring the potential role of this hERG segment in the ALQTS. This was done by studying the binding of four LQTS-prone drugs, i.e. bepridil, cetirizin, diphenhydramine and pentamidine.