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Arrhythmogenic risk of cenobamate in patients with myocardial lesions by inhibition of Nav1.5 and Cav1.2 ion channels

Cenobamate is a highly effective third generation antiseizure drug used for treatment of adults with focal onset seizures. We performed whole-cell patch-clamp experiments on HEK293T cells with persistent/inducible expression of human cardiac ion channel isoforms hNav1.5 (INa), hCav1.2 (α1c+β2+ α2δ1) (ICaL), hKv7.1+minK (IKs), and hKv11.1 (hERG) (IKr) and Ncyte® ventricular cardiomyocytes, finding apparent cenobamate IC50 of 87.6μM (peak INa), 46.5μM (late INa), and 509.75μM (ICaL). In experiments on Ncyte® ventricular cardiomyocytes APD90 was reduced with 28.6±13.5% (mean±SD) by cenobamate 200μM. With multi-pulse protocols we estimated hNav1.5 state-specific blocking/unblocking rates: for open-state k_{ob}=0.00215$\mu M^{-1}ms^{-1}$, k_{ob}^{-1}=0.189ms^{-1}, for inactivated-state k_{ib}=0.0006698$\mu M^{-1}ms^{-1}$, k_{ib}^{-1}=0.18252ms^{-1}. We developed an open conformation hNav1.5 3D model and used it to assess binding affinity via molecular docking and MD followed by MM/PBSA for wild-type channels and 8 point mutants, finding by docking an estimated K_d=90.37μM for wild-type and lower for N1463K(rs1064795922) (27.62μM), N1463Y(rs199473614) (38.13μM), and M1766R(rs752476527) (36.84μM). Applying these data to a 50-cardiomyocytes string with reduced gap-junction coupling (1000pS/pF) yielded for cenobamate 17μM a conduction velocity of 8.0 cm/s and even lower for mutants N1463K, N1463Y, M1766R. Marked INa inhibition by cenobamate raises the theoretical possibility of cardiac arrhythmia induction at therapeutic concentrations in the context of preexisting myocardial pathology, in the presence of action potential conduction and repolarization heterogeneity, via mechanisms consistent with known effects of class Ib antiarrhythmics (Roden DM 2014 Card Electrophysiol Clin 6(4): 695–704). The arrhythmogenic risk could be more elevated for the three point mutants with higher predicted cenobamate binding affinity than wild-type. In addition, ICaL inhibition may contribute to the QT-shortening effects reported in pre-approval animal studies and clinical trials.

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Keywords: cenobamate, Nav1.5, ventricular cardiomyocyte tissue model, molecular docking, molecular dynamics, point mutant

Biography

Bogdan P. Amuzescu, MD, PhD, researcher of ion channel biophysical properties, mathematical modeling of complex biological systems. Fellowships at Katholieke Universiteit Leuven (2000-2003). Currently associate professor at Dept. Biophysics & Physiology, Faculty of Biology, University of Bucharest. Managerial experience: advisory board of Romanian Society of Neuroscience (2004-2012), Romanian Society against Epilepsy (2015). Research of biophysical and pharmacological properties of ENaC/Deg and TRP channels, applied research in cardiac electrophysiology and cardiac safety drug testing. Expert reviewer of journals like European Journal of Pharmacology. Author of >40 research articles, 6 books/book chapters. Member of Biophysical Society, AAAS, FENS, and other scientific societies.

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