MOLECULAR PATHOPHYSIOLOGY AND PHARMACOLOGY OF NEURONAL KCNQ CHANNELS

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Potassium (K^+) currents with distinct kinetic properties, modulation, and pharmacological profile are primary regulators of cellular excitability. The KCNQ family is formed by five genes (KCNQ1-5) encoding for K^+ channel subunits with diverse functional roles. KCNQ1 subunits underlie the slow repolarizing current (I_{Ks}) of the cardiac action potential affected in the Long QT Syndrome; by contrast, KCNQ2-5 subunits form heteromultimeric complexes whose functional properties recapitulate those of the M-current (I_{KM}), a neuronal K^+ current widely distributed in the peripheral and in the central nervous system. I_{KM} plays a dominant role in controlling neuronal excitability and is characterized by a low activation threshold, slow activation kinetics and absence of inactivation. Mutations in KCNQ2 and KCNQ3 genes cause Benign Familial Neonatal Convulsions (BFNC), a rare autosomal-dominant epilepsy of the newborn. In addition to its pathophysiological role in BFNC, I_{KM} is emerging as a novel therapeutic target for CNS diseases; in fact, I_{KM} activators such as retigabine and flupirtine appear as promising therapeutic tools against epilepsy, pain, anxiety, dystonia, and neurodegenerative disorders. The presentation will cover two main aspects; in the first part, the heterogeneity of the molecular mechanisms responsible for I_{KM} dysfunction prompted by several BFNC mutations will be discussed. Mutation-induced I_{KM} impairment may in fact occur by several mechanisms: some mutations preferentially alter the intracellular stability and trafficking of subunits (1), whereas others interfere with their polarized neuronal targeting (2), or with their function once normally inserted into the plasmamembrane (3,4). In the second part, using pharmacological tools directed against KCNQ2/3 channels, evidence will be provided suggesting that presynaptic I_{KM} incorporating KCNQ2 subunits controls dopamine release from isolated striatal nerve endings evoked by depolarization and is involved in the potentiation of the release of the catecholamine triggered upon activation of presynaptic muscarinic receptors.

References

1. Soldovieri MV, et al. (2006) J Biol Chem 281:418-28.
2. Chung HJ, et al., (2006) Proc Natl Acad Sci USA 103:8870-5.
3. Dedek K, et al., (2001) Proc Natl Acad Sci USA 98:12272-12277.
4. Castaldo P, et al. (2002) J Neurosci 22: RC199.