Pharmacological characterization of a hNav1.4 sodium channel mutation causing paramyotonia congenita

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Gain-of-function mutations of the Nav1.4 voltage-gated sodium channel are responsible for paramyotonia congenita or sodium channel myotonia, two human diseases characterized by a delay in muscle relaxation after contraction leading to skeletal muscle stiffness. The sodium channel blocker mexiletine was recently approved as orphan drug in non-dystrophic myotonias, caused by mutations in either chloride or sodium channel genes. By blocking voltage-gated sodium channels in skeletal muscle, mexiletine reduces sarcolemma excitability and counteracts myotonia. Yet, lack of efficacy or lack of tolerability have been observed for a significant number of patients, who critically need alternative therapeutic options. We previously showed that the G1306E hNav1.4 mutant causing myotonia permanens, a severe form of sodium channel myotonia, is less sensitive to mexiletine in vitro compared to wild-type channel, and that patients carrying G1306E can gain benefits by shifting treatment to flecainide, another sodium channel blocker, thereby opening the way toward a bench-to-bedside pharmacogenetics approach (Desaphy et al., 2001; 2004; 2013). Here we studied the function and pharmacology of another mutation hNav1.4 mutation, T1313M, which is associated with paramyotonia congenita (Yang et al., 1994). The mutation was previously shown to be less sensitive to lidocaine compared to wild-type in vitro (Fan et al., 1996), and the case of a T1313M carrier was reported to be intolerant to mexiletine due to gastrointestinal disturbance and confusion (Alfonsi et al., 2007). Interestingly, the T1313M mutation is located close to G1306E, in the intracellular linker between domains III and IV of the protein, which is thought to serve as the fast inactivation gate of the channel. The T1313M mutant was expressed in HEK293 cells and sodium currents were recorded with patch-clamp technique. We observed that T1313M induce defects in channel gating similar to G1306E, including a marked slowing of channel inactivation and a shift of fast inactivation voltage dependence toward positive voltages. Such effects likely account for the sarcolemma hyperexcitability and muscle stiffness in carriers. A reduced sensitivity of T1313M to mexiletine was observed, while studies regarding the effects of flecainide are being completed. Supported by Telethon-Italy (grant GGP14096), Association Française contre les Myopathies (grant #19027), and Italian Department of Health (grant GR-2009-1580433).

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