Pharmacology of Nav1.4 sodium channel mutations to address personalized medicine in non-dystrophic myotonias.

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Paramyotonia congenita or sodium channel myotonia are characterized by a delay in muscle relaxation after contraction leading to skeletal muscle stiffness. These rare diseases are caused by a gain-of-function mutations of hNav1.4 voltage-gated sodium channel. By blocking hNav1.4 channels, the orphan drug mexiletine reduces sarcolemma excitability and counteracts myotonia. Yet, lack of efficacy or tolerability is reported by a significant number of patients, who critically need alternative therapeutic options. We have shown that the G1306E mutant sodium channel causing myotonia permanens, a severe form of sodium channel myotonia, is less sensitive to mexiletine in vitro compared to wild-type hNav1.4 channel, and that patients carrying G1306E can gain benefits by shifting treatment to flecainide, another sodium channel blocker (1-3). Here we studied the function and pharmacology of known and novel myotonic hNav1.4 mutations located close to the channel fast inactivation machinery, as G1306E. WT and mutated sodium channel were expressed in tsa201 cells and whole-cell sodium currents were recorded with patch-clamp technique. Similarly to G1306E, many mutations induce a marked slowing of channel inactivation and a shift of fast inactivation voltage dependence toward positive voltages, which explain sarcolemma hyperexcitability and muscle stiffness in carriers. Those mutant channels showed a reduced sensitivity to mexiletine, while flecainide effects were preserved. Thus flecainide appears as a valuable antimyotonic drug, especially in patients carrying mutations inducing a positive shift of fast inactivation voltage dependence. Accordingly, therapy was successfully shifted to flecainide in a patient carrying one of the new mutations (4). This study opens the way toward a bench-to-bedside pharmacogenetics strategy in myotonia caused by sodium channel mutations.

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(1) Desaphy et al. (2001). *Neurology* 57, 1849-57.
(2) Desaphy et al. (2004). *J Physiol.* 554, 321-34.
(3) Desaphy et al. (2013). *Eur J Clin Pharmacol.* 69, 1037-9.
(4) Desaphy et al. (2016). *Neurology* 86, 2100-2108