New tocainide derivatives are lead blockers of $Na_v1.4$ channels for hyperexitability disorders of skeletal muscle

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The skeletal muscle sodium channel isoform $Na_v1.4$ is the molecular target of current first-line therapies against myotonic syndromes. Lidocaine (LA)-like drugs are widely used antimyotonic compounds because they block $Na_v1.4$ in a state- and use-dependent manner. This blocking mechanism relies on the high-affinity drug binding to the channel in its open or inactivated state, and to a slow recovery from inactivation of the drug bound channel. These actions dampen membrane excitation and prevent reexcitation during membrane repolarization (1, 2). However, LA-like compounds can cause undesirable effects and this has led to the discontinuation of tocainide (Toc) in some countries. Therefore, there is a need for new and selective $Na_v1.4$ blocking drugs. In an attempt to find potent use-dependent blockers of $Na_v1.4$ channels, we have screened new analogs of tocainide synthesized on the bases of the previous studies for the inhibitory action on native skeletal muscle sodium currents (3).

The compounds were tested on sodium currents of single frog skeletal muscle fibers by means of voltage-clamp recordings. Steps to -20mV from the holding potential of -100mV at different stimulation frequencies (0.3 up to 10Hz), were applied in order to evaluate tonic (TB) and use-dependent blocks (UDB) by drugs. Our previous studies have shown that the introduction of the benzyl group directly on the pharmacophore amino group strongly enhances the potency and the use-dependent behavior, probably for the establishment of specific hydrophobic interactions with the binding site (3). On the basis of these data, we have evaluated whether the introduction of a group more lipophilic and sterically hindered, as a naphthyl moiety, on the amino terminal group in α- (To041) or β- (To043) position with respect to the chirality centre, could improve the potency. Interestingly, an improvement of potency was observed with both compounds with the following order of potency: To041 < To043< Toc. In particular, To041 was about 7 and 75 fold more potent than tocainide in producing tonic (IC50= 78.4 ± 13 μM) and use-dependent block (IC50= 3.3 ± 1.2 μM), respectively. Based on previous evidences that the elongation of the alkyl chain increases the use-dependent behavior (4), we decided to evaluate the effect of this latter modification in the To041 molecule. We found that this modification (To042) causes a remarkable increase in the potency up to hundred and two thousand fold for tonic and use-dependent block, respectively, with respect to tocainide, indicating a better interaction with the binding site. In particular, the compound To042, showed the greatest use-dependent behavior with a ratio (IC50 TB/IC50 10-Hz UDB) of 36.4 vs. 23.7 and 2 for To041 and Toc, respectively. Interestingly, an increased potency and use-dependent behavior was also observed with the combination of the alkyl chain elongation with the presence of a group less lipophilic and sterically hindered such as the benzyl one as in To040.

Since the use-dependence properties selectively address the activity of a sodium channel blocker against pathological conditions, the new compounds To040 and To042 deserve further investigation of their potency against membrane hyperexcitability both in vitro and in vivo.

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