ORPHENADRINE BLOCKS VOLTAGE-GATED SODIUM CHANNEL BY BINDING TO THE LOCAL ANESTHETIC RECEPTOR

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Orphenadrine, a monomethylated derivative of diphenhydramine, is a skeletal muscle relaxant used for musculoskeletal disorders and Parkinson's Disease. Its mechanism of action is unclear, although it probably includes muscarinic antagonism. Evidences are also growing for an analgesic effect of orphenadrine through a yet unknown mechanism. In this study we verified whether orphenadrine is able to block human voltage-gated sodium channel (hNav1.4) expressed in a mammalian cell line, using patch-clamp technique. We measured the reduction of sodium current (INa) elicited from the holding potential (hp) of -120 mV to -30 mV at 0.1 and 10 Hz frequency stimulation. The concentration-response curves were fitted with a first-order binding function, given the half-maximum inhibitory concentration (IC_{50}) of 93 ± 12 µM at 0.1 Hz and of 31 ± 2 µM at 10 Hz. The use-dependent effect of orphenadrine suggests different drug binding affinities for the various channel states (1). We observed that INa block increased with the hp from -180 mV to -90 mV, indicating different affinities for closed and inactivated channels. Through specific protocols, we measured the affinity of orphenadrine for resting channels (K_R) at hp = -180 mV and we calculated the affinity for inactivated channels (K_I) from INa block measured at hp = -90 mV. The K_R value on WT channels was 161 ± 23 µM and K_I value was 2,19 µM. Sodium channel block features and chemical analogy with local anesthetics (LAs), suggested that orphenadrine may bind to the LA receptor. To test this hypotesis we engineered the F1586C mutation into hNav1.4, because this aromatic residue is part of the local anesthetic (LA) binding site within the channel pore (2). The IC_{50} values for F1586C mutant block at hp of -120 mV were 206 ± 10 µM at 0.1 Hz and 127 ± 14 µM at 10 Hz. This results demonstrate that orphenadrine blocks sodium channel by interacting with the LA binding site. The use-dependence of orphenadrine on sodium channel may be important to explain its analgesic effect, as observed in a recent clinical trial (3).
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References:

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