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Exploring the heterogeneity of use-dependent sodium channel inhibitor drugs. II: Drugs described by the modulated receptor hypothesis (MRH) and/or the guarded receptor hypothesis (GRH)

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All therapeutically used sodium channel inhibitor drugs seem to act similarly: in a use-dependent and state-dependent manner. These properties, however, can be caused by multiple mechanisms, as we and others have previously shown [1]. The two major hypotheses that explain use- and state-dependent inhibition are the MRH [2] and the GRH [3]. In this study we investigated which hypothesis better describes inhibition by various drugs, and whether drugs can be classified based on this aspect of their mechanism of action. We assumed that the two hypotheses are not mutually exclusive, and speculated that both altered affinity (as predicted by the MRH) and altered accessibility (as predicted by the GRH) to the inactivated state can be expressed as changes in association and dissociation rates upon conformational transition. We developed a method to test the relative contribution of affinity and accessibility in the effect of the drugs based on the degree of inhibition (reflecting affinity) and the time constant of the onset of inhibition (reflecting accessibility) as a function of changes in the voltage protocol. We tested the method by simulations and found that original parameters of a simulated drug can be deduced using the method. Experiments using 12 fast-inactivated state-preferring use-dependent sodium channel inhibitors suggest significant differences in this aspect of the mechanism.

References

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