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Exploring the heterogeneity of use-dependent sodium channel inhibitor drugs. I: Fast- vs. slow-inactivated state preference

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Certain drugs evidently exert their therapeutic effects via sodium channel inhibition: local anesthetics, class I antiarrhytmics and certain anticonvulsants. Novel sodium channel inhibitor compounds are actively investigated for other indications involving stroke, ischemia, various neurodegenerative conditions and pain syndroms. All these drugs cause voltage- and use-dependent inhibition of sodium channels. However, biophysical properties of inhibition can differ widely even between use-dependent sodium channel inhibitors which seem to act similarly. Recently it has been proposed that the mechanism of inhibition can be more important than potency or isoform selectivity regarding the therapeutical potential of the drugs (e.g. [1]). One important question is which conformational state is preferred by the drug. In this study we attempted to discriminate preference to fast- vs. slow-inactivated conformations. Slow association to fast-inactivated state and fast association to slow-inactivated state cannot be distinguished using traditional protocols. We have recently developed a protocol to test fast- vs. slow-inactivated state preference using electrophysiology only, i.e. without mutagenesis or enzymatic treatment experiments. We tested 28 use-dependent sodium channel inhibitors of different chemical structure and therapeutic indication using this protocol, and found that the mechanisms primarily overlap with the latter.

References

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