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Voltage protocols for the identification of distinct types of sodium channel inhibitors

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In order to establish a structure – activity relationship for a group of compounds, it is essential that the binding site is the same for all investigated drugs. This condition is unmet in the case of sodium channel inhibitors, where mutagenesis studies showed binding sites to be either only partially overlapping, or – for some drugs – clearly different. Sodium channel inhibitors also differ in the properties of inhibition (such as resting- and inactivated-state affinity, state-dependence, use-dependence, onset and offset kinetics, reversibility), as it has been shown in our recent study. We believe, therefore, that conventional screening for sodium channel inhibitor activity is a misguided approach, and we aimed to develop protocols which provide information not only on potency, but also on the mode of action of individual compounds. We recorded more than forty individual parameters, and used them to derive further parameters, which could give a low redundancy, high information content characterization of inhibition, while not requiring more time or cost than a conventional measurement of potency. The method is adaptable to automated patch clamp systems. We presume that determination of multiple aspects of inhibition will help to understand structure – activity relationship for sodium channel inhibitors, and to design sodium channel inhibitor drugs for specific therapeutic applications.