Sodium channel selectivity of three anti-epileptic drugs

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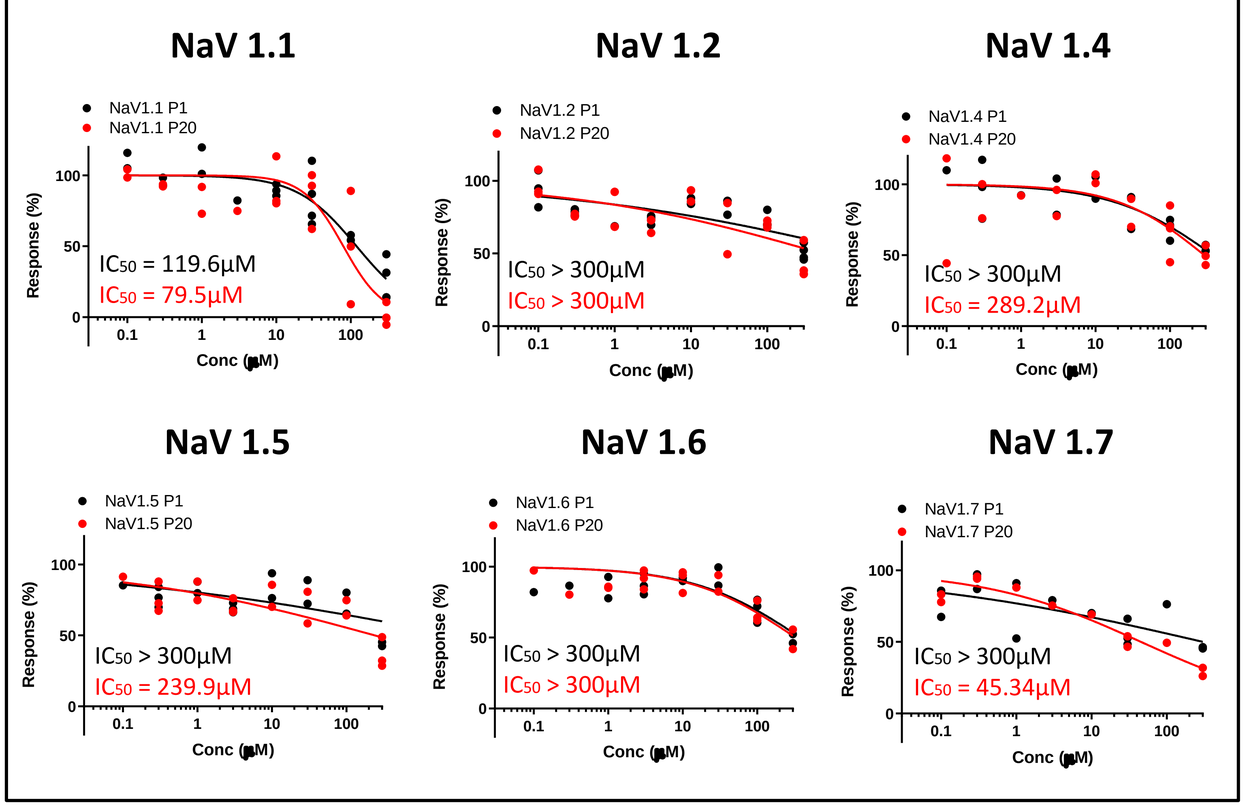
Characterised by seizures and convulsions, epilepsy is the most common neurological disorder affecting 50 million people worldwide. The aetiology of the disorder is complex, however genetic and pharmacological evidence suggests that ion channels play an important role in the disturbance of electrical activity responsible for seizure phenotypes. In particular, voltage-gated sodium channels have been implicated in causing seizure. Many marketed anti-epileptic drugs (AEDs) are ion channel modulators, however their molecular targets and mechanism of action are often poorly characterised. In order to gain a greater understanding of the effects of AEDs on voltage-gated sodium channels, this work aimed to characterise the sodium channel subtype selectivity of three common AEDs: carbamazepine, lamotrigine and phenytoin.

METHODS

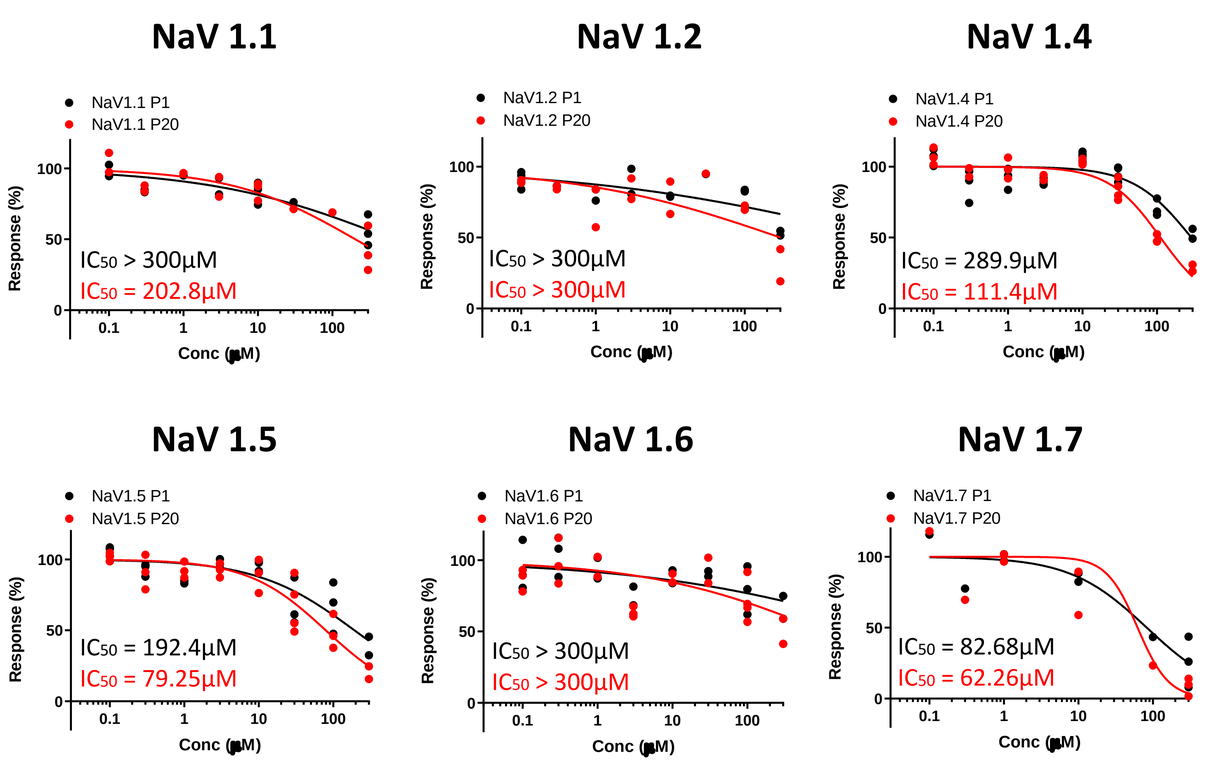
- The activity of carbamazepine, lamotrigine and phenytoin was tested against 6 sodium channel subtypes: **Human NaV1.1, 1.2, 1.4, 1.5, 1.6 and 1.7,** which were stably expressed in recombinant Chinese hamster ovary or Human embryonic kidney cell lines
- Ion currents were measured by automated patch-clamp (PatchLiner, Nanion Technologies/Ion Works Quattro, Molecular devices) at ambient temperature
- IC_{50} values were estimated from 8-point concentration-response curves generated using a 3.16-fold serial dilution from top concentrations of 300µM
- Resting and use-dependence block was assessed by analysis of recorded currents at the first (P1) and final (P20) voltage steps
- Tetracaine was used as a positive control from a top concentration of 100µM

RESULTS

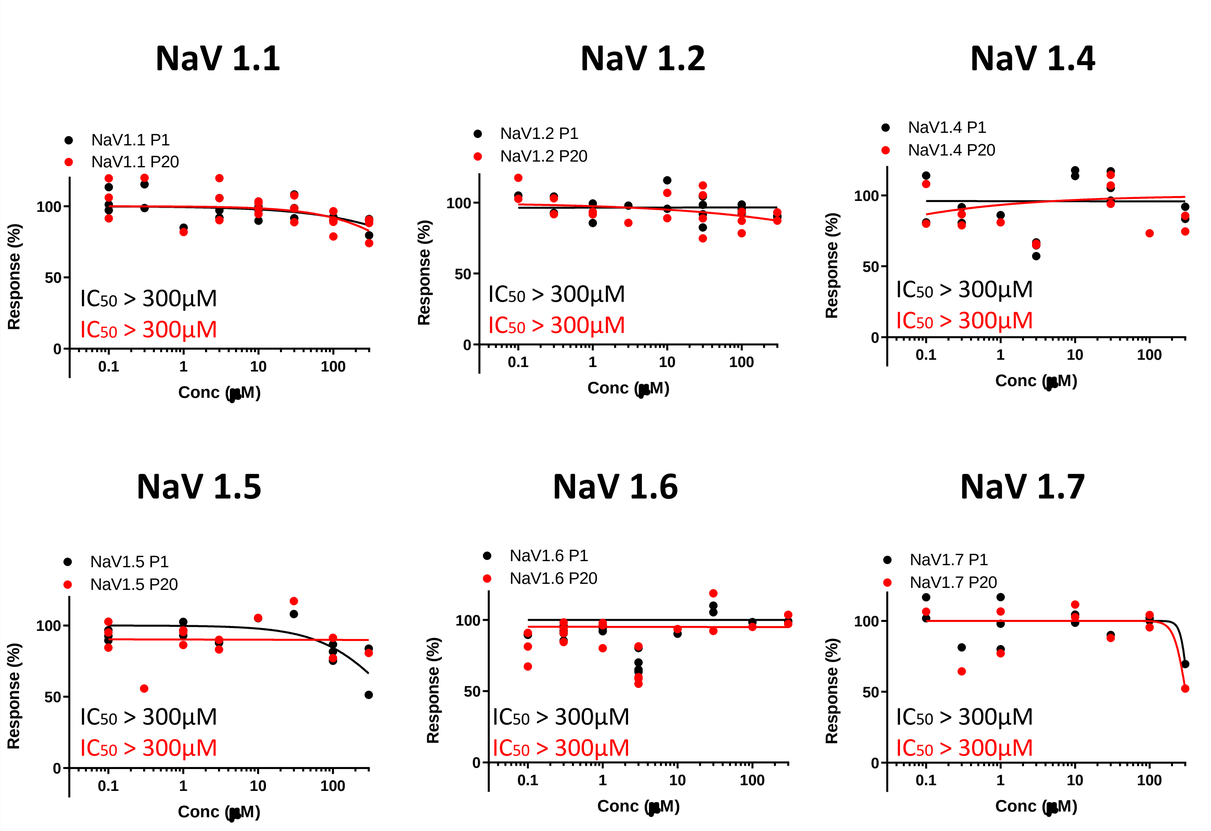
1. Carbamazepine selectively inhibits the NaV 1.1 subtype and shows use dependence in other sodium channel subtypes



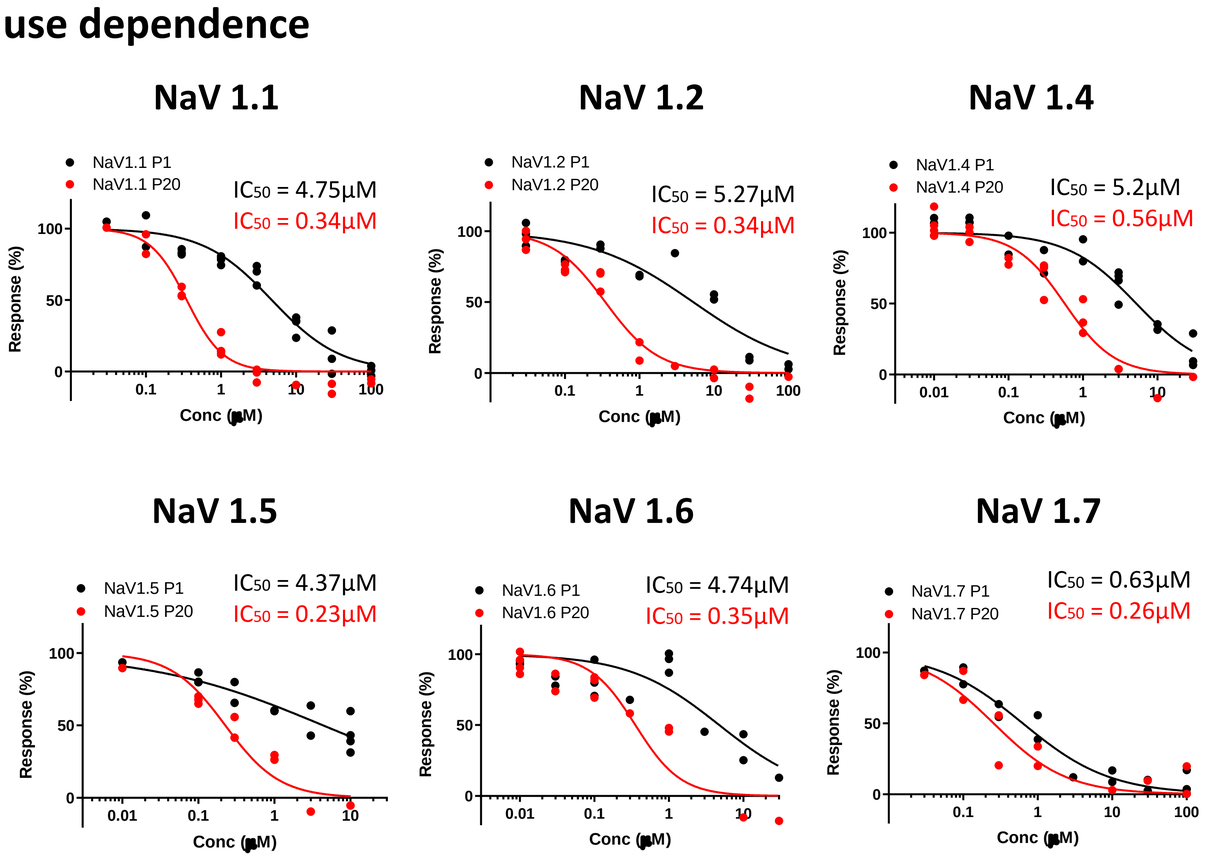
2. Lamotrigine selectively inhibits the NaV 1.4, 1.5 and 1.7 subtypes and shows use dependence



3. Phenytoin showed no activity in any sodium channel subtype



4. Tetracaine inhibits all sodium channel subtypes and shows use dependence



DISCUSSION AND CONCLUSIONS

- The inhibition of all sodium channel subtypes by tetracaine demonstrates the utility of these cells and electrophysiological platforms to accurately detect sodium channel inhibition.
- The selectivity of carbamazepine for the NaV 1.1 subtype and lamotrigine for the NaV 1.4, 1.5 and 1.7 subtypes suggests that these subtypes are specific targets of the drugs which play a role in their anti-epileptic activities.
- The inhibition of NaV 1.5 by lamotrigine may be responsible for the cardiac-related side-effects of the drug such as arrythmias
- The lack of activity observed with phenytoin suggests that this AEDs mechanism of action is independent of sodium channel inhibition

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