Anti-epileptic drugs differentially affect sodium channel subtypes IIA and IIIA stably expressed in HEK293 cells

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The voltage-dependent sodium channel determines the upstroke of the action potential and is crucially involved in the regulation of cellular excitability. Most successful anti-epileptic drugs (AEDs) target the sodium channel and try to reduce repetitive firing as occurs during highly synchronized epileptic bursts of action potentials. Despite this obviously effective mechanism about 20-40% of epileptic patients is not well controlled by current anti-epileptic medication and is considered pharmacoresistant. It is not yet clear whether this is caused by a non-effective interaction between the drug and the channel or whether it is related to complications at the network level. Changes in specific expression of brain sodium channel subtypes have been reported in animal models of epilepsy as well as in epileptic patients.
The IIA and IIIA α subunits of the human brain voltage-gated sodium channel were cloned and stably expressed in human embryonic kidney cells (HEK293). Their biophysical and pharmacological properties were investigated using the whole-cell voltage clamp technique. The voltage dependence of activation and inactivation of the IIA and IIIA subtypes were similar as were most of their kinetic properties. Carbamazepine (CBZ), lamotrigine (LTG) and phenytoin (DPH) shifted the steady-state inactivation in hyperpolarizing direction in a concentration- and drug-dependent manner. They hardly affected the activation properties. LTG and CBZ had more pronounced effects on the IIIA subtype than on the IIA subtype, while DPH equally affected both subtypes. The recovery from inactivation was fastest in the IIA subtype.
The differential sensitivity of the sodium channel subtypes for CBZ, LTG and DPH may have therapeutic implications, particularly when epileptogenesis is associated with a shift in sodium channel subtype expression.

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