

## CHANGING CHANNELS: MECHANISMS AND RESPONSIVENESS TO ANTIEPILEPTIC DRUGS IN CHRONIC EPILEPSY

### Anticonvulsant Pharmacology of Voltage-gated Na<sup>+</sup> Channels in Hippocampal Neurons of Control and Chronically Epileptic Rats

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Voltage-gated Na<sup>+</sup> channels are a main target of many first-line anticonvulsant drugs, and their mechanism of action has been extensively investigated in cell lines and native neurons. Nevertheless, it is unknown whether the efficacy of these drugs might be altered after chronic epileptogenesis. We have, therefore, analyzed the effects of phenytoin (PHT; 100  $\mu$ M), lamotrigine (LTG; 100  $\mu$ M), and valproate (VPA; 600  $\mu$ M) on Na<sup>+</sup> currents in dissociated rat hippocampal granule neurons in the pilocarpine model of chronic epilepsy. In control animals, all three substances exhibited modest tonic blocking effects on Na<sup>+</sup> channels in their resting state. These effects of PHT and LTG were reduced (by 77% and 64%) in epileptic compared with control animals. PHT and VPA caused a shift in the voltage dependence of fast inactivation in a hyperpolarizing direction, whereas all three substances shifted the voltage dependence of activation in a depolarizing direction. The anticonvulsant effects on Na<sup>+</sup> channel voltage dependence proved to be similar in control and epileptic animals. The time course of fast recovery from inactivation was potently slowed by LTG and PHT in control animals, whereas VPA had no effect. Interestingly, the effects of PHT on fast recovery from inactivation were significantly reduced in chronic epilepsy. Taken together, these results reveal that different AEDs may exert a distinct pattern of effects on native Na<sup>+</sup> channels. Furthermore, the reduction of PHT and, to a less pronounced extent, LTG effects in chronic epilepsy raises the possibility that reduced pharmacosensitivity of Na<sup>+</sup> channels may contribute to the development of drug resistance.

### COMMENTARY

It is estimated that ~30% of epilepsy patients do not respond adequately to currently available medication (1). Individuals with localization-related seizures of hippocampal origin appear most at risk (2). Two schools of thought have arisen in an attempt to explain the phenomenon of therapeutic failure in this population. The pharmacokinetic hypothesis suggests that antiepileptic drugs (AEDs) do not reach the epileptic focus in sufficient concentration, possibly because of active efflux that is mediated by locally overexpressed drug-transporter proteins (3). The pharmacodynamic theory proposes a seizure-associated reduction in pharmacologic sensitivity of the ion channels and neurotransmitter receptors that represent the molecular targets of AEDs. Remy and colleagues have conducted an elegant series of experiments that address this latter proposition. The research follows their earlier studies (4), which demonstrated the abolition of carbamazepine (CBZ) effects in isolated neurons taken from both surgically resected human epileptic tissue and an animal model of chronic epilepsy (see commentary in recent *Epilepsy Currents*) (5).

In the current investigation, Remy and colleagues report a reduced sensitivity to the sodium channel-blocking effects of phenytoin (PHT) and, to a lesser extent, lamotrigine (LTG) in dissociated hippocampal dentate granule cell neurons, after the induction of chronic seizures in the rat pilocarpine model. The observation of diminished effectiveness of PHT at the cellular level in the chronic epileptic state, together with the complete loss of CBZ activity reported previously (4), may be construed as potentially important contributions to our understanding of the phenomenon of clinical pharmacoresistance. Altered sensitivity of voltage-gated sodium channels, alongside accumulating evidence of other acquired channelopathies (6), lends support to the pharmacodynamic hypothesis underlying resistance to multiple, mechanistically diverse AEDs.

A potentially confounding factor is the authors' submission that although the pharmacologic sensitivity of isolated hippocampal neurons may be reduced, PHT remains effective in preventing chronic convulsive seizures in pilocarpine-treated rats. Their explanation of a locally diminished PHT efficacy, restricted to the dentate granule cells themselves, is plausible and

not entirely inconsistent with the traditionally held premise that sodium channel-blocking drugs primarily act to restrict seizure spread rather than to prevent the generation of ictal discharges. Nevertheless, in attempting to unravel the mechanisms of drug resistance in epilepsy, it is important to remember that currently available models may not adequately represent the clinical condition and that focusing on a single system, such as drug transporters in the blood-brain barrier or a subset of neurons in the hippocampus, may not be sufficient to define the pharmaco-resistant phenotype.

Another interesting aspect to the investigation by Remy and co-workers is the apparently differential influence of pilocarpine-induced chronic seizures on drug action at the cellular level. Of the agents under investigation, all of which are reported to exert their pharmacologic effects, at least in part, by an action on neuronal voltage-gated sodium channels (7), only PHT efficacy is significantly impaired. The observed reduction in the modest tonic blocking effects of LTG on resting sodium currents is unlikely to influence its clinical efficacy significantly, whereas the action of sodium valproate (VPA) appears largely unaltered. These findings support the distinction of individual sodium channel blockers at the molecular level (8) and, in theory, say more about the pharmacology of LTG and VPA than about potential mechanisms of pharmaco-resistance.

Elucidating the mechanisms of drug resistance has the potential to revolutionize the treatment of epilepsy and, with the development of appropriate interventions, alleviate the dele-

terious consequences of uncontrolled seizures. These are the first steps in what is likely to prove to be a protracted journey with many blind alleys and false dawns before the undoubtedly multifactorial nature of AED responsiveness is revealed.

by Graeme J Sills, Ph.D.

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