

## ALTERED SODIUM CHANNELS UNDERLIE ANTICONVULSANT DRUG INSENSITIVITY

### A Novel Mechanism Underlying Drug Resistance in Chronic Epilepsy

Remy S, Gabriel S, Urban BW, Dietrich D, Lehmann TN, Elger CE, Heinemann U, Beck H

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The development of resistance to pharmacologic treatment is common to many human diseases. In chronic epilepsy, many patients develop resistance to anticonvulsant drug treatment during the course of their disease, with the underlying mechanisms remaining unclear. We have studied cellular mechanisms underlying drug resistance in resected hippocampal tissue from patients with temporal lobe epilepsy by comparing two groups of patients, the first displaying a clinical response to the anticonvulsant carbamazepine (CBZ) and a second group with therapy-resistant seizures. With patch-clamp recordings, we show that the mechanism of action of CBZ, use-dependent block of voltage-dependent Na<sup>+</sup> channels, is completely lost in CBZ-resistant patients. Likewise, seizure activity elicited in human hippocampal slices is insensitive to CBZ. In marked contrast, CBZ-induced use-dependent block of Na<sup>+</sup> channels and blocked seizure activity *in vitro* in patients clinically responsive to this drug. Consistent with these results in human patients, we also show that use-dependent block of Na<sup>+</sup> channels by CBZ is absent in chronic experimental epilepsy. Taken together, these data suggest that a loss of Na<sup>+</sup>-channel drug sensitivity may constitute a novel mechanism underlying the development of drug-resistant epilepsy.

mally these channels are closed at resting membrane potential but open rapidly on depolarization. The resultant sodium currents then decrease rapidly toward baseline levels, as the sodium channels inactivate with prolonged depolarization. After inactivation, sodium channels require hyperpolarization to return to their resting state. The transition between these functional states is rapid and occurs on a time scale of milliseconds, enabling sodium channels to sustain fast action potentials. CBZ inhibits voltage-dependent sodium currents by two mechanisms: (a) a modest block of sodium channels in their resting state at hyperpolarized membrane potentials; and (b) inhibition of sodium currents in an activity- or use-dependent manner (i.e., blockade is more pronounced when the cell membrane is repetitively depolarized at high frequencies). This latter action induces a preferential decrease in sodium-channel availability during high- but not low-frequency firing and is thought to be the key factor in the efficacy of this anticonvulsant to inhibit epileptiform activity.

The actions of CBZ were studied in a series of experiments using whole-cell patch-clamp recordings of dissociated dentate granule cells from the hippocampi of control and pilocarpine-treated rats. The authors found that the main action of CBZ on control neurons was to prolong the time constant of sodium channel fast recovery from inactivation, which would enhance the decrement of sodium current amplitude in response to high-frequency action potentials, as it did with their mock series of spikes. As noted in the abstract, this effect was absent in granule cells obtained from pilocarpine-treated rats and from human temporal lobe epilepsy patients who were known to be resistant to CBZ treatment. However, sodium currents in cells from slices from drug-sensitive (non-temporal lobe) epilepsy patients showed the same sensitivity to CBZ as did those recorded in rat control neurons.

Thus the main conclusions of this study are that (a) drug resistance to CBZ appears to arise as a result of an (unknown) alteration in sodium channels, conferring drug insensitivity; and (b) live human tissue can be valuable in the study of such problems as drug resistance. Whether the changes in sodium channels occur as a consequence of seizure activity or the epileptogenic process is a matter of speculation. All of the drug-resistant tissue was obtained from temporal lobe epilepsy patients with hippocampal sclerosis. Could the development of resistance

### COMMENTARY

The research by Remy and colleagues was aimed at elucidating the mechanism of drug resistance to carbamazepine (CBZ) in intractable epilepsy patients. The primary mode of action of CBZ is well known and is thought to be based primarily on its effects on voltage-gated sodium channels. Nor-

occur as an epiphenomenon of this pathological process? Further questions arise, such as: what are the actions of CBZ on other hippocampal neuron types in drug-resistant patients, and what are the effects on the neurons in the overlying neocortex? Is it only the epileptogenic focus that is insensitive to the drug? One can only wonder what the results might be in a CBZ-sensitive patient with temporal lobe epilepsy and hippocampal sclerosis. Likely these are issues the authors have already been considering.

Of note, the concentration of CBZ applied ranged from 50 to 128  $\mu M$  in this study. This dosing range was said to be only somewhat higher than serum concentrations measured in human plasma, and it was speculated that CBZ, being lipophilic, may have an even higher concentration in brain tissue. However, this contention would seem to be true only if there were active uptake and storage of the drug, but as the researchers indicate,

there is no transporter for CBZ. CBZ has a serum therapeutic level of 4–12  $\mu g/mL$ , which is roughly 17–50  $\mu M$ . Like many other antiepileptic drugs, CBZ is highly protein bound—a fact that the authors apparently did not take into account. CBZ is 76% protein bound, leaving 24% unbound, which corresponds well with the measured cerebrospinal fluid/serum ratio of 0.22, and what is available to brain is actually the free fraction of the drug, rather than the measured plasma concentration. Once protein binding is considered, the usual clinically relevant range of CBZ concentration bathing brain tissue is closer to 3–10  $\mu M$ . Therefore it could be of value to explore what effects lower CBZ concentrations have on sodium-channel kinetics in control and experimental preparations. Perhaps concentration-related effects of the drug would prove interesting.

*by Larry S. Benardo, M.D., Ph.D.*