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Carbamazepine Inhibition of Neuronal Na^+ Currents: Quantitative Distinction from Phenytoin and Possible Therapeutic Implications

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SUMMARY

Carbamazepine and phenytoin, two of the most commonly prescribed antiepileptic drugs, have been proposed to share a similar mechanism of action by use-dependent inhibition of Na^+ channels. The proposed similar mechanism of action, however, cannot explain the common clinical experiences that the two drugs are different; in some patients, one drug may be more effective than the other. This may occur even when optimal therapeutic concentrations are reached with both medications in plasma or the cerebrospinal fluid. In this study, we show that the action of the two drugs on Na^+ channels are quantitatively very different. The affinity between inactivated Na^+ channels and carbamazepine (apparent dissociation constant ~25 μM) is ~3 times lower than that of phenytoin, yet the binding rate constant of carbamazepine onto the inactivated Na^+ channels is ~38,000 M^{-1}/sec^{-1}, or ~5 times faster than that of phenytoin. It is speculated that carbamazepine may be more effective than phenytoin in treating seizures whose ictal depolarization shift is relatively short, whereas a better response to phenytoin may imply abnormal discharges characterized by more prolonged depolarization.

Epilepsy is a common neurological disorder, and control of seizures relies mostly on appropriate antiepileptic medications. A more sophisticated choice of the available antiepileptics depends on further characterization of the molecular mechanisms underlying anticonvulsant action, together with deliberate correlation of such mechanisms with various possible patterns of seizure discharges. In this approach, an essential consideration is why an anticonvulsant is effective against some neuronal discharges but not against others. For example, why could normal neuronal activities be preserved in the presence of effective inhibition of seizures? Thus far, the experimental finding most relevant to this issue is probably the use-dependent block of neuronal discharges produced by some antiepileptics such as DPH and CBZ (1–3).

DPH and CBZ, two widely prescribed antiepileptics, have been shown to inhibit high-frequency firings but not lower frequency firings. Such a use- or frequency-dependent block is analogous to that obtained with local anesthetics (for review, see ref. 4) and is similarly ascribed to a voltage-dependent inhibitory effect on voltage-gated Na^+ channels. It has been shown that DPH and CBZ inhibit Na^+ currents in peripheral axons and cultured neuroblastoma cells and that the inhibition is more potent at more depolarized potentials (5–8). Na^+ channels are more likely to adopt the deactivated (resting or closed) conformation at hyperpolarized potentials but tend to be transiently activated (open) and then inactivated at depolarized potentials; therefore, the voltage-dependent inhibition may be explained by the speculation that the inactivated conformation of Na^+ channels has a higher affinity to the drug than the resting conformation [the modulated receptor hypothesis (9, 10)], along with a related finding that drug binding slows remarkably the recovery of inactivated channels back to the resting state (11, 12).

The use-dependent inhibition of neuronal discharges, however, cannot be completely understood by the different binding affinities between the drug and different gating conformations of the Na^+ channel. For example, after only one action potential, most Na^+ channels would be in the inactivated state. DPH and CBZ cannot bind to the inactivated channels and inhibit Na^+ currents in this situation; otherwise, normal firings would also be blocked by these drugs. The requirement of high-frequency discharges or prolonged depolarization for the inhibition to occur seems to imply that the drug binding onto the inactivated channels is slow. Thus, one probably should consider both the steady state effects

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ABBREVIATIONS: CBZ, carbamazepine; DPH, phenytoin; EGTA, ethylene glycol-bis-(β-aminoethyl ether)-*N*,*N*,*N*′,*N*′-tetraacetic acid; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid.

and their kinetics to understand the antiepileptic effect of DPH and CBZ through the action on Na^+ channels. Recently, Kuo and Bean (13) demonstrated a relatively high affinity [apparent dissociation constant (K_{app}) ~7 μM] and a slow binding rate constant (~9,000 M^{-1}/sec^{-1} at room temperature and −20 mV) of DPH binding to inactivated Na^+ channels in hippocampal neurons. The former explains the strong blocking effect of DPH on repetitive discharges superimposed on prolonged depolarization shift, and the latter assures a negligible effect of DPH on normal low-frequency firings or very transient high-frequency bursts.

Although the use-dependent block of repetitive firing and the inhibition of Na^+ channels by CBZ and DPH are apparently similar, the two drugs are different. It is not a rare experience that in some seizure patients, one drug may be quite more effective than the other, even when optimal therapeutic concentrations are reached with both medications in plasma or cerebrospinal fluid. It is therefore desirable to investigate the steady state effect and kinetics of CBZ inhibition of neuronal Na^+ channels, especially to see whether there are any significant differences between CBZ and DPH. Here we show that the affinity between CBZ and the inactivated Na^+ channels in hippocampal neurons (apparent dissociation constant ~25 μM) is ~3 times lower than that of DPH. However, the binding rate constant between CBZ and the inactivated Na^+ channels is ~38,000 M^{-1}/sec^{-1}, or ~5 times faster than that of DPH. These results could have significant pharmacotherapeutic implications when correlated with various possible ictal cellular discharge patterns (see Discussion).

Materials and Methods

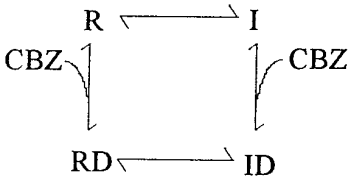
Cell preparation. Coronal slices of the whole brain were prepared from 7- to 14-day-old Long-Evans rats. The CA1 region was dissec[1]ted from the slices and cut into small chunks. After treatment for 5–10 min at 37° in dissociation medium (82 mM Na_2SO_4, 30 mM K_2SO_4, 3 mM $MgCl_2$, 5 mM HEPES, and 0.001% phenol red indicator, pH 7.4) containing 0.5 mg/ml trypsin (type XI; Sigma, St. Louis, MO), tissue chunks were moved to dissociation medium containing no trypsin but containing 1 mg/ml bovine serum albumin (Sigma) and 1 mg/ml trypsin inhibitor (type II-S; Sigma). Each time the cells were needed, 2–3 chunks were picked and triturated to release single neurons.

Whole-cell recording. The dissociated neurons were put in a recording chamber containing Tyrode's solution (150 mM NaCl, 4 mM KCl, 2 mM $MgCl_2$, 2 mM $CaCl_2$, and 10 mM HEPES, pH 7.4). Whole-cell voltage clamp recordings were obtained using pipettes pulled from borosilicate micropipettes (absorbance 1.55–1.60 mm; Hilgenberg, Malsfeld, Germany), fire polished, and coated with Sylgard (Dow-Corning, Midland, MI). The pipette resistance was 1–2 MΩ when filled with the internal solution containing 75 mM CsCl, 75 mM CsF, 2.5 mM MgCl2, 5 mM HEPES, 2.5 mM EGTA, pH adjusted to 7.4 by CsOH. A seal was formed, and whole-cell configuration was obtained in Tyrode's solution. The cell was then lifted from the bottom of the chamber and moved in front of an array of flow pipes (microcapillary from Hilgenberg; content 1 μl, length 64 mm) emitting either control- or drug-containing external recording solutions (Tyrode's solution with or without 10–300 μM CBZ and 10–100 μM DPH). CBZ and DPH were dissolved in dimethylsulfoxide to make a 100-mM stock solution, which was then diluted in Tyrode's solution to attain the desired final concentrations. The final concentration of dimethylsulfoxide (0.3% or less) was not found to have detectable effect on Na^+ currents. The solubility of DPH is lower than CBZ, and it was not possible to obtain DPH concentrations greater than 100 μM in Tyrode's solution (pH 7.4, 25°). Currents were recorded at room temperature (~25°) with an Axoclamp 200A amplifier, filtered at 5 kHz with a four-pole Bessel filter, digitized at 20- to 50-μsec intervals, and stored using a Digidata-1200 analog/digital interface along with the pCLAMP software (all from Axon Instruments, Foster City, CA). Residual series resistance is generally smaller than 1 MΩ after partial compensation (typically >90%), and the product of residual series resistance and cell capacitance was generally <20 μsec. All statistics are given as mean ± standard deviation.

Results

Stronger inhibition of Na^+ current by carbamazepine at more depolarized holding potentials. Fig. 1 demonstrates the voltage-dependent effect of CBZ on neuronal Na^+ currents. At a holding potential of −100 mV, 10 μM CBZ has negligible effect on the Na^+ currents, and even 100 μM CBZ produces no more than ~10% inhibition of the Na^+ currents. However, at a holding potential of −70 mV, 10 and 100 μM CBZ significantly inhibit the Na^+ currents (Fig. 1A). Similar experiments were performed at different holding potentials, and the dose-response curves are plotted in Fig. 1B. The effect of various concentrations of CBZ on Na^+ currents could be fit by a simple one-to-one binding curve for each holding potential. CBZ inhibits neuronal Na^+ currents with a K_{app} of ~20 μM at a holding potential of −60 mV. In contrast, the K_{app} at −100 mV is ~900 μM (a rough estimate, because even 300 μM CBZ could block the current by no more than 30%), which indicates an affinity change of almost 50 times between membrane potentials −60 mV and −100 mV.

As the steady state inactivation curve of Na^+ channels also shows a steep change between −60 to −100 mV (see the control curves in Fig. 2A), the above finding is consistent with the notion that CBZ binds to the inactivated channels with high affinity but to the resting channels with low affinity. This point can be illustrated in a more quantitative manner with the following scheme:



in which R and I are the resting and inactivated states of the channel, and RD and ID are the CBZ-bound (and inhibited) resting and inactivated states, respectively. The activated (open) state is omitted because most activated Na^+ channels inactivate so quickly that, in a steady state condition, one might consider only the R and I states for simplicity. According to this scheme, at any particular holding potential, the fraction of channels in state R (the channels that may be activated or the current that may be elicited upon membrane depolarization) would be reduced by CBZ with a K_{app} given by (13, 14):

$$K_{app} = \frac{1}{[h/K_R + (1 - h)/K_I]}$$

in which h is the fraction of channels in state R in the absence of drug ('fraction available' in the control condition in Fig.

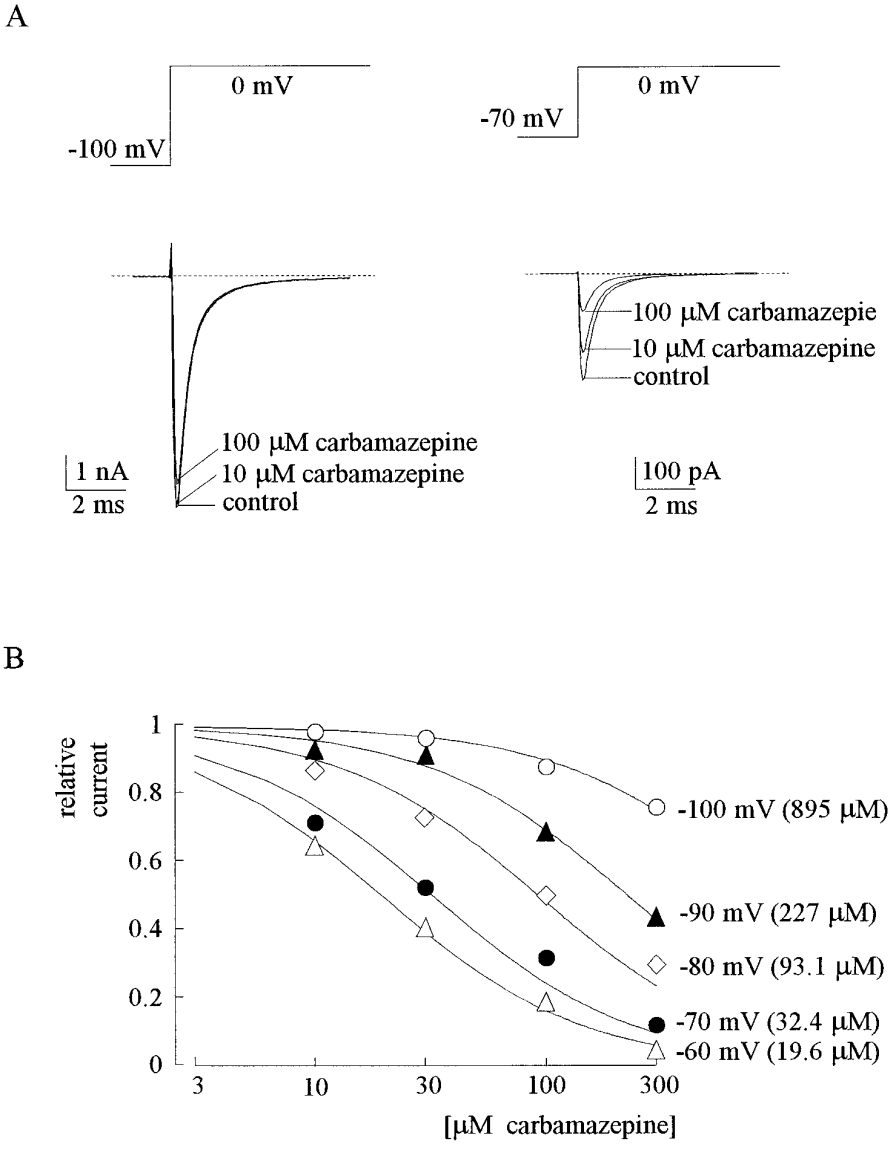


Fig. 1. Inhibition of Na^+ currents by CBZ at different holding potentials. A, Currents in control, 10, or 100 μM CBZ in a cell held at −100 mV or −70 mV and stepped to 0 mV for 6 ms every 2 sec. *Dashed lines*, zero current level. B, Dose-response curves for inhibition of Na^+ currents by 10–300 μM CBZ at different holding potentials. The cell was held at −60 to −100 mV and stepped every 2 sec to 0 mV for 6 msec. The peak currents in the presence of CBZ were normalized to the control peak currents at each holding potential and plotted against [CBZ], the concentration of CBZ in micromolar. The lines are best fits for each set of data of the form: relative current = $1/[1 + ([CBZ]/K_{app})]$. The holding potential along with the corresponding K_{app} is shown to the *right* of each curve.

2A), and K_R and K_I are the dissociation constants for the resting and inactivated states, respectively. This is as if the overall affinity of CBZ to the channel (which may be represented by $1/K_{app}$ because the dissociation constant is inversely proportional to affinity) is a weighted average of the affinity to each state of the channel (Σ fraction of a state × the affinity toward that state, or $h/K_R + (1 - h)/K_I$). Thus, a large K_{app} of ~900 μM at −100 mV, in which h is >0.95, and a small K_{app} of ~20 μM at −60 mV, in which h is <0.05 (Figs. 1B and 2A), would clearly indicate that $K_R \gg K_I$. Along with the values of h at these potentials, one may also assume that K_I should be close to 20 μM, whereas K_R must be somewhat larger than 900 μM.

Measurement of the affinity between inactivated Na^+ channels and CBZ by shift of the inactivation curve. A K_I of ~20 μM for CBZ is significantly larger than the value previously reported for DPH [~7 μM (13)]. Because the inactivated state is probably the major target of CBZ and DPH, a further comparison of K_I is of great interest. Based on the foregoing scheme, K_I can be estimated by another approach. In the control condition, the inactivation curve (the fraction of channels in state R at various membrane potentials) can be approximated by a Boltzmann distribution, $1/[1+\exp(V - V_h)/k]$ (Fig. 2A), in which V is the membrane potential, V_h is the half-inactivated potential (at which half of the channels are in state R and the other half are in state I), and k is the slope factor. When CBZ is added, according to the foregoing scheme, the shape of the curve should remain the same, but the midpoint (V_h) would be shifted by ΔV, with $\exp(\Delta V/k)$ equal to $[1+(D/K_I)]/[1+(D/K_R)]$, in which D is the concentration of CBZ (13, 15). Fig. 2A shows that with 10–300 μM CBZ added, the inactivation curves are indeed shifted to the left. Fig. 2, B and C illustrate that the shift of CBZ is dose-dependent and that the slope of the curves remains unchanged in the presence of CBZ. Cumulative results of $\Delta V/k$ in various concentrations of CBZ and DPH are shown in Fig. 3, A and B. Fig. 3C plots the exponentials of the mean values of $\Delta V/k$, which shows that the affinity of CBZ to the inactivated Na^+ channel (K_I ~25 μM) is ~3 times lower than that of DPH (K_I ~9 μM).

Slow unbinding rate of CBZ from the inactivated Na^+ channels. It has been demonstrated in hippocampal

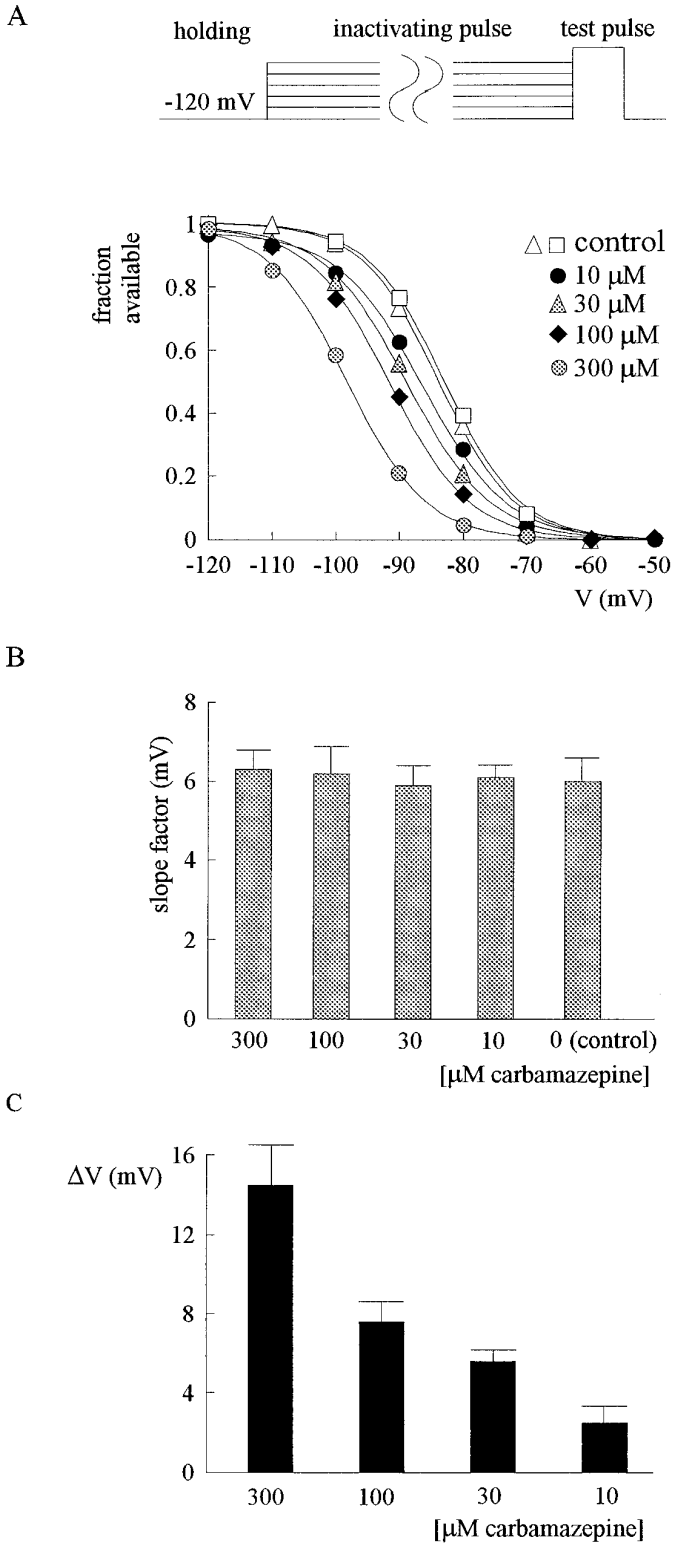


Fig. 2. Shift of the inactivation curve by CBZ. A, The cell was held at −120 mV and stepped every 15 sec to the inactivating pulse (−120 to −50 mV) for 9 sec. The channels that remained available after each inactivating pulse were assessed by the peak currents during the following short test pulse to 0 mV. The fraction available is defined as the normalized peak current (relative to the current evoked with an inactivating pulse at −120 mV) and is plotted against the voltage of the inactivating pulse. Two sets of control data were obtained before and after the four sets of data in 10, 30, 100, and 300 μM CBZ to assure that there had been no significant voltage drift during this long experiment. The lines are fits of a Boltzmann function $1/(1 + \exp[(V - V_h)/k])$, with V_h values of −83 mV, −83.9 mV, −86.4 mV, −88.9 mV, −91.8 mV, and −98.2 mV and k values of 6.0, 6.0, 6.6, 6.5, 6.7, and 6.2 for control (before CBZ), control (after CBZ), 10, 30, 100, and 300 μM CBZ, respectively. B, The slope factor k was not changed by CBZ. Average values of k in control, 10, 30, 100, and 300 μM CBZ are 6.0 ± 0.6 (n = 5), 6.1 ± 0.3 (n = 4), 5.9 ± 0.5 (n = 4), 6.2 ± 0.7 (n = 7), and 6.3 ± 0.5 (n = 7), respectively. C, Dose-dependent shift of the midpoint (V_h) of the inactivation curve. The shifts (ΔV, in mV) are 2.5 ± 1.0 (n = 4), 5.5 ± 0.7 (n = 4), 7.5 ± 1.1 (n = 7), and 14.5 ± 2.1 (n = 7) for 10, 30, 100, and 300 μM CBZ, respectively.

neurons that DPH-bound inactivated Na^+ channels recover much slower than the inactivated channel in the control condition (12). Fig. 4 shows that CBZ also has a similar effect. From the time course of recovery in Fig. 4A, and especially from the expanded time courses of initial recovery in Fig. 4B, it is clear that CBZ-bound inactivated channels recover much more slowly than normal inactivated channels. Despite the fact that the residual or resting block is more pronounced in higher concentrations of CBZ, the kinetics of recovery in 100 and 300 μM CBZ are similar. The *gray bar* area in Fig. 4B indicates that after just a few milliseconds at the recovery gap potential, the majority of normal inactivated channels recover, whereas most CBZ-bound channels do not. This would be useful later for studying the binding rate of CBZ.

The binding rate of CBZ is faster than that of DPH. According to the *gray bar* area in Fig. 4B, the binding rate of CBZ onto inactivated Na^+ channels may be assessed by a voltage protocol similar to that in Fig. 4A, but the prepulse is gradually lengthened with the −120-mV gap fixed at 5 msec in duration. The decrease of the Na^+ currents elicited during the subsequent test pulse mostly reflects the increase of the drug-bound inactivated channels, with some contamination from the concomitant increase of the normal inactivated channels, which have not recovered during the 5-msec gap (Fig. 5A). The contamination is corrected by calculating the difference between the Na^+ currents in the control and in the presence of drug (Fig. 5B). It is evident that 300 μM CBZ approaches the steady state block faster than 100 μM CBZ, and it is especially interesting to compare the time courses of 100 μM CBZ and of 100 μM DPH. Consistent with the aforementioned conclusion that DPH has a higher binding affinity to the inactivated Na^+ channel than CBZ, the steady state block is larger for DPH. However, the binding rate of CBZ is significantly faster than that of DPH because the steady state block is reached much earlier in CBZ. The two time courses thus cross, and for short depolarization, CBZ may actually have a stronger inhibitory effect on Na^+ channels than equimolar DPH. Fig. 5C shows that the macroscopic binding rates increase linearly with drug concentration, which supports the presumption in Fig. 1B that CBZ (and DPH) interacts with Na^+ channels via a simple one-to-one binding (bimolecular) reaction. It is also demonstrated that the binding rate constant of CBZ (~38,000 M^{-1}/sec^{-1}) is ~5 times faster than that of DPH (~7,700 M^{-1}/sec^{-1}).

Discussion

Although use-dependent block of repetitive discharges resulting from inhibition of Na^+ channels is viewed as the major antiepileptic mechanism for both CBZ and DPH, no clear-cut differences between these two drugs has been forwarded to explain the clinical experience that some patients

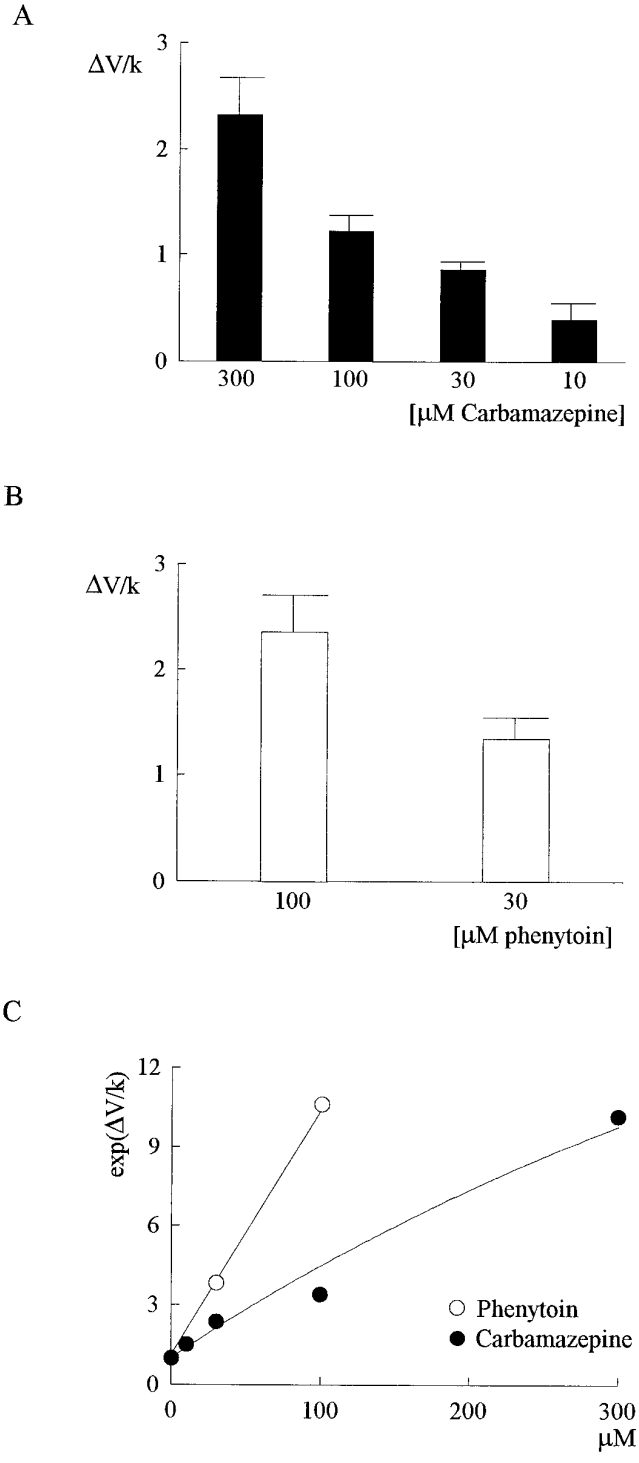


Fig. 3. Determination of the affinity between neuronal Na^+ channels and CBZ as well as DPH by $\Delta V/k$. A, $\Delta V/k$ versus CBZ concentration (data from the same cells as in Figs. 2, B and C). $\Delta V/k$ was 0.40 ± 0.16, 0.86 ± 0.09, 1.22 ± 0.16, and 2.32 ± 0.37 for 10, 30, 100, and 300 μM CBZ, respectively. B, $\Delta V/k$ versus DPH concentration. Similar experiments in DPH in the same cells. $\Delta V/k$ was 1.35 ± 0.21 and 2.36 ± 0.37 for 30 and 100 μM DPH, respectively. C, Exp($\Delta V/k$) versus CBZ or DPH concentration (data from the mean values in A and B). The lines are best fits of the form: $\exp(\Delta V/k) = [1+(D/K_I)]/[1+(D/1000)]$ in which D denotes concentrations of CBZ or DPH in μM, 1000 represents the presumed apparent dissociation constant between the resting state of Na^+ channel and the drug (i.e., K_R set at 1000 μM for both drugs), and K_I is 25 μM for CBZ or 9 μM for DPH.

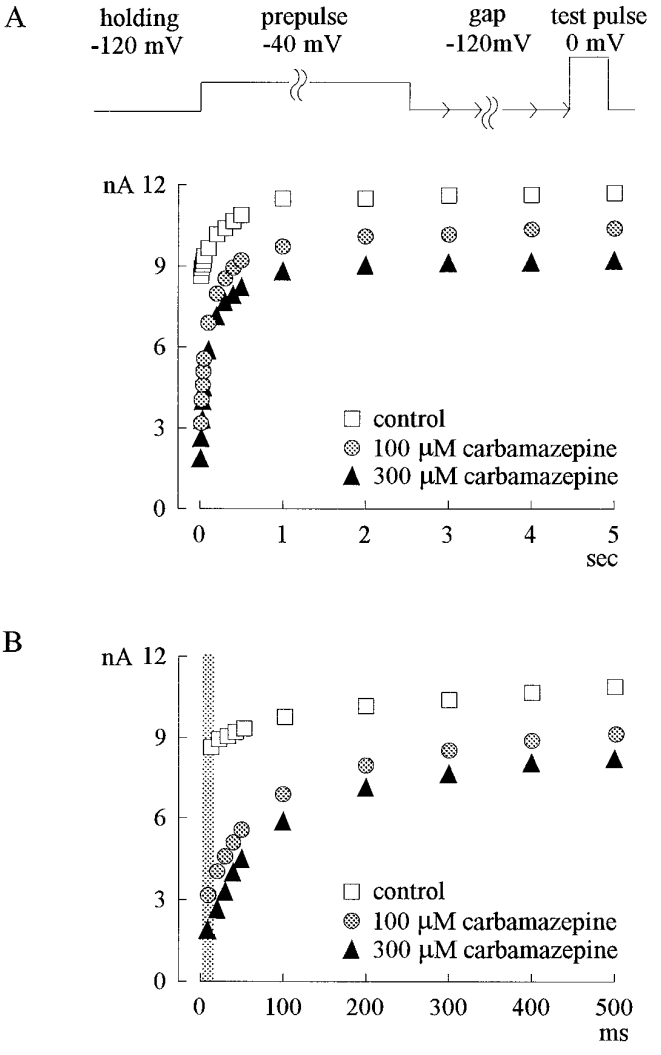


Fig. 4. Recovery from CBZ block at −120 mV. A, In the presence of 100 or 300 μM CBZ, the cell was held at −120 mV and then pulsed to −40 mV for 9 sec to reach a maximal (steady state) block of Na^+ current by CBZ. The cell was then stepped back to a recovery gap potential at −120 mV for variable length before being stepped again to a short test pulse at 0 mV to assess the available current. The pulse protocol was repeated every 15 sec. The time course of recovery is obtained by plotting the peak current at the test pulse against the length of the recovery gap potential. B, The first 500 msec of the plot in A was redrawn with an expanded scale of the horizontal axis. *Gray bar*, difference between the control currents and the currents in CBZ is most prominent with a very short (e.g., 5- to 10-msec) recovery gap when the majority of control currents have recovered but when most currents in CBZ have not.

respond much better to one drug than to the other and that some patients require both drugs (combined therapy) to reach a satisfactory control. We have shown that the effects of CBZ and DPH on central neuronal Na^+ currents are quite different in both binding affinity and binding kinetics. These differences, when correlated with the established cellular mechanisms of epilepsy, may be helpful in contemplating the pathophysiology and pharmacotherapy for individual seizure patients.

The significance of different binding affinities. In most focal epilepsy, the cellular events that characterize ictal discharges are prolonged (sustained) depolarization superimposed with high-frequency bursts of action potentials (16, 17;

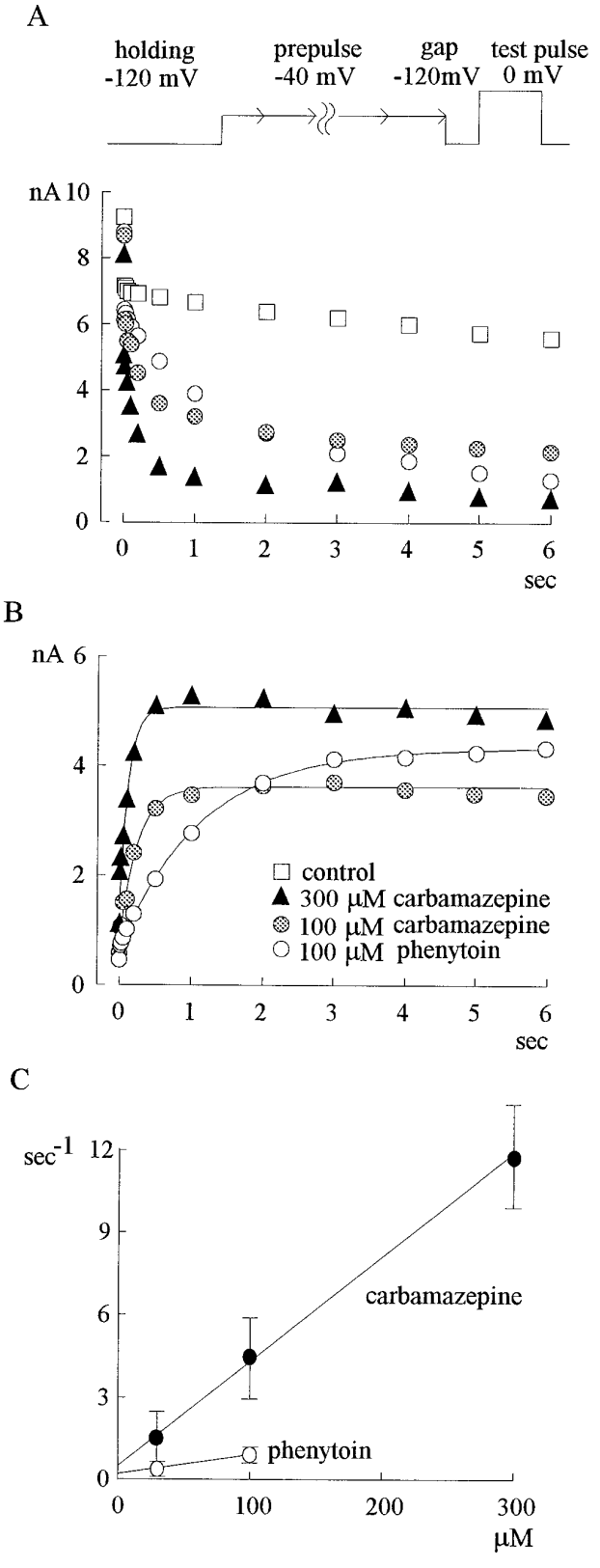


Fig. 5. Binding rate of CBZ and DPH. A, In the presence of 100 or 300 μM CBZ, the cell was held at −120 mV and was prepulsed to −40 mV for variable lengths every 15 sec. Immediately after the prepulse, the cell was stepped back to a recovery gap potential at −120 mV for 5 msec to recover most normal (not CBZ- or DPH-bound) inactivated Na^+ channels, and the peak current during the subsequent short test pulse to 0 mV was plotted against the duration the prepulse. B, The differences between the currents in drugs and the currents in control (data from part A) were plotted against the duration of the prepulse. The lines are monoexponential fits of the form: current (nA) = 5.1–3.5 × Exp(−*t*/0.12) for 300 μM CBZ (*t* denotes length of prepulse in seconds, the horizontal axis), current = 3.6–2.8 × Exp(−*t*/0.25) for 100 μM CBZ, and current = 4.3–3.7 × Exp(−*t*/1.13) for 100 μM DPH. C, The macroscopic binding rates for CBZ (the inverses of the time constants in B) from five cells are: 11.9 ± 2.0 sec^{-1} (300 μM), 4.6 ± 1.7 sec^{-1} (100 μM), and 1.6 ± 0.9 sec^{-1} (30 μM). Similar data for DPH from three cells are 0.39 ± 0.18 sec^{-1} (100 μM) and 0.90 ± 0.31 sec^{-1} (30 μM). The lines are linear regression fits to the mean values. The intercept and slope are 0.6 sec^{-1} and 38,000 M^{-1}/sec^{-1} for CBZ and are 0.15 sec^{-1} and 7,700 M^{-1}/sec^{-1} for DPH.

for reviews, see refs. 18, 19). Normally, the Na^+ current in hippocampal neurons is huge, and blocking part of it may not affect cellular firings. However, during ictal discharges, prolonged depolarization may drive many Na^+ channels into the inactivated state. Some further reduction of the available Na^+ channels could therefore successfully inhibit the superimposing bursts of action potentials.

The binding affinity between CBZ and the inactivated neuronal Na^+ channel is ~3 times lower than that of DPH. With high therapeutic concentrations in the cerebrospinal fluid [e.g., ~8 μM for DPH, ~13 μM for CBZ (20–23)] and apparent dissociation constants at ~7 μM (DPH) or ~25 μM (CBZ), the available Na^+ channels would be decreased by ~53% (DPH) or ~34% (CBZ) when the steady state of drug action is reached after prolonged depolarization (assuming one-to-one binding). With its stronger steady state inhibition, DPH potentially could be more effective than CBZ against seizures characterized by a relatively long depolarization shift, especially seizures that require such a long depolarization and the superimposing bursts of action potentials to develop and spread (i.e., to drive more neurons to join the hypersynchronous discharge). If the Na^+ channels in skeletal muscles also carry the same differential affinities to DPH and CBZ as those in central neurons, then the stronger steady state inhibition of Na^+ channels by DPH may also explain why DPH is probably better than CBZ in the treatment of myotonia, a disorder also characterized by prolonged membrane potential perturbation associated with repetitive discharges. Because the symptomatic abnormal depolarization of the affected muscle cell is likely quite longer than a few seconds and because the dampening of the repetitive discharges a few hundred milliseconds earlier or later is not critical in this case, DPH may represent a better choice than CBZ for this disorder.

The significance of different binding kinetics. From the kinetic point of view, the length of interictal or ictal depolarization shift is crucial in discussing the antiepileptic action of DPH and CBZ. With high therapeutic concentrations in the cerebrospinal fluid at ~8 μM (20, 21) and a binding rate constant at ~8,000 M^{-1}/sec^{-1} at room temperature, DPH would have a macroscopic binding rate (the product of drug concentration and the binding rate constant) of ~0.064 sec. With such a slow rate, DPH would apparently require a sustained depolarization for at least a few seconds to significantly approach its steady state blocking effect on Na^+ channels. However, because a large proportion of Na^+ channels may have been inactivated during ictal depolarization, DPH may not necessarily reach its steady state effect to abolish the bursts of firings superimposed on the sustained depolarization. Moreover, at body temperatures, the binding must be faster than it is at room temperature. Thus, in most

clinical situations, DPH would probably not require seconds of long ictal depolarization to exert its antiepileptic effect, although depolarization for a few hundred milliseconds might still be needed. Such an attribute would ensure that most normal firings are preserved in the presence of DPH but may also make DPH relatively ineffective against seizures characterized by shorter ictal depolarization. This seems to be consistent with a common electroencephalographic concept that DPH blocks seizures but may have much less effect on the frequency of interictal bursting in the cortex. Because the interictal discharges are usually characterized by much shorter paroxysmal depolarization shift, DPH may not have enough time to accomplish the job it could do with more prolonged (sustained) ictal depolarization.

The binding rate constant of CBZ is ~5 times faster than that of DPH. Along with the ~1.5 times higher therapeutic concentrations of CBZ in cerebrospinal fluid [5–13 μM (22, 23)], the macroscopic binding rate of CBZ would be ~7.5 times faster than DPH in clinical conditions. The remarkably faster binding rate of CBZ may make it more effective than DPH against the bursts of discharges superimposed on relatively short depolarization. Those seizures and neuralgias that have a better response to CBZ than to DPH may have underlying cellular correlates that fall into this category. In this regard, it would be interesting to examine whether CBZ is more effective than DPH in decreasing interictal discharges in some seizure patients.

Further arguments for the quantitative concepts. It is not uncommon to have a patient in whom seizure control is dramatically improved by a small increment in anticonvulsant dose and an increase of the plasma drug concentration from the low to the high therapeutic range, which usually means an increase of anticonvulsant concentration in the cerebrospinal fluid to no more than 1.5 or 2 times the original level. The experiences of different clinical effects with a small change in drug concentration support the view that a ~3-fold difference in affinity and a ~5-fold difference in binding rate constant are probably important attributes in accounting for the different clinical effects of DPH and CBZ. The quantitative arguments also provide more insight into the mechanistic rationale underlying combined therapy with CBZ and DPH. With the exception that CBZ might cover shorter ictal depolarization and DPH might have a stronger steady state inhibitory effect on Na^+ channels, the clinically relevant concentrations of DPH or CBZ in the cerebrospinal fluid are usually no more than the measured K_I of each drug. This indicates that the binding sites in the inactivated Na^+ channels are not saturated by CBZ and DPH in most clinical conditions. The combination of the two drugs thus should block significantly more Na^+ channels and increase the possibility of abolishing seizure discharges.

Although it is ideal to classify epilepsy and to institute appropriate pharmacotherapy according to the ictal cellular events in each individual seizure patients, so far no practical clinical means could effectively yield such information. On the other hand, correlation of the molecular action of different anticonvulsants with their therapeutic effect in individual patients may represent an indirect but realistic approach to elucidating the underlying pathophysiological events in the patient. Characterization of the molecular action of anticonvulsants may therefore not only contribute to a more sophisticated use of medication but also be helpful in delineating the manifold ictal cellular attributes of human epilepsy.

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