Responsiveness of Ictaform Discharges to Pharmacotherapy: The Bigger They Are, the Harder They Fall

Antiepileptic Drugs Abolish Ictal But Not Interictal Epileptiform Discharges In Vitro. D'Antuono M, Köhling R, Ricalzone S, Gotman J, Biagini G, Avoli M. *Epilepsia* 2010;51(3):423–431. PURPOSE: We established the effects of the antiepileptic drugs (AEDs) carbamazepine (CBZ), topiramate (TPM), and valproic acid (VPA) on the epileptiform activity induced by 4-aminopyridine (4AP) in the rat entorhinal cortex (EC) in an in vitro brain slice preparation. METHODS: Brain slices were obtained from Sprague-Dawley rats (200–250 g). Field and intracellular recordings were made from the EC during bath application of 4AP (50 μm). AEDs, and in some experiments, picrotoxin were bath applied concomitantly. RESULTS: Prolonged (>3 s), ictal-like epileptiform events were abolished by CBZ (50 μm), TPM (50 μm), and VPA (1 mm), whereas shorter (<3 s) interictal-like discharges continued to occur, even at concentrations up to 4-fold as high. γ-Aminobutyric acid $(GABA)_A$–receptor antagonism changed the 4AP-induced activity into recurrent interictal-like events that were not affected by CBZ or TPM, even at the highest concentrations. To establish whether these findings reflected the temporal features of the epileptiform discharges, we tested CBZ and TPM on 4AP-induced epileptiform activity driven by stimuli delivered at 100-, 10-, and 5-s intervals; these AEDs reduced ictal-like responses to stimuli at 100-s intervals at nearly therapeutic concentrations, but did not influence shorter interictal-like events elicited by stimuli delivered every 10 or 5 s. CONCLUSIONS: We conclude that the AED ability to control epileptiform synchronization in vitro depends mainly on activity-dependent characteristics such as discharge duration. Our data are in keeping with clinical evidence indicating that interictal activity is unaffected by AED levels that are effective to stop seizures.

COMMENTARY

At first glance, the recent paper by D'Antuono and colleagues seems to support the long-held view that antiepileptic drugs (AEDs) are highly effective at suppressing seizures but may be less effective with interictal phenomena. The authors elicited epileptiform activity in the in vitro entorhinal cortex by exposing brain slices to the potassium blocker 4-aminopyridine (4AP), a commonly used experimental convulsant, and tested three AEDs. None of the AEDs tested had a significant effect on interictal burst frequency, even when tested at twice the dose effective for abolishing ictal discharges. From a clinical perspective, does it really matter if AEDs fail to suppress interictal discharges? It has long been assumed that the presence or frequency of interictal spikes on EEG is not necessarily an indication of poor seizure control or AED failure (1), and the dose of AED therapy generally is not increased to try to suppress interictal activity, as these discharges are clinically silent. Instead, the general consensus has been to use AEDs only to suppress clinically expressed seizures. Clinicians are therefore taught to take a good history and treat the patient, not the EEG.

There is growing controversy, however, regarding the significance of interictal activity. Although interictal and ictal discharges are both believed to arise from the epileptic focus, questions have been raised as to whether they are part of one continuum or have independent generation mechanisms. Results from animal studies have not always been in agreement with those from clinical studies. Some experimental data have suggested that interictal activity may actually be protective, suppressing the expression of full-blown ictal events (2,3), but in vivo clinical findings do not seem to support this view (4,5). This area of research was a subject of a point–counterpoint series of articles in the November–December 2006 issue of *Epilepsy Currents* (6–8).

However, any attempt to draw conclusions regarding the significance of interictal activity by reviewing the literature is further muddied by the fact that the clinicians and the basic scientists use the terms "ictal" and "interictal" differently.

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D'Antuono and colleagues admitted that their distinction between ictal and interictal was arbitrary, referring to discharges under 3 seconds in length as interictal and those 3 to 40 seconds long as ictal. This practice is common in the basic science community, in which differences in responses of longer versus shorter in vitro discharges to experimental paradigms leads to laxity in use of the descriptive terms ictal and interictal, in part to simplify presentation of results to the clinical community. Meanwhile, although clinicians may know the definitions of interictal and ictal, they would be hard-pressed to provide the basic neuroscientists precise cut-offs in terms of burst length. All clinicians would agree that the term interictal is appropriately used to describe the clinically silent, classically recognized brief EEG discharges, such as spikes and sharp waves, which are typically under 200 milliseconds in duration on scalp recordings and have no motor, sensory, behavioral, or functional impairment accompanying the discharge. However, there is no consensus on an absolute intracellularly recorded discharge length that would constitute ictal as opposed to interictal, and there may be differences in the distinguishing discharge length depending on which area of cortex is involved. Indeed, it has long been recognized that individual spikes arising in occipital cortex can impair perception (9). Furthermore, recent technological advances and careful testing have revealed appreciable functional disturbances accompanying focal cortical discharges as brief as 800 milliseconds; oftentimes, these discharges are recordable on subdural grids but missed on scalp EEG (10,11).

Hence, in light of these observations, one should be cautious in drawing conclusions from the D'Antuono paper regarding interictal bursts, per se. The discharges they call interictal more likely represent a mixed pool of ictal and interictal discharges by clinical standards. Nevertheless, their data are significant in that they suggest that, indeed, the longer the in vitro discharge, the more susceptible it is to suppression by AED therapy. A careful glance at the figures in their paper tells the real story: 1) Although none of the agents tested eliminated interictal bursts, the data demonstrated a clear trend for each AED to reduce interictal discharge length in a dose-dependent fashion—an observation not mentioned by the authors due to lack of statistical significance, likely stemming from limited sample sizes. 2) Examining slices that exclusively expressed interictal bursts at least 500-milliseconds in length, the authors showed that the longer the discharge duration, the greater the impact of the AED, with a seemingly linear relationship between percent reduction and initial mean burst length. The range of burst lengths observed in this subset was 500 milliseconds to 1.6 seconds, and they showed that while there was negligible impact of AED treatment on 500 milliseconds bursts, the discharges that were 1.6 seconds in duration were reduced in length by approximately 50%. If the data presented in a linear manner is extrapolated, one would predict that discharges over 2.6 seconds should be completely eliminated, which is consistent with the authors' findings that the ictal discharges (i.e., those over 3 seconds) were abolished. Furthermore, if it is assumed that a 1.5 second discharge occurring in vivo is likely to be accompanied by a clinical perturbation and therefore constitutes an ictal phenomenon, then reducing the discharge to 750 milliseconds may indeed convert it to interictal length and completely suppress the associated seizures. 3) When the authors applied electrical stimuli at regular intervals to evoke epileptiform activity in the presence of 4AP, they demonstrated that ictal-length discharges, evoked at the longest interstimuli intervals, were not abolished in the presence of AEDs—instead they were dramatically abbreviated (approximately 80% reduction in length). In contrast, faster stimulation paradigms elicited shorter bursts, and these were suppressed only 5 to 20 percent by AED therapy. These findings seem to suggest that the relationship between burst length and suppression with AED use is not as linear as previously suggested, but rather plateaus as it approaches 100%, such that ictal-length discharges are abbreviated by AEDs, hopefully to the point that they are converted to interictal length with no clinical manifestation.

So, in summary, there are valuable data in this paper that are unfortunately obscured by the overreaching title. The point of the paper is not to distinguish the differences in AED effects on interictal and ictal phenomena. Rather, a more representative title to summarize the main findings of this paper would be: "Length of Epileptiform Discharges Determines Response to Antiepileptic Therapy" or, if you will, "The Bigger They Are, the Harder They Fall."

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