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Invited review

Does interictal synchronization influence ictogenesis?

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ABSTRACT

The EEG recorded from epileptic patients presents with interictal discharges that are not associated with detectable clinical symptoms but are valuable for diagnostic purposes. Experimental studies have shown that interictal discharges and ictal events (i.e., seizures) are characterized intracellularly by similar (but for duration) neuronal depolarizations leading to sustained action potential firing, thus indicating that they may share similar cellular and pharmacological mechanisms. It has also been proposed that interictal discharges may herald the onset of electrographic seizures, but other studies have demonstrated that interictal events interfere with the occurrence of ictal activity. The relationship between interictal and ictal activity thus remains ambiguous. Here we will review this issue in animal models of limbic seizures that are electrographically close to those seen in TLE patients. In particular we will: (i) focus on the electrophysiological and pharmacological characteristics of, at least, two types of interictal discharge; (ii) propose that they play opposite roles in leading to ictogenesis; and (iii) discuss the possibility that mimicking one of these two types of interictal activity by low frequency repetitive stimulation can control ictogenesis. Finally, we will also review evidence indicating that specific types of interictal discharge may play a role in epileptogenesis.

This article is part of the Special Issue entitled 'New Targets and Approaches to the Treatment of Epilepsy'.

1. Introduction

The electroencephalogram (EEG) of patients with partial epileptic disorders presents, between seizures, with interictal discharges that include *spikes* (<50 ms duration) and *sharp waves* (50–200 ms duration) (Chatrian et al., 1974; de Curtis and Avanzini, 2001), as well as high frequency oscillations (not specifically addressed in the present review, but see Bragin et al., 1999, 2004; Jefferys et al., 2012). Interictal discharges are not associated with detectable clinical symptoms and are valuable both for diagnosing the epileptic condition and for localizing the epileptogenic area (Jacobs et al., 2010; de Curtis and Avanzini, 2001).

Experimental work performed in both *in vivo* and *in vitro* animal models of seizures and epilepsy have demonstrated that interictal spikes/sharp waves and ictal discharges are characterized intracellularly by similar (but for duration) neuronal depolarizations that lead to sustained action potential firing (Ayala et al., 1973; Sherwin, 1984; Prince, 1993; Lopantsev and Avoli, 1998). Therefore, interictal and ictal discharges may share similar cellular and pharmacological mechanisms.

It has also been proposed that interictal events may herald the onset of electrographic seizures. For instance, experiments performed in the early 1970s led to the hypothesis that the fading of post-interictal spike hyperpolarizations could play a role in the transition from interictal to ictal discharge (see Ayala et al., 1973). However, clinical studies have later shown that the rate of occurrence of interictal discharges does not change before seizure onset in temporal lobe epilepsy (**TLE**) (Lange et al., 1983; Gotman and Marciani, 1985; Gotman, 1991). Moreover, evidence obtained in both *in vivo* (Engel and Ackermann, 1980) and *in vitro* animal models (Swartzwelder et al., 1987; Bragdon et al., 1992; Barbarosie and Avoli, 1997; Librizzi and de Curtis, 2003; see for review Avoli and de Curtis, 2011) indicates that interictal spiking may interfere with the occurrence of ictal discharges. The relationship between interictal and ictal activity thus remains ambiguous.

Here we will review this issue in animal models of limbic seizures that are electrographically close to those seen in TLE patients. In particular we will: (i) focus on the electrophysiological

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and pharmacological characteristics of, at least, two types of interictal discharge that are recorded in brain slices maintained *in vitro*; (ii) propose that they play opposite roles in leading to ictogenesis; and (iii) discuss the possibility that mimicking one of these two types of interictal activity by low frequency repetitive stimulation can control ictogenesis. In addition, we will briefly review experimental and clinical evidence indicating that specific types of interictal discharge may play a role in epileptogenesis.

2. Two interictal identities

Focal application of $GABA_A$ receptor antagonists to the cortex in intact preparations or superfusion of brain slices maintained *in vitro* with medium containing these drugs have represented the core of basic epilepsy research for more than half a century. These studies, however, rarely addressed the relation between interictal and ictal discharges, since the latter seldom occur under these experimental conditions. This problem has been solved by using manipulations that do not fully block $GABA_A$ receptor inhibition and even enhance it. Accordingly, it has been shown that prolonged epileptiform events, which may represent the equivalent of ictal phenomena, along with interictal activity are induced by application of the K^+ channel blocker 4-aminopyridine (**4AP**; see for review Avoli and de Curtis, 2011), the cholinergic agonist pilocarpine (Nagao et al., 1996), or medium containing either high $[K^+]$ (Jensen and Yaari, 1988) or nominally zero Mg^{2+} (Dreier and Heinemann, 1991; Kohling et al., 2000). Since TLE patients present with seizure discharges in several limbic structures, most of these studies have been carried out on rodent brain slices that include interconnected portions of hippocampal and parahippocampal areas.

As illustrated in Fig. 1A, these "extended" brain slices – when treated, for instance, with 4AP – generate epileptiform activity resembling both interictal and ictal events. Ictal discharges (dotted line in Fig. 1A): (i) depend on the activation of both NMDA and non-NMDA glutamatergic and $GABA_A$ receptors and (ii) in the adult brain slice they appear to initiate outside the hippocampus proper. In fact, depending upon how brain slices are cut (and thus which parahippocampal structures are included and how they are reciprocally interconnected), ictal activity can originate from the entorhinal cortex (**EC**) (Fig. 1A and B, ictal onset panel), the perirhinal cortex (**PC**), the amygdala, as well as the insular or cingulate cortices (Avoli and de Curtis, 2011). Clinically these are all brain structures that are prone to generate seizures in patients with complex partial epilepsies (Rutecki et al., 1989; Gloor, 1992; Spencer and Spencer, 1994; Isnard et al., 2000; Bartolomei et al., 2005; Vaugier et al., 2009).

Close inspection of interictal activity recorded during 4AP application also reveals two distinct types of discharge: one type has a relatively low rate of occurrence (intervals can last up to 50 s), appears in all limbic areas, and has variable site of initiation (Fig. 1A and B, asterisks); the other type (Fig. 1A and B, arrows) occurs at short intervals (approx. every 1–4 s), originates in the CA3 area and can propagate to the EC/PC via the subiculum and then re-enter the hippocampus proper through the dentate gyrus (Fig. 1C). Moreover, both the dynamics and the velocity of spread of the first type of interictal discharge are slower than those characterizing CA3-driven interictal events (Perreault and Avoli, 1991, 1992); hence, these two types of discharges will be thereafter referred to as *slow* and *fast* interictal discharges, respectively.

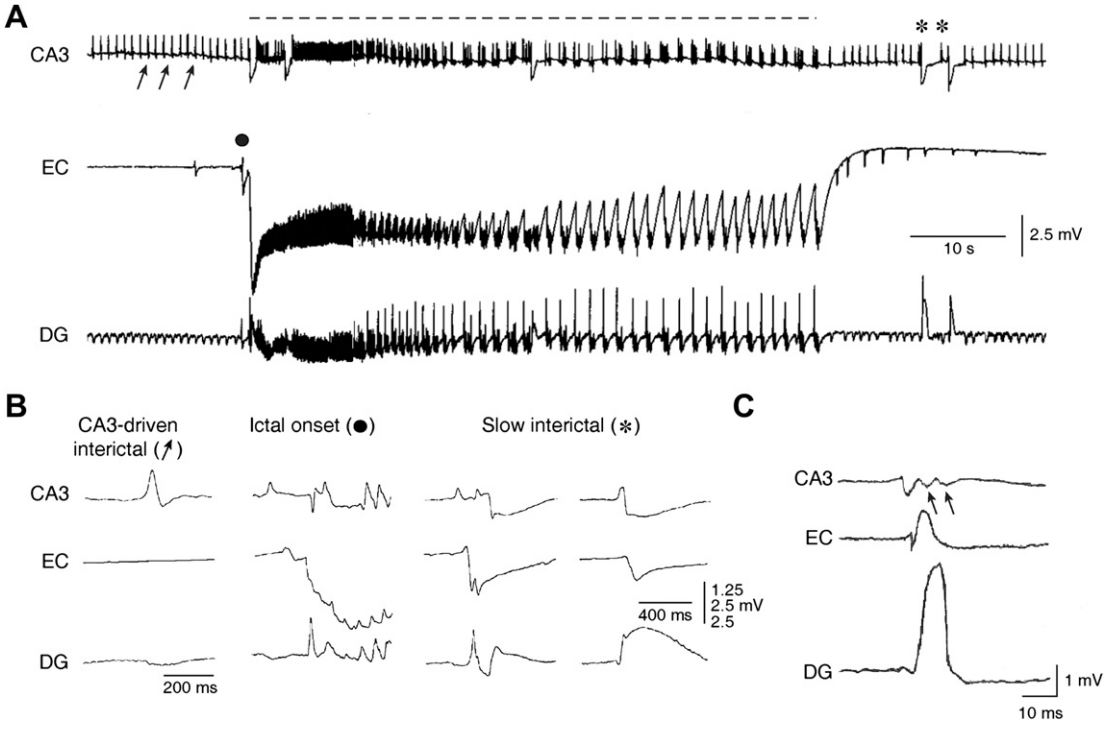

Fig. 1. Epileptiform patterns induced by 4AP in rodent hippocampus-entorhinal cortex slices. (A) Field potential recordings performed simultaneously in the rat CA3 subfield, EC and dentate gyrus demonstrate the occurrence of three different types of activity; the first (discontinuous line) is recorded synchronously in all areas and consists of a sustained ictal-like epileptiform discharge; the second type (arrows) consists of continuous *fast* interictal-like events, and it is seen in the CA3 and dentate areas only; the third type (asterisk) is recorded in all areas and is characterized by a *slow* field potential. (B) Expanded traces of the field potential recordings illustrated in A show the modalities of onset and spread of CA3-drive interictal events, ictal discharge onset, and *slow* interictal discharge; note that the ictal discharge initiates in the EC while different sites of origin characterize the two examples of *slow* interictal events. (C) Expanded traces of a CA3-driven interictal discharge recorded from a mouse hippocampus-EC slice; note that this interictal discharge initiates in the CA3 region and propagates to the EC and DG; arrows point at the "late" components of the CA3-driven interictal discharge recorded in CA3, presumably representing the re-entry of synchronous activity from the DG. In this and following figures abbreviations are: entorhinal cortex (EC); dentate gyrus (DG).