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Cellular and molecular mechanisms of epilepsy in the human brain

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Abstract

Animal models have provided invaluable data for identifying the pathogenesis of epileptic disorders. Clearly, the relevance of these experimental findings would be strengthened by the demonstration that similar fundamental mechanisms are at work in the human epileptic brain. Epilepsy surgery has indeed opened the possibility to directly study the functional properties of human brain tissue in vitro, and to analyze the mechanisms underlying seizures and epileptogenesis. Here, we summarize the findings obtained over the last 40 years from electrophysiological, histochemical and molecular experiments made with the human brain tissue. In particular, this review will focus on (i) the synaptic and non-synaptic properties of neocortical neurons along with their ability to produce synchronous activity; (ii) the anatomical and functional alterations that characterize limbic structures in patients presenting with mesial temporal lobe epilepsy; (iii) the issue of antiepileptic drug action and resistance; and (iv) the pathophysiology of seizure genesis in Taylor's type focal cortical dysplasia. Finally, we will address some of the problems that are inherent to this type of experimental approach, in particular the lack of proper controls and possible strategies to obviate this limitation.

Keywords: Epilepsy; Pathophysiology; GABA; Temporal lobe; Focal dysplasia; Electrophysiology; Histology

Contents

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1. Introduction

Over the last few decades, the refinement and advancement of neurobiological investigative tools along with the proliferation of epilepsy surgery have offered the possibility to study in detail some network, cellular and molecular properties of the human brain (cf. Avoli, 1993; Avoli and Schwartzkroin, 1993; Avoli and Williamson, 1996). Such analyses, which have been most often performed on brain tissue obtained from epileptic patients, not only have revealed some basic principles of network and cellular physiology of human nerve cells but also have provided direct information on the pathophysiology underlying this disease.

Here, we will review these studies and in particular we will address four main topics. First, in Section 2, we will evaluate the knowledge acquired by studying the in vitro electrophysiological properties of human neocortical networks from patients who most often present with partial epileptic disorders such as mesial temporal lobe epilepsy (MTLE). It is well established that seizure discharges in MTLE patients initiate from mesial limbic structures such as the hippocampus, the entorhinal cortex and the amygdala; moreover these limbic areas present with histopathological changes that are undetected in the neocortex. Therefore, neocortical neurons in MTLE patients (since they do not display any remarkable histopathological change) may represent an investigative system for assessing the cellular and pharmacological mechanisms underlying human brain function. Second, we will summarize the findings identified in the limbic structures of MTLE patients; in doing so, we will compare these data with those obtained from animal models mimicking this epileptic disorder (Section 3). Third, we will review some data pertaining to the effects of antiepileptic drugs on human neurons as well as recent evidence that identifies new mechanisms underlying pharmacoresistance (Section 4). Fourth, we will focus on studies carried out on Taylor's type, focal cortical dysplasia (FCD); this neurological condition, which corresponds to a localized disruption of the normal neocortical lamination with an excess of dysmorphic neurons, is associated with seizures (Section 5).

Some remarks should to be made at this point. For instance, it must be emphasized that the majority of human data have resulted to date from in vitro methodological approaches, and in particular the brain slice preparation; therefore, these findings do reflect the activity of a ''reduced'' system that does not possess the capabilities of an intact brain (Steriade, 2001). In addition, the majority of these experiments have been performed in patients presenting with partial epileptic disorders that are often pharmacoresistant and thus amenable for in-depth investigations leading to neurosurgical interventions. It is also important to note that the interpretation of data obtained from human slice experiments is hampered by the absence of ''normal'' human controls. Such a problem has been partially worked out by employing ''non-epileptic'' cortical samples (for instance, tissue resected during removal of a tumor located deep in the brain). However, even in such cases, it is unlikely that this brain tissue was ''normal''. These aspects will be addressed in detail in Section 6. Throughout this review we will also compare the findings obtained by studying the human tissue with evidence gathered in animal models.

2. Functional properties of human neocortical networks in patients with mesial temporal lobe epilepsy

2.1. Intrinsic electrophysiological properties and repetitive firing

Intracellular recordings have been widely used to characterize the fundamental electrophysiological properties as well as the patterns of repetitive firing of cells in human neocortical slices maintained in vitro (Avoli and Olivier, 1989; Avoli et al., 1994; McCormick and Williamson, 1989; Foehring

et al., 1991; Lorenzon and Foehring, 1992; Foehring and Waters, 1991; Sayer et al., 1993; Schwartzkroin et al., 1983; Cummins et al., 1994; Vreugdenhil et al., 1998). In most cases the neocortical tissue was obtained from patients with MTLE, that is to say, neocortex that does not show any obvious damage or structural aberration, but only a mild to moderate degree of gliosis.

Overall, these studies have demonstrated that human neocortical neurons are characterized by subthreshold responses that are remarkably similar to those recorded in animal tissue (Fig. 1A and B). These features reflect the presence of fast and persistent Na^+ currents and several K^+ outward currents including a muscarine-sensitive K^+ current and a hyperpolarization-activated inward conductance (also termed I_h) (Halliwell, 1986; Foehring and Waters, 1991; Lorenzon and Foehring, 1992; Cummins et al., 1994; Vreugdenhil et al., 1998). In addition, human neocortical neurons possess at least three types of Ca^{2+} currents when studied as acutely isolated cells (Sayer et al., 1993); these currents are similar to those identified in rodent neocortical cells but the T type current appears to be smaller in human than in animal tissue.

As illustrated in Fig. 1C, human neocortical cells respond to intracellular injection of suprathreshold depolarizing current by generating regular, repetitive firing that shows various degrees of adaptation, presumably caused by different types of K^+ currents. In keeping with this view, McCormick and Williamson (1989) have reported that several modulators such as histamine, methacholine, norepinephrine and serotonin reduce firing adaptation and a Ca^{2+}-dependent K^+ current in human neocortical cells. Moreover, plots of the repetitive firing rate versus current injection have demonstrated the existence of two distinct linear segments of firing (so-called primary and secondary ranges of firing) (Avoli and Olivier, 1989; Avoli et al., 1994). Once more, these characteristics are analogous to those of regularly firing neurons of the rodent and feline neocortex both in vivo (Calvin and Sypert, 1976) and in vitro (McCormick et al., 1985; Stafstrom et al., 1984). However, at variance with data obtained in rodent neocortical slices (Chagnac-Amitai et al., 1990; McCormick et al., 1985), neurons recorded from human neocortical slices rarely generate overt action potential bursts during injection of depolarizing current (Avoli and Olivier, 1989; Avoli et al., 1994; but see Foehring and Waters, 1991).

2.2. Excitatory synaptic responses

As reported in several studies performed in animal cortical areas in both in vivo and in vitro preparations, human neocortical neurons usually respond to focal extracellular stimuli by generating a short-lasting depolarizing synaptic event (Avoli and Olivier, 1989; McCormick, 1989; Schwartzkroin et al., 1983). This EPSP—which is often followed by a hyperpolarizing IPSP—is presumably caused by the activation of

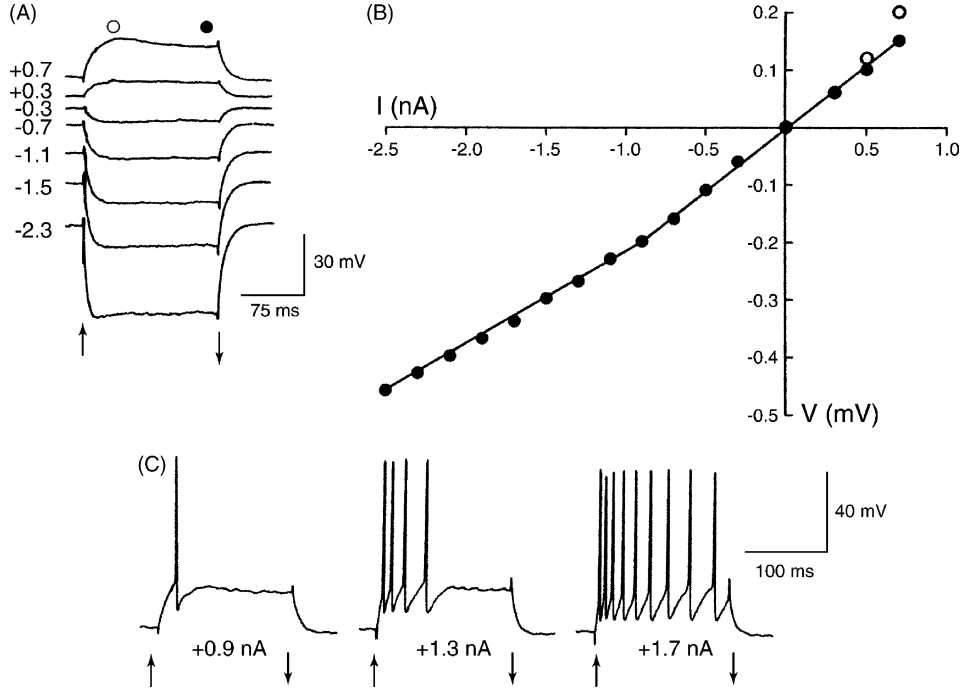

Fig. 1. Subthreshold responses and repetitive firing properties of a human neocortical neuron recorded in a slice of the second temporal gyrus. (A) Intracellular responses to pulses of depolarizing and hyperpolarizing current reveal membrane rectification, including inward rectification in the depolarizing direction and the appearance of a depolarizing "sag" during large amplitude hyperpolarizing pulses. (B) *I–V* plot obtained by measuring the depolarizing and hyperpolarizing responses induced by the intracellular current pulses at the time indicated in (B) by the open and filled circle. (C) Fast action potentials are generated during pulses of depolarizing current of increasing intensity. The amount of current injected is provided in each sample. Note that this neuron firing has adapting properties and each single action potential is followed by a pronounced fast afterhyperpolarization. Up- and down-going arrows below the intracellular recordings identify the onset and offset of the intracellular current pulse, respectively. Modified from Avoli et al. (1997), with permission.

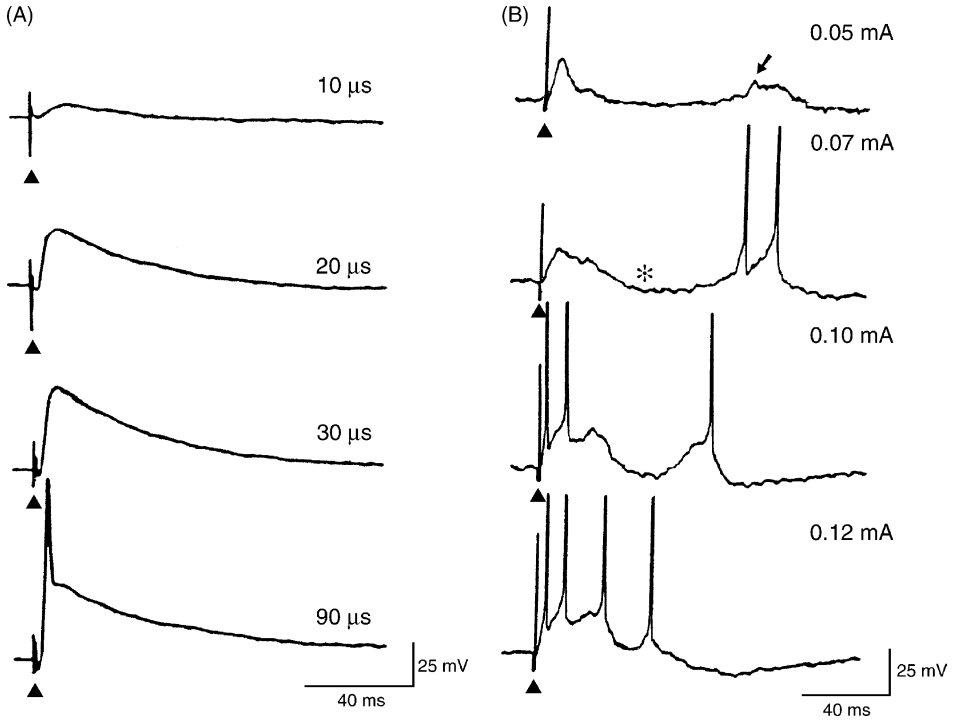

Fig. 2. Synaptic responses evoked by extracellular focal stimuli in two neurons recorded in the deep layers of the human temporal neocortex. (A) Single shock stimuli delivered in the white matter at progressively higher strength evoke an EPSP that becomes larger in amplitude and is finally capable of eliciting a single action potential (90 μs panel). (B) In a different neurons the synaptic response to low-strength stimulation (0.05 mA) consists of a short-latency EPSP followed by a low-amplitude (≈2 mV) hyperpolarizing IPSP that is interrupted by a late (onset at 180 ms) depolarizing event (arrow). When the intensity of the stimulus is brought to 0.07 mA, both the initial EPSP and the hyperpolarizing IPSP (asterisk) increase in amplitude, whereas the late depolarization is capable of triggering two action potentials. Further increasing the stimulus strength (0.10 and 0.12 mA frames), causes the appearance of a full-blown burst, which is followed by a late hyperpolarization. In this and following figures the extracellular focal stimulus is identified by a triangle. Modified from Avoli and Olivier (1989), with permission.

non-NMDA glutamatergic receptors since it is not influenced by bath application of NMDA receptor antagonists (Fig. 2A) (Hwa and Avoli, 1992). However, it has also been reported that human neocortical cells can generate bursts of action potentials following robust stimuli (Avoli and Olivier, 1989; Kato et al., 1973; Prince and Wong, 1981; Schwartzkroin et al., 1983; Wuarin et al., 1992). These stimulus-induced bursts are graded and thus dependent on the intensity of the electrical stimuli (Fig. 2B).

It has also been shown that these synaptic burst responses are caused by the activation of NMDA receptors (Avoli and Olivier, 1989; Wuarin et al., 1992). This characteristic is common to neurons recorded in neocortical slices obtained from adult MTLE patients (Avoli and Olivier, 1989; Avoli, 1991) and to those in slices from children with intractable epilepsy (Wuarin et al., 1992). It should also be mentioned that Strowbridge et al. (1992) have found that 81% of the neurons analyzed in neocortical slices obtained from near epileptogenic lesions generate prolonged excitatory postsynaptic potentials without any sign of inhibitory activity even at high stimulus intensities. In addition, long-latency, all-or-none paroxysmal depolarization shift-like discharges could be observed. Similar findings were also reported in human tissue in the vicinity of cavernous malformations (Williamson et al., 2003). By contrast, in another study performed in human neocortical slices obtained from spiking areas as determined by electrocorticography, interneurons were found to be normally innervated and receiving excitatory input (Menendez de la Prida et al., 2002). NMDA receptors have been implicated in the occurrence of epileptiform activity as well as in epileptogenesis (Rogawski, 1992; Meldrum and Chapman, 1999; Moshe, 2000). However, the relevance of the presence of NMDA receptor-mediated synaptic bursting responses in human neocortical slices remains as yet unclear.

2.3. GABA receptor-mediated inhibition

2.3.1. Stimulus-induced IPSP

Focal extracellular stimuli delivered within the neocortical layers or in the white matter of human slices evoke sequences of EPSP-IPSP (Avoli and Olivier, 1989; McCormick, 1989; Avoli et al., 1997; Deisz, 1999) that are similar to those identified in several studies performed in cerebral neurons in several animal species (see for review Krnjevic, 1980; Connors et al., 1988; Contreras, 2004; Thomson and Deuchars, 1994). The stimulus-induced IPSPs generated by human neocortical neurons are indeed characterized by two components (identified in Fig. 3A and B with a filled circle and a triangle, respectively) that have been pharmacologically characterized as being caused by the activation of post-synaptic $GABA_A$ and $GABA_B$ receptors (Olsen and Avoli, 1997).

In addition, extracellular focal stimuli delivered to human neocortical slices can induce a transient depolarizing response

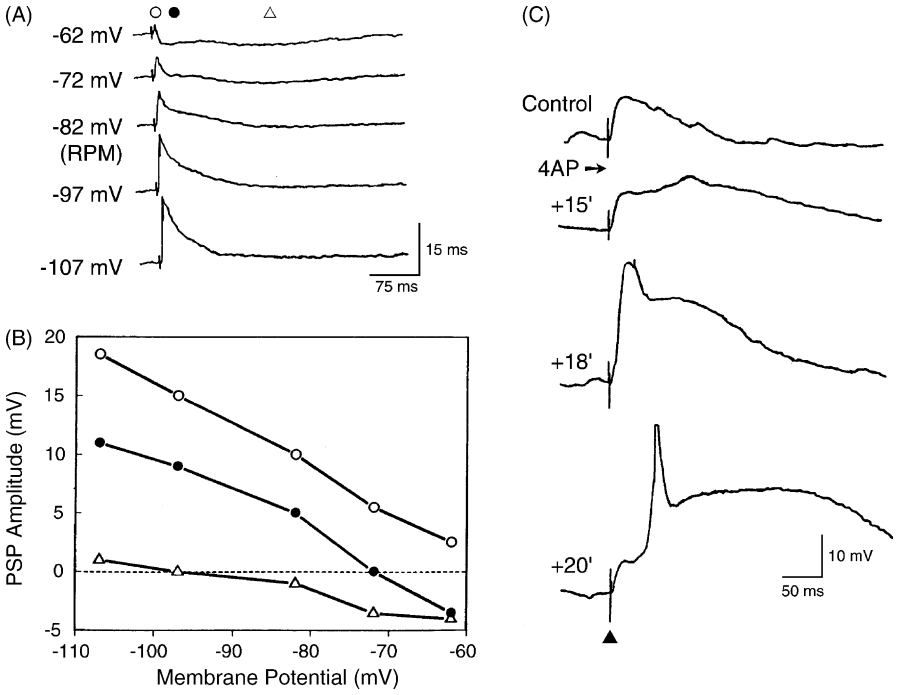

Fig. 3. Voltage-dependency of the synaptic responses generated by human neocortical cells and effects induced by 4-aminopyridine. (A) Synaptic responses recorded in a temporal neocortex neuron at different membrane potentials (resting membrane potential = −82 mV) following single shock stimulation. Note that depolarizing this neuron with steady current injection causes the appearance of a hyperpolarization that is characterized by a biphasic shape at −62 mV. (B) Plot of the amplitude of the responses measured at different latencies from the stimulus as shown by the symbols in (A). Note that the fast component of the hyperpolarizing potential (filled circles) changes in polarity at about −72 mV, while the slow component of the hyperpolarization (triangles) has revesal at −98 mV; note also that the initial EPSP (open circles) does not reverse within this range of membrane potentials. (C) Effects induced by bath application of low concentrations (50 μM) 4-aminopyridine (4AP) on the synaptic responses recorded with a KCl-filled microelectrode. In the control panel, the stimulus-induced response is purely depolarizing; moreover, this depolarizing response progressively grows in amplitude and duration in the presence of 4AP. (A and B) modified from Avoli et al. (1997), with permission; (C) modified from Avoli and Williamson (1996).

that is also presumably caused by the activation of $GABA_A$ receptors. Accordingly, focal application of GABA to human neocortical neurons can produce a predominantly depolarizing response (McCormick, 1989), while GABA receptor-dependent depolarizing potentials are recorded in the presence of 4-aminopyridine (which is a K^+ channel blocker leading to an increase in transmitter release from excitatory and inhibitory terminals, Hermann and Gorman, 1981; Buckle and Haas, 1982; Rutecki et al., 1987; Perreault and Avoli, 1991) (Figs. 3C and 5D). It should also be emphasized that similar findings have been obtained while analyzing rodent cortical neurons during bath application of 4-aminopyridine (Perreault and Avoli, 1989, 1992; Avoli et al., 1996a,b; Benardo, 1997; Kaila, 1994; Lamsa and Kaila, 1997; Lopantsev and Avoli, 1998; Michelson and Wong, 1991).

2.3.2. *Spontaneous GABAergic potentials*

An interesting difference that emerges when comparing electrophysiological data obtained from animal with human neocortical tissue is the widespread presence of spontaneous inhibitory potentials in the latter instance (Schwartzkroin and Knowles, 1984; Schwartzkroin and Haglund, 1986; Köhling et al., 1998). These events, which are primarily observed in supragranular layers, are sufficiently synchronous to support field potential discharges that are initiated within foci of less than 300 μm diameter (Köhling et al., 1998), or even when they appear synchronously across the entire slice (Fig. 4A). Even though population spikes are sometimes superimposed on these discharges, most neurons show hyperpolarizing potentials in conjunction with these discharges, with reversal potentials around −70 mV (Fig. 4B), suggesting that these synaptic potentials are mainly caused by an increase in Cl^- conductance. It has also been shown that this spontaneous network activity relies on both glutamatergic and GABAergic transmission; in line with this view, bath application of the $GABA_A$-receptor antagonist bicuculline, which usually acts as an epileptogenic drug, blocks these network discharges (Köhling et al., 1998, 1999, 2000) (Fig. 4C).

Do these potentials have any functional relevance for epilepsy? It is indeed conceivable that they represent merely physiological activity of the primate brain since they were also observed in the monkey hippocampus (but not neocortex) (Schwartzkroin and Haglund, 1986). However, one cannot exclude the possibility that they may also reflect some form of epileptiform hyperexcitability of the human tissue. What argues in favor of the latter option is the fact that this type of synchronization is strong enough to generate field potentials and that these rhythmic discharges also occur in human neocortical tissue, while they were not observed under physiological conditions in primate tissue (Schwartzkroin and Haglund, 1986). Further, there is a striking resemblance to the rhythmic activity occurring in the subiculum of epileptic

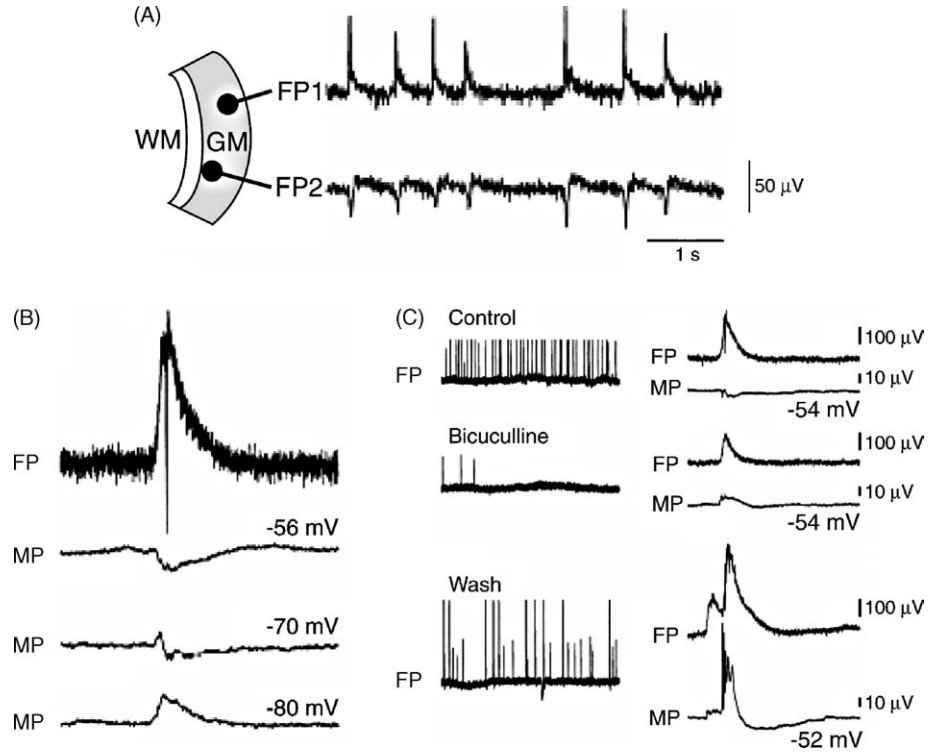

Fig. 4. Spontaneous network discharges in human neocortical slices from epileptic patients. (A) Synchronous network discharges monitored by field potential (FP) recordings from two sites in the slice (FP1 and FP2). In this experiment, the spontaneous activity ecompassed the entire slice. (B) Intracellular (MP) events obtained from a presumed pyramidal neuron during spontaneous field potential discharges (with population spike superimposed) at different membrane potential levels as indicated on the right of each trace. Note that the intracellular events are mainly hyperpolarizing at −56 and −70 mV and become depolarizing at membrane potential >75 mV. (C) The occurrence of network discharges are dependent on GABA receptor-mediated transmission and can be abolished by the $GABA_A$-receptor antagonist bicuculline. Modified from Köhling et al. (1998), with permission.

patients; these similarities include pharmacological properties, discharge morphology and rhythmicity suggesting that the phenomena reported by Cohen et al. (2002; see below) and the spontaneous discharges generated by neocortical slices reflect similar mechanisms. In addition, it may be speculated that they might subserve either a reset function allowing for greater synchrony or, as in the subiculum, a pacing role since GABA appears to exert a depolarizing action in a small subset of neocortical neurons, which, however, remain to be identified yet.

Overall, these data suggest that GABA is the major inhibitory transmitter in the human neocortex. This conclusion is in line with anatomical data demonstrating the presence of GABAergic cells in this tissue (Babb et al., 1989; Marco et al., 1996). However, discreet functional alterations in inhibition can be observed in chronically epileptic human slices, such as the appearance of spontaneous GABA receptor-dependent network discharges or a possible reduction of inhibition in circumscribed regions. More prominently, a regionally circumscribed loss of chandelier cells, powerfully inhibitory interneurons in the neocortex, may contribute to epileptogenesis (DeFelipe, 1999). As discussed below, even more pronounced differences have been found in human mesial temporal structures in MTLE patients (Section 3).

The notion that GABAergic function may be altered in human neocortical tissue from patients with focal epilepsy is supported by the finding that this tissue has an inherent resistance to the induction of spreading depressions (SD) following application of low concentrations of the $GABA_A$ receptor antagonist bicuculline, a procedure that readily induces SD episodes in normal rat tissue (Köhling et al., 2003). Correspondingly, it has also been found that neocortical slices obtained from pilocarpine-treated, chronically epileptic rats, showed an identical resistance to SD induction (Köhling et al., 2003).

2.4. Epileptiform synchronization in the human neocortical tissue

Human neocortical tissue maintained in vitro can generate overt epileptiform activity under appropriate pharmacological conditions. These procedures include superfusion with medium containing the $GABA_A$ receptor antagonist bicuculline, or the K^+ channel blocker 4-aminopyridine, or zero Mg^{2+} (i.e., artificial cerebrospinal fluid that does not contain, at least nominally, any Mg^{2+}).

2.4.1. Epileptiform activity induced by $GABA_A$ receptor antagonists

It is well established that bicuculline application to human neocortical slices causes the appearance of interictal-like epileptiform discharges that are intracellularly mirrored by bursts of action potentials (Avoli and Olivier, 1989; Hwa et al., 1991; McCormick, 1989; Tasker et al., 1992) (Fig. 5A). Interestingly, electrical focal stimuli are required for eliciting this type of epileptiform discharge since neither interictal- nor

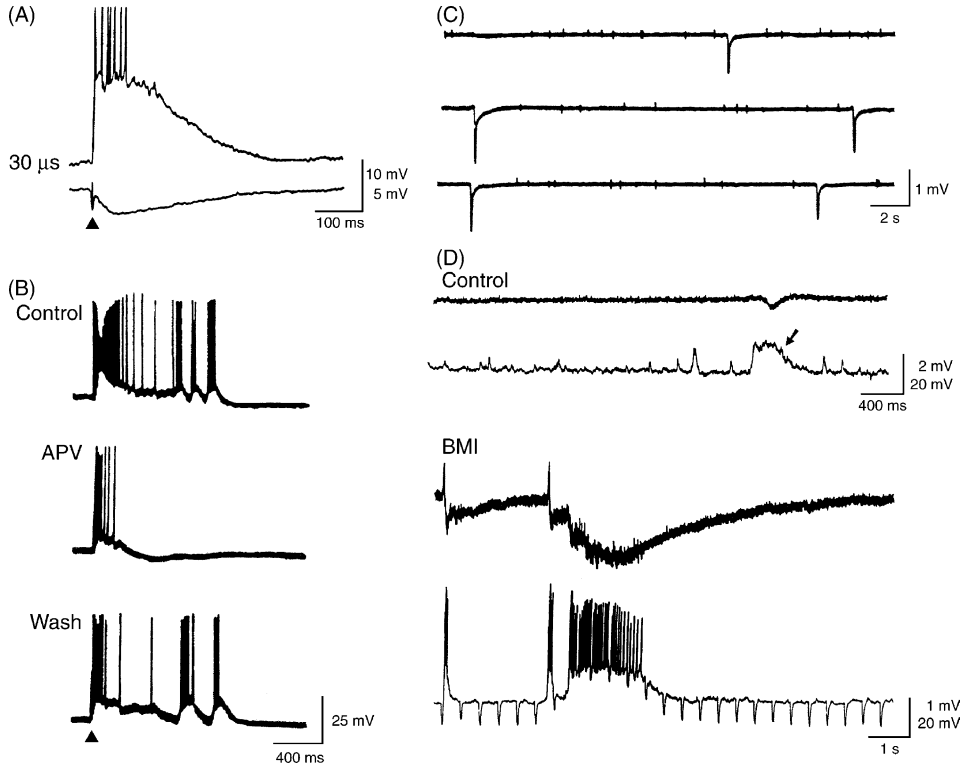

Fig. 5. Characteristics of the stimulus-induced synchronized bursts recorded in human neocortical slices treated with biculline methiodide (BMI). (A) The paroxysmal depolarization shift (upper trace) is a synchronous epileptiform event being concurrent with the field discharge (lower trace) which represents the simultaneous activities of a large population of neurons. The intracellular and extracellular recording electrodes were approximately 500 μM apart. (B) Aminophosphonovaleric acid (APV, 100 μM) attenuates the late phase of the paroxysmal depolarization shift. (C) Characteristics of the synchronous field potentials induced by 4AP in slices of the human neocortex. Continuous extracellular recordings show spontaneous, synchronous negative-going field potentials recorded approximately 100 μM from the pia. (D) Epileptiform discharges are induced by application of BMI to a human neocortical slice that was already superfused with 4AP-conaining medium (control trace). Simultaneous extra- and intracellular recordings (upper and lower traces, respectively) show the blockade of the long-lasting depolarizations (which were associated with the synchronous field potentials under control conditions; arrow) and of the spontaneous "non-synchronous" depolarizing potentials. These changes were accompanied by the appearance of robust epileptiform discharges. During BMI, intracellular negative pulses (−0.3 nA) were continuously injected at 3 Hz to monitor the input resistance of the neuron membrane. The resting potential was held at −75 mV by injecting DC current. Panels (A) and (B) are modified from Hwa et al., 1991. Panel (C) is from Avoli et al. (1994), with permission.

ictal-like epileptiform activity occurs spontaneously during blockade of $GABA_A$ receptors; this evidence further suggests that inhibition may be required for the occurrence of spontaneous synchronization within human neocortical networks maintained in vitro.

Pharmacological analysis of the epileptiform activity recorded in human neocortical slices during application of $GABA_A$ receptor antagonists has also indicated that these synchronous stimulus-induced discharges are contributed by ionotropic glutamatergic receptor-mediated conductances. In particular, it was demonstrated that NMDA receptor-mediated interactions may participate in the late afterdischarge (Fig. 5B), while non-NMDA receptor mediated mechanisms are a sine qua non conditio for making electrical stimuli elicit epileptiform responses. It should be emphasized that these human findings are similar to those obtained in rodent neocortical slices that were bathed in medium containing $GABA_A$ receptor antagonists (Gutnick et al., 1982; Hwa and Avoli, 1991).

2.4.2. Epileptiform activity induced by 4-aminopyridine

In contrast to what recorded during application of $GABA_A$ receptor antagonists, 4-aminopyridine—which is known to enhance transmitter release at both excitatory and inhibitory terminals (Hermann and Gorman, 1981; Buckle and Haas, 1982; Rutecki et al., 1987; Perreault and Avoli, 1991)—readily induces spontaneous, network-driven interictal-like discharges that are usually characterized by single population events (Avoli et al., 1988, 1994) (Fig. 5C).

As already mentioned in Section 2.3.1, this field potential pattern is mirrored at the intracellular level by long-lasting depolarizing potentials (Fig. 5D, arrow in the control panel) that are associated with either no or a relative small number of fast action potentials. Studies performed in rat hippocampal neurons have shown that this type of network-driven activity is contributed by a $GABA_A$ receptor-mediated bicarbonate conductance (Kaila et al., 1997; Smirnov et al., 1999; Staley and Soldo, 1995). Moreover, bath application of bicuculline transforms the 4-aminopyridine-induced activity events into complex events associated with epileptiform afterdischarges (Fig. 5D, BMI panel). Hence, these data demonstrate that spontaneous network synchronization in the human neocortex maintained in vitro can be supported by GABAergic interactions. However, $GABA_A$ receptor-mediated inhibition is also instrumental in controlling the duration of the

discharge as well as the generation of associated action potentials.

Louvel et al. (2001) have indeed reported that the interictal-like discharges induced by 4-aminopyridine continue to occur synchronously during application of ionotropic glutamatergic receptor antagonists (see also Section 4.2; cf. Avoli et al., 1994) as well as that they are abolished by bath applying the $GABA_B$ receptor agonist baclofen. This evidence underscores the involvement of $GABA_B$ presynaptic receptors (which are presumably located on interneuron terminals; see also Section 5.2.3) in regulating the phasic transmitter release that leads to the occurrence of this 4-aminopyridine-induced, synchronous activity.

It has also been proposed in that study that the propagation of glutamategic-independent, 4-aminopyridine-induced events is mainly due to the transient increases in $[K^+]_o$ that accompany them (Fig. 6A). In particular, the $[K^+]_o$ elevations should lead to excitation of neighboring interneurons thus recruiting them in a

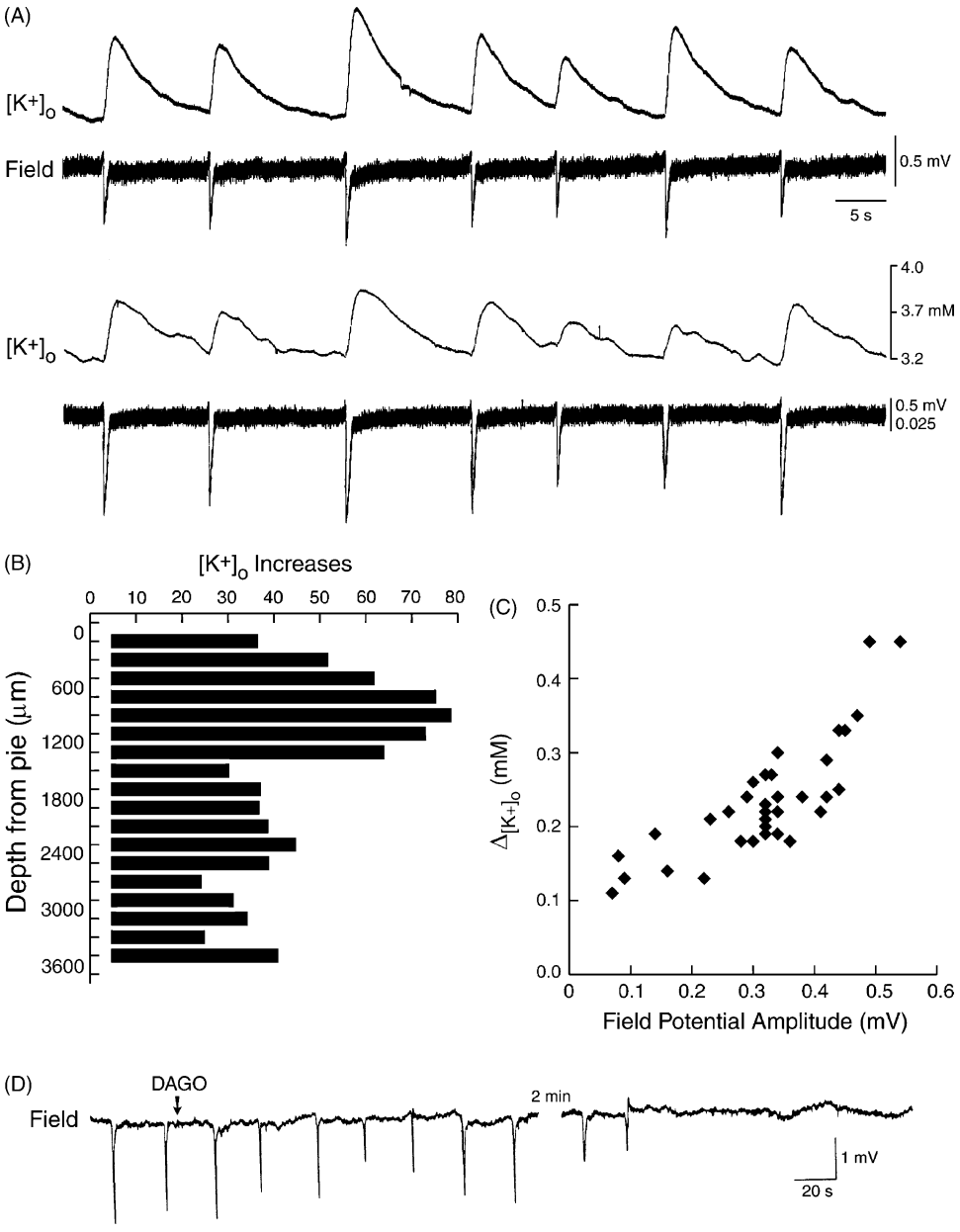

Fig. 6. Field potential and $[K^+]_o$ recordings in the human neocortex during application of medium containing 4AP, CNQX and CPP. (A) Field potential and $[K^+]_o$ recordings were made simultaneously at two sites located 1300 μm apart along a line parallel to the pia at a depth of approximately 1000 μm. Note that negative-going field potentials occur simultaneously at these two locations despite the blockade of ionotropic excitatory amino acid receptors. Moreover, these potentials are associated with transient increases in $[K^+]_o$, up to 4.1 mM from a baseline of approximately 3.2 mM. Note the different calibration of the two field potential traces. (B) Plot of the peak increases in $[K^+]_o$ associated with the spontaneous negative-going field potentials measured at different depths from the pia. Normalized data were obtained from six experiments. (C) Plot of the increments in $[K^+]_o$ (peak value minus baseline value) vs. the amplitude of the negative-going field potentials occurring spontaneously in one slice. Note the close relation between these two parameters. (D) Effects induced by bath application of the μ-opioid receptor agonist DAGO (10 μM) on the spontaneous field potentials recorded during application of medium containing 4AP, CNQX and CPP. Note that DAGO abolishes the synchronous, negative-going field potentials. Modified from Louvel et al. (2001), with permission.

synchronous mode that leads to the spread of the GABA receptor-mediated event. This view is also supported by the ability of the μ-opioid receptor agonist D-(Ala2-N-Me-Phe,Gly-ol)enkephalin (DAGO) to reduce and eventually abolish the periodic GABAergic events (Fig. 6D). This pharmacological procedure is known to hyperpolarize interneurons, thus decreasing their ability to release GABA (Madison and Nicoll, 1988; Capogna et al., 1993). Similar data have been obtained from rat brain slices treated with 4AP (Morris et al., 1996; Avoli et al., 1995a, 1996a; Lamsa and Kaila, 1997).

The evidence obtained with 4-aminopyridine in human neocortical slices from MTLE patients indicates that this tissue responds (as with other epileptogenic procedures, see Sections 2.4.1 and 2.4.3) in a way similar to that extensively reported in studies performed on rodent slices. Hence, it further suggests that the neocortical slices obtained from MTLE patients or individual presenting with non-epileptic disorders (e.g., brain tumor) are characterized by network connectivity with characteristics analogous to what seen in animals. At the same time these data emphasize the ability of $GABA_A$ receptor-mediated events to synchronize neuronal networks and to contribute to the spread of synchronous activity, an evidence that supports the potential role of spontaneous GABA receptor-mediated potentials in epileptogenic neocortex (Köhling et al., 1998) and subiculum (Cohen et al., 2002).

2.4.3. Epileptiform activity induced by Mg^{2+}-free medium

An alternative experimental tool for inducing spontaneous epileptiform discharges in human neocortical slices rests on the application of Mg^{2+}-free medium (Avoli et al., 1987, 1991, 1995b; Köhling et al., 1998, 1999). These epileptiform events are often characterized by duration and shape that resemble the electrographic seizures recorded in vivo (Fig. 7A and B) and are accompanied by transient increases in $[K^+]_o$ and decreases in $[Ca^{2+}]_o$ (Fig. 7D, Control). As reported in studies carried out in animal neocortical slices (Telfeian and Connors, 1999), the Mg^{2+}-free epileptiform events generated by the human tissue are readily blocked by both competitive and non-competitive NMDA receptor antagonists, while application of non-NMDA glutamatergic receptor antagonists fails in abolishing this type of epileptiform synchronization although it can at times reduce the duration and/or the rate of occurrence of the Mg^{2+}-free epileptiform discharges (Avoli et al., 1991).

Human neocortical slices superfused with Mg^{2+}-free medium can also generate spreading depression-like episodes that are associated with $[K^+]_o$ elevations in the 100 mM range (Avoli et al., 1991). By studying the cellular mechanisms of Mg^{2+}-free-induced epileptiform synchronization in human neocortical slices it was possible to identify the participation of GABA receptor-mediated potentials to these epileptogenic process. First, it was reported that spontaneous $GABA_A$ receptor-mediated events can occur between ictal-like discharges (Fig. 7C) as well as that the rate of occurrence of these IPSPs decreases shortly before the onset of ictal synchronization. Second, by using ion-selective electrodes it was found that antagonism of the $GABA_A$ receptor by bath application of bicuculline increases the changes in $[Ca^{2+}]_o$ and $[K^+]_o$ that are associated with the epileptiform discharges by 42.8 and 31.2%, respectively (Avoli et al., 1995b; Louvel et al., 1996) (Fig. 7D).

These data indicate therefore that $GABA_A$ receptor-dependent inhibition can control the ionic movements that occur during epileptiform activity. Specifically, such a mechanism may be relevant for controlling Ca^{2+} entry into neurons and glial cells during seizures, a process that has been implicated in neuronal death (Meldrum, 1991; Schousboe et al., 1994). Kostopoulos et al. (1989) have reported Mg^{2+}-free-induced epileptiform activity recorded in human neocortical slices is reduced by adenosine receptor agonists or by inhibting adenosine uptake. Later, these investigators have found an upregulation of adenosine A1 receptors in epileptic neocortical tissue as compared to control neocortex from non-epileptuc patients (Angelatou et al., 1993). Therefore, these findings suggest that adenosine receptors may constitute a protective mechanism in the human epileptic brain.

3. Functional and morphological changes in limbic areas of patients presenting with mesial temporal lobe epilepsy

MTLE is the most common form of partial epilepsy in adulthood and it is often poorly controlled by antiepileptic drugs (Wiebe et al., 2001). Hence, it represents an epileptic disorder that is amenable for surgical treatment. Seizure discharges in MTLE patients involve the temporal neocortex and limbic structures such as the hippocampus, the entorhinal cortex and the amygdala (Rutecki et al., 1989; Spencer and Spencer, 1994; Maillard et al., 2004; Bartolomei et al., 2001; Blumenfeld et al., 2004). These mesial limbic areas appear to be the sites of origin of epileptic discharges and display the most conspicuous morphological changes. Indeed, the brain of MTLE patients is characterized by a typical pattern of brain damage that is known as mesial temporal sclerosis (also termed Ammon's horn sclerosis, AHS) (Sommer, 1880). AHS is believed to result from status epilepticus or prolonged febrile seizures in early childhood (Gloor, 1997; Jackson et al., 1998; Lewis, 1999; Harvey, 1999).

The hallmark of AHS is a rather selective loss of neurons in the layer III of the entorhinal cortex (mainly in the medial portion), in the dentate hilus, and in the areas CA3 and CA1 of the hippocampus. In contrast, the granule cells of the dentate gyrus and the area CA2 of the hippocampus as well as the subiculum are relatively spared (Gloor, 1997; Du et al., 1993). Even though these histopathological changes have been confirmed in several studies performed in animal models of MTLE (e.g., Du et al., 1995), we are far from understanding the relation between this type of pathology and the epileptogenic processes that occur in MTLE patients.

3.1. Histopathological changes

Several studies have focused on the cell damage and consequent reorganization that characterize the dentate gyrus of MTLE patients. This reorganization consists of aberrantly sprouted granule cell axons projecting to the granule cell or

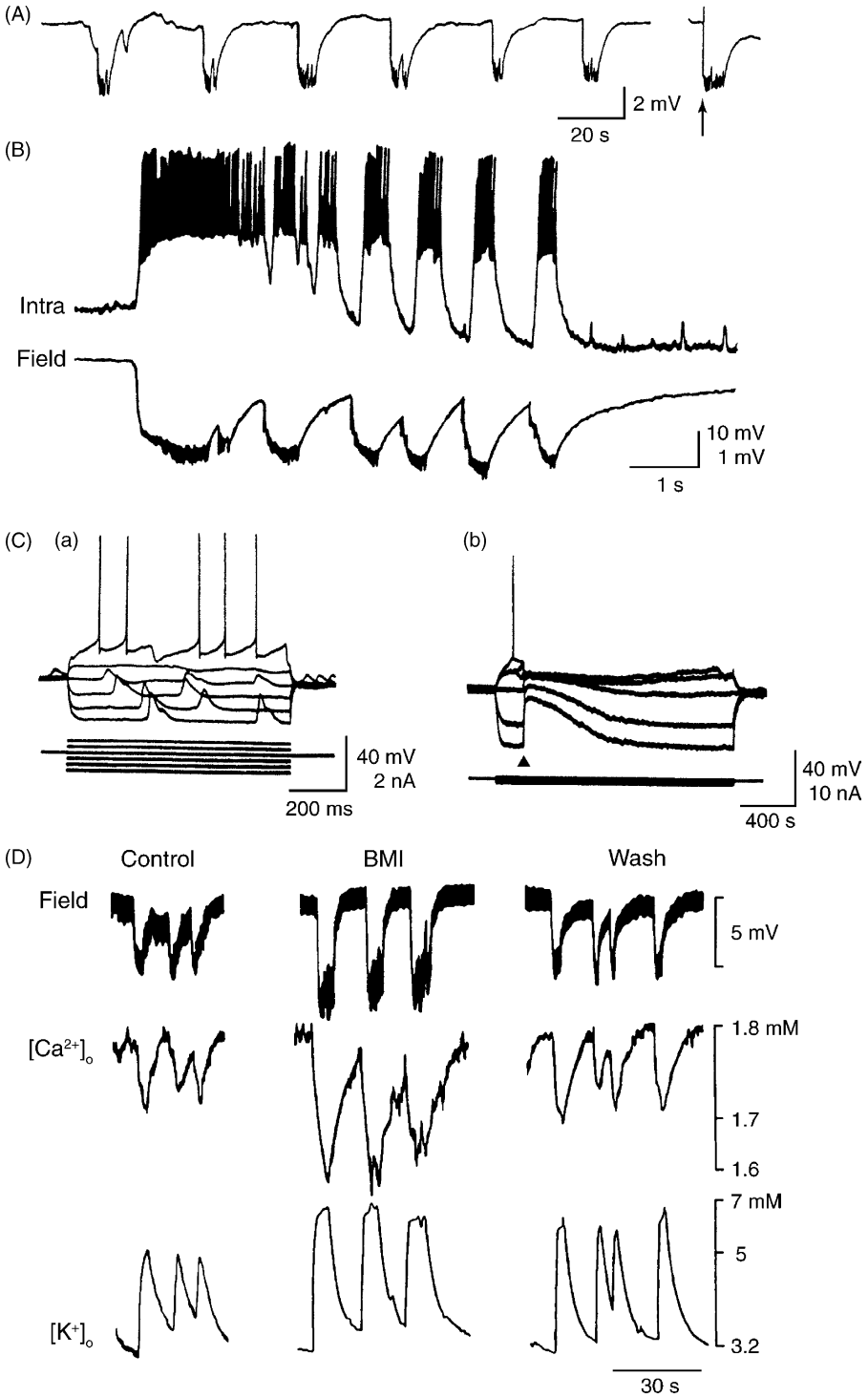

Fig. 7. Extracellular and intracellular features of the synchronous epileptiform discharges recorded in human neocortical slices during application of Mg^{2+}-free medium. (A) Field potential recordings of the spontaneous and a stimulus-induced (arrow) epileptiform discharges. (B) Typical intracellular and filed potential activity associated with a prolonged epileptiform discharge that is characterized by a "tonic" and "clonic" seizure-like pattern. During the "tonic" phase the neuron membrane depolarizes steadily and tonic firing of action potential occurs. The "clonic" phase is characterized by recurrent discharges of action potentials, and termination of each action potential burst is associated with a pronounced repolarization of the membrane. (C) Electrophysiological features of the spontaneous rhythmic potentials generated by a human neocortical neuron between epileptiform discharges induced by Mg^{2+}-free medium. Note the changes induced by varying the membrane potential with intracellular injection of prolonged pulses of current of the spontaneous (a) and stimulus-induced (b) potentials. Both spontaneous and stimulus-induced potentials show a reversal potential of approximately −60 mV. (D) Simultaneous recordings of field potential (field) extracellular Ca^{2+} ($[Ca^{2+}]_0$) and extracelluar K^+ ($[K^+]_0$) during spontaneous epileptiform activity induced by perfusion with Mg^{2+}-free medium. Signals were recorded ≈600 μM from the pia. Note that addition of BMI (20 μM) to the medium produces an increase in all measured signals. A washout period of approximately 2 h was required to bring back the $[Ca^{2+}]$ changes to control levels, although at this time both the field potential and the $[K^+]_0$ changes had not completely recovered to control values. Modified from Avoli et al. (1995b), with permission.

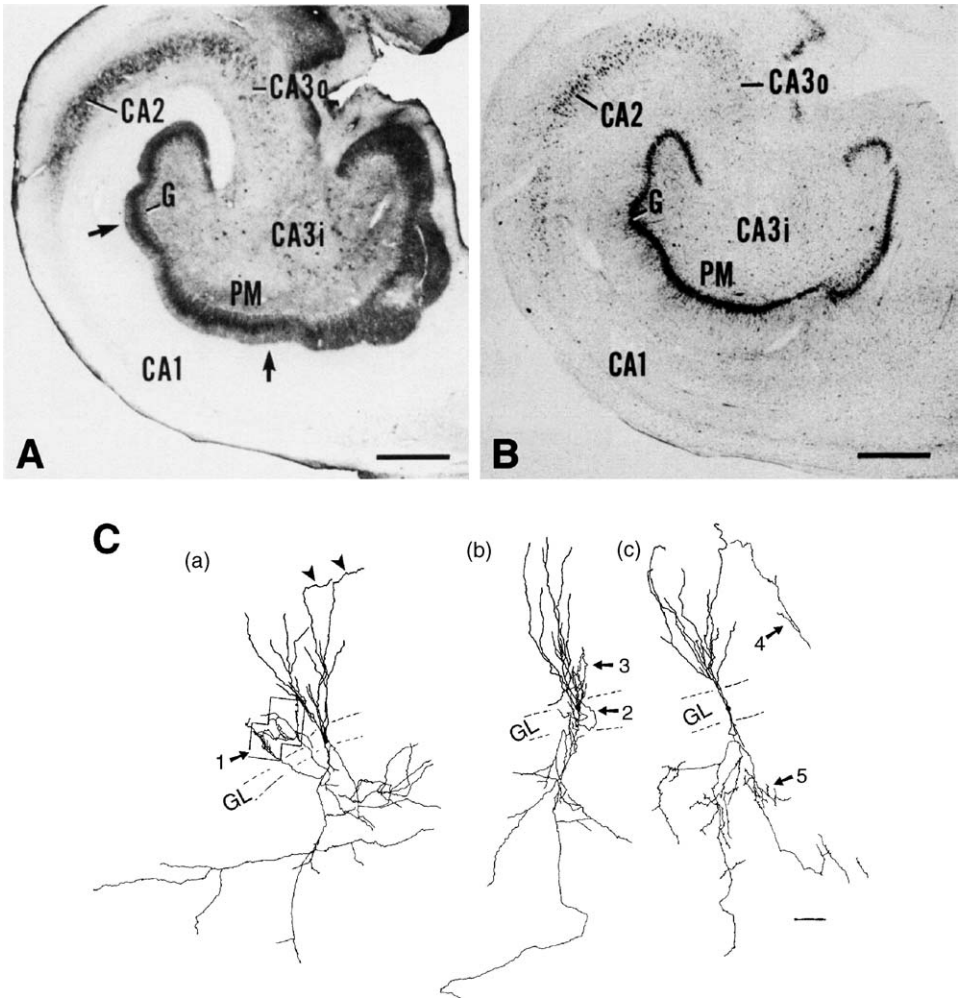

Fig. 8. Morphological characteristics of the hippocampus in MTLE. Patterns of dynorphin-like immunoreactivity (A) and cresyl violet staining of neuronal cell bodies (B) in adjacent coronal sections of the hippocampal formation obtained from a patient with MTLE. Note in (A) that densely stained band of dynorphin-like immunoreactivity is evident in the inner molecular layer and extends throughout the medial-lateral extent of the dentate gyrus (arrows). The narrow, lightly stained region immediately parallel to the band is the granule cell layer identified as G. Note also that relatively low concentrations of reaction product are present in the polymorph (PM) and CA3i (inner) field, where there is neuronal loss as demonstrated in the section shown in (B). Higher concentrations of reaction product are also evident in the distal part of CA3o and extend into the CA2 area. In (B), neurons in the dentate granule cell (G) layer and the CA2 field appear relatively well preserved. However, severe neuronal loss is evident in the polymorph (PM), CA3i and CA1 regions. Varying degrees of cell loss are also found in CA3o (outer). Scale bars, 1 mm. Modified from: Houser et al., 1990, with permission. (C) Aberrant collaterals of three individual granule cell axons identified in camera lucida drawings of biocytin or lucifer yellow-stained neurones. Arrowheads in **a** point at the distal ends of the dendrites where flexing at the outer edge of the molecular layer occurs. The formation of dense aberrant axon plexus in the molecular layer and around soma are identified with numbers 1 (boxed) and 2, respectively. The extensions of fibres of the somatal plexus into the molecular layer are identified with 3, while 4 points at single collateral in the molecular layer. Finally, 5 indicates a mossy fibre plexus in the hilus. Scale bar: 160 μm. Modified from Isokawa et al. (1993), with permission.

molecular layers in the way of recurrent excitation (Houser et al., 1990; Isokawa et al., 1993; Sutula et al., 1989) (Fig. 8). Together with granule cell dispersion, aberrant, recurrent sprouting of mossy fibers is apparent from widespread dynorphin immunoreactivity around the granule cell layer (Fig. 8A), the pattern of which is identical to results observed with TIMM staining.

Such sprouting is demonstrated in more detail in Fig. 8C where axons of individual granule cells appear to form dense, aberrant plexus, both on somata and in molecular layer (Isokawa et al., 1993). It should also be emphasized that sprouting in the dentate gyrus of MTLE patients has been found to be associated with an increase in spine density, suggesting very efficacious innervation by these newly-formed axon collaterals (Isokawa, 2000).

Besides hippocampal alterations, both neuronal cell loss and fibrillary gliosis can extend to other mesiotemporal regions such as the amygdala and the entorhinal cortex. It has been reported that these changes may at times occur independent of AHS (Yilmazer-Hanke et al., 2000).

By analyzing the distribution of granule cells in the dentate gyrus of the hippocampal formation in control autopsy and MTLE specimens, Houser (1990) has identified that granule cell somata in the latter cases were dispersed and formed a wider than normal granule cell layer. These dispersed granule cells were frequently aligned in columns, and many of these

neurons were characterized by elongated bipolar forms. It is worth noting that the extent of granule cell dispersion identified in this study appeared to be related to the amount of cell loss in the polymorph layer of the dentate gyrus. The most common features in the histories of the MTLE cases with granule cell dispersion were severe febrile seizures; indeed, these findings suggest the possibility of some alteration in the patterns of cell migration in some cases of severe MTLE. Moreover, it has been proposed that the resultant ectopic positions of these granule cells may cause important functional changes in both the afferent and efferent connections of these neurons and, thus, contribute to the altered circuitry of the hippocampal formation in MTLE.

Recent data also suggest that the epileptic hippocampus retains or reverts to an ontogenetically younger developmental stage: Cajal-Retzius cells, which usually disappear during development, persist in hippocampi presenting with AHS (Blümcke et al., 1996, 1999). Likewise, increased dentate gyrus neurogenesis has been reported particularly in tissue that was obtained from young (<2 years) patients (Blümcke et al., 2001, 2002). On the other hand, Haas et al. (2002) have reported that reelin expression by Cajal-Retzius cells appears to be decreased. Together, these changes are likely to play a role in the structural reorganization of the epileptic hippocampus.

3.2. Changes in limbic network excitability

3.2.1. Fundamental electrophysiological properties and repetitive firing

Similar to the findings reported in the neocortex (Section 2.1), the fundamental electrophysiological properties of neurons in the human epileptic hippocampus (and in particular granule cells that were investigated most extensively) do not differ substantially from what was reported in studies performed in normal animals. Thus, Na^+ action potentials and action potential discharge patterns were found to be largely identical to animal preparations (Isokawa et al., 1991; Strowbridge et al., 1992), as were indeed their corresponding currents, except for conspicuously high current densities (Reckziegel et al., 1998) and enlarged persistent Na^+ currents in subicular neurons (Vreugdenhil et al., 2004). Likewise, voltage-gated K^+ and Ca^{2+} currents analyzed in human granule cells appear to be remarkably similar to those found in rodent brain tissue (Beck et al., 1996, 1997a,b; Schumacher et al., 1998).

However, Bender et al. (2003) have reported changes in hyperpolarization-activated cyclic nucleotide-gated cation channels (HCNs). In particular, they found a marked increase HCN1 mRNA expression in the dentate gyrus granule cell layer and in individual granule cells from MTLE patients. Moreover, in autopsy and in most hippocampi presenting with no AHS, the HCN1 mRNA expression was substantial in pyramidal cell layers and lower in dentate gyrus granule cells. These changes were accompanied by enhanced immunoreactivity in the granule cell dendritic fields and more modest changes in HCN2 mRNA expression. Finally, a similar robust and isoform-selective augmentation of HCN1 mRNA expression was also evident in the pilocarpine animal model of MTLE (Bender et al., 2003).

3.2.2. Glutamatergic receptor mechanisms

Whereas parameters of intrinsic neuronal excitability may be rather 'normal' in human epileptic hippocampal neurons, synaptic mechanisms are not. Thus, it has been reported that dentate granule cells generate particularly prolonged, NMDA-dependent postsynaptic potentials or currents (Fig. 9A)

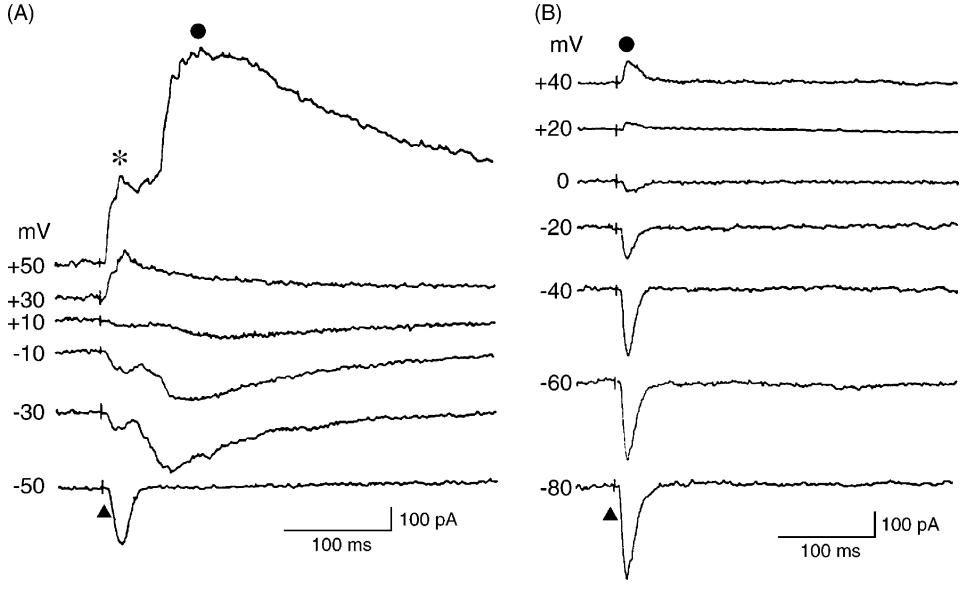

Fig. 9. Polyphasic, prolonged excitatory postsynaptic currents (EPSC) recorded in granule cells in hippocampal slices from MTLE patients. (A) Glutamate-mediated EPSCs recorded at different voltages in voltage-clamped granule cell. The first peak (asterisk) is AMPA-receptor dependent, while the second larger peak at a holding potential of +50 mV (dot) is NMDA-receptor dependent. These large, NMDA-receptor dependent EPSC, which had variable latencies, could be observed in a subpopulation of granule cells only. (B) Only AMPA-receptor-dependent EPSCs are recorded in a different cell. Modified from Isokawa et al. (1997), with permission.

(Isokawa and Levesque, 1991; Isokawa et al., 1997). These electrophysiological findings were correlated to loss of spine density, a finding that may likely be explained by a high variability of NMDA-current slope conductances, while alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)-mediated EPSC were uniform in amplitude and comparable to those obtained from animal brain tissue (Fig. 9B).

Molecular studies performed by Mathern et al. (1997, 1998, 1999) have shown that temporal lobe seizures are associated with changes in ionotropic glutamate receptor mRNA levels and in receptor subunit composition. These investigators have found increased NMDAR2 hybridization densities in dentate granule cells and increased AMPA GluR3 mRNA densities in CA pyramids of non-AHS epileptic hippocampi as compared with autoptic material. Moreover, when correcting for the changes in neuron densities occurring in sclerotic epileptic hippocampi, they reported increased AMPA and NMDA mRNA levels in MTLE tissue (Mathern et al., 1997). They have also found that epileptic patients presenting with either non-AHS or AHS have increased NR2A and NR2B hybridization densities per dentate granule cell, while non-AHS hippocampi show increased NR1 and NR2B mRNA levels per CA2/3 pyramidal neuron compared with autopsy cases (Mathern et al., 1999). Finally, these experiments have revealed that AHS epileptic patients have decreased NR2A hybridization densities per CA2/3 pyramidal neuron compared with non-HS and autopsy cases. This evidence points therefore at important changes in ionotropic glutamatargic mechanisms that vary by area and clinical-pathological category, and supports the hypothesis that NMDA receptor-mediated transmission is increased in MTLE dentate granule cells. Similar changes in ionotrophic glutamate receptor subunits were found in rats that had experienced self-sustained limbic status epilepticus (Mathern et al., 1998). Another study has shown that the distribution of polyamines, which are possibly involved in the control of the NMDA receptor-channel, is differentially altered in the seizure onset versus propagation areas in tissue from MTLE patients (Laschet et al., 1999). Therefore, these results point to a significant disturbance of excitatory synaptic transmission that may be crucial for the epileptogenicity of this type of tissue.

In addition to ionotropic glutamatergic mechanisms, a study by Dietrich et al. (1999) has focused on glutamatergic metabotropic receptors in human MTLE tissue. Presynaptic actions of metabotropic glutamate receptors are thought to constitute an important negative, inhibitory feedback mechanism that controls synaptic release of glutamate in the hippocampus. In their study, Dietrich et al. (1999) have reported that this control of synaptic transmission is lost in hippocampi presenting with AHS, while it remained preserved in specimens originating from hippocampal lesions without AHS.

Functional consequences of synaptic alterations are also evident when investigating synaptic plasticity and modulation, rather than straightforward synaptic activation per se. In this context, some studies have concentrated on the question whether short- and long-term plasticity is altered in human epileptic tissue, and whether modulatory synaptic mechanisms differ from those in less affected or healthy brain. Investigations on evoked field potentials recorded from depth electrodes stereotactically implanted in hippocampal structures from MTLE patients have revealed that short-term plasticity is disturbed in sclerotic hippocampi as compared to unaffected, non-sclerotic mesial structures (Wilson et al., 1998). Thus, paired-pulse depression was found to be increased in the perforant path and decreased in intrinsic associational pathways of sclerotic hippocampi (Fig. 10A). Such an increase of inhibition in the hippocampus input pathway might be interpreted as an intrinsic protection mechanism against seizures. On the other hand, a decreased inhibition within hippocampal circuits as suggested by the lower paired-pulse depression in response to stimuli delivered in intrinsic associational pathways might support the synchronizing drive for seizure generation.

In addition to some forms of short-term plasticity such as the paired-pulse stimulation protocol, long-term potentiation of synaptic transmission appears to be severly affected in in vitro slices that were obtained from sclerotic hippocampi during epilepsy surgery. Thus, well in agreement with a poor verbal memory performance of these MTLE patients, long-term potentiation in the perforant path was found to be severly reduced (Beck et al., 2000). Remarkably, such a finding was not seen in non-sclerotic hippocampi obtained from epileptic patients with normal memory performance (Fig. 10B).

The presence of AHS in MTLE (and thus the existence of mossy fiber sprouting and network reorganization) may play a crucial role in determining the type of synchronous epileptiform activity generated by granule cell populations in response to low-frequency hilar stimulation in the presence of elevated $[K^+]$ in the bathing medium (Gabriel et al., 2004). These investigators have found that seizure-like events could be readily recorded with 10 mM $[K^+]$ in sclerotic tissue slices, while in nonsclerotic slices a further increase in $[K^+]$ to 12 mM was required. These epileptiform responses were indeed abolished by ionotropic glutamatergic receptor antagonists.

3.3. GABA receptor inhibition

3.3.1. Interneurons and GABA receptors

One classical theory of epileptogenesis rests on the hypothesis that reduced inhibition within neuronal networks causes hyperexcitability thus leading to the occurrence of seizures (reviewed by Krnjevic, 1991; Olsen and Avoli, 1997; Avoli, 2000). In support of this view, histochemical studies have demonstrated that in addition to cell damage and sprouting, the number of $GABA_A$ receptors or $GABA_A$-receptor subunits (see also Section 3.3.3) is reduced in the hippocampus resected from MTLE patients during neurosurgical interventions (McDonald et al., 1991; Johnson et al., 1992; Olsen et al., 1992; Wolf et al., 1994). In addition, positron emission tomography imaging has identified a decrease of benzodiazepine binding sites for $GABA_A$ receptors in these patients (Savic et al., 1988; Henry et al., 1993; Sata et al., 2002). However, it has been proposed

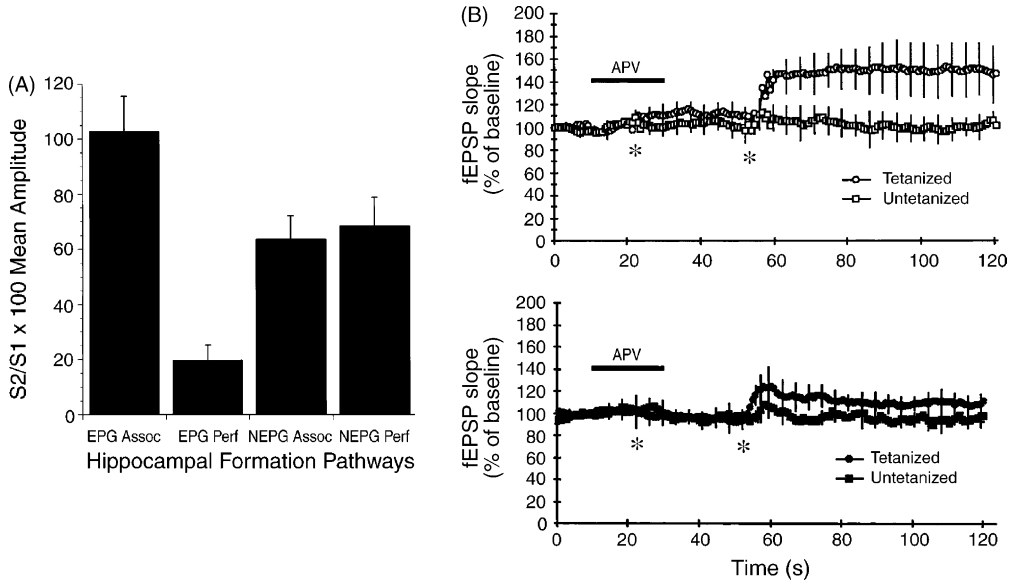

Fig. 10. Short and long-term plasticity in the human hippocampus in vivo and in vitro. (A) Summary of the mean excitability differences in specific hippocampal pathways in relation to epileptogenicity. Both epileptogenic and non-epileptogenic perforant pathway and hippocampal associational pathways were compared on the basis of the S2/S1 response amplitude ratio that was averaged across the first four interstimulus intervals (20, 50, 100 and 200 ms) of all paired pulse measures (vertical lines indicate S.E.M.). Note that epileptogenic hippocampal associational pathways are significantly more facilitated than non-epileptogenic pathways as well as that epileptogenic perforant pathways are significantly more suppressed than those in non-epileptogenic patients. Abbreviations are: Assoc, associational pathways; EPG, epileptogenic; NEPG, non-epileptogenic; Perf, perforant pathway. Modified from Wilson et al. (1998), with permission. (B) NMDA receptor-dependent long-term potentiation (LTP) in the dentate gyrus of the human hippocampus. LTP was induced in two experiments carried out on slices obtained from a non-AHS patient (top graph) and a patients that had severe AHS (bottom graph) by application of theta-burst stimulation (asterisks). Note in the experiment carried our in a non-AHS patient slice that this protocol induces potentiation of the fEPSP slope in the tetanized path only as well as that application of the NMDA receptor antagonist APV (horizontal bar) blocks the induction of LTP. Note also in the bottom graph that application of a theta-burst stimulation in the slice obtained from an AHS patient (asterisk) induces only modest potentiation of the fEPSP slope in the stimulated pathway. Modified from Beck et al. (2000), with permission.

that these changes may most likely be secondary to the neuronal loss associated with AHS.

GABAergic interneuron loss has also been reported to occur in the hippocampus of MTLE patients by using markers for $GABA_A$ receptors, for glutamic acid decarboxylase (GAD, the enzyme promoting synthesis of GABA from glutamate), and dynorphin (an endogenous opioid modulating neuronal excitability; Houser et al., 1990). More recently, Arellano et al. (2004) have reported that the sclerotic hippocampus of MTLE patients is characterized by reorganization of Chandelier cells in the dentate gyrus and hippocampal formation but not in the subiculum. Chandelier cells represent a unique type of interneuron whose axon terminals form synapses with the axon initial segments of cortical pyramidal cells and granular cells of the dentate gyrus. It should be, however, mentioned that Babb et al. (1989) have found evidence indicating a relative survival of GABAergic cells in this type of tissue. Moreover, these authors have proposed that changes (and indeed increases) in GAD content in MTLE tissue may result from cell sprouting, compensatory upregulation or new cell birth (Babb et al., 1989). As discussed in Section 3.3.2, a reduced function of GABAergic mechanisms per se may not occur in MTLE tissue. Accordingly, some data obtained from animal models of MTLE suggest that reduced inhibition is not necessary for the appearance of limbic network hyperexcitability (reviewed by Avoli et al., 2002).

3.3.2. GABA receptor-mediated functions in human MTLE tissue and in MTLE animal models

Histopathological and histochemical findings similar to those reported to occur in MTLE limbic structures have been obtained in animal models such as those induced by prolonged stimulation of hippocampal inputs (Sloviter, 1991), kindling procedures (Cavazos et al., 1991) and systemic injections of kainic acid (Cronin et al., 1992) or pilocarpine (Cavalheiro et al., 1991; Cossart et al., 2001). As in the human condition, these models are characterized by AHS including extensive loss of hilar cells and synaptic reorganization of the dentate gyrus. Although interneurons—contrary to the above cited histopathological findings in human epilepsy—may not be injured and still capable of releasing GABA in animal models, the function of GABA-mediated inhibition is likely to be changed in some of these models of temporal lobe epilepsy. For instance, electrically kindled rats show reduced $GABA_A$ receptor function and binding in the CA1 subfield of the hippocampus and other areas as well (Titulaer et al., 1994). In a more detailed analysis, Poulter et al. (1999) could show that it is perhaps not a global reduction of GABAergic function, but rather a re-emergence of onogenetically immature GABA-receptor expression patterns that may be responsible for epileptogenesis. Thus, comparing particularly seizure-prone rats to a strain less susceptible to kindling epileptogenesis (‘‘fast-’’ versus ‘‘slow-kindling’’ animals), the mature $\alpha 1$ subunit expression in the fast kindling strain was approximately half the abundance of control

rats, whereas in the slow kindling strain, it was 70% greater than that of controls. By contrast, juvenile α2, α3, and α5 subunits displayed a 50–70% higher density in fast than in control rats, whereas the opposite was the case for slow kindling rats.

An interesting hypothesis regarding the role of GABA-mediated mechanisms in MTLE has been proposed by Sloviter (1991), who concluded that loss of the mossy cells would make the surviving GABAergic basket cells dormant thus disinhibiting granule cells. Data supporting this "dormant cell hypothesis" have been obtained by Bekenstein and Lothman (1993) as well as by Williams et al. (1993). However, recent studies have argued against this hypothesis, finding interneurons to be rather active in two animal models of temporal lobe epilepsy (Bernard et al., 1998). Furthermore, it has been reported that it is not the loss of granule cells per se, but rather the modulation of excitatory drive projecting to interneurons that appears to be responsible for the reduction of functional inhibition (Doherty and Dingledine, 2001) or even increased rebound firing after inhibition due to alterations in I_h (Chen et al., 2001).

Apart from GABAergic interneurons losing their excitatory drive, or GABA responses being outright reduced, GABAergic function may be changed with epileptic, high-frequency activity in the MTLE hippocampal circuit. Thus, Isokawa (1996) has reported that while GABAergic responses in dentate granule cells of the human epileptic tissue appear to be normal with single-shock stimulation protocols, they strongly decrease with repetitive stimulation (Fig. 11). In addition, in non-sclerotic tissue, GABA-mediated responses recover significantly faster than in sclerotic hippocampal tissue. Similar evidence has been obtained by studying the dentate gyrus in pilocarpine-treated rats, a well-established animal model of MTLE (Isokawa, 1996).

Moreover, Cossart et al. (2001) have found in two animal models of MTLE (i.e., those following kainate and pilocarpine treatment) that spontaneous GABAergic inhibition is increased in the soma, but reduced in the dendrites of CA1 pyramidal neurons. These investigators have proposed that increased somatic inhibition results from hyperactive interneurons projecting to the soma, whereas the decreased dendritic inhibition is caused by degeneration of a subpopulation of

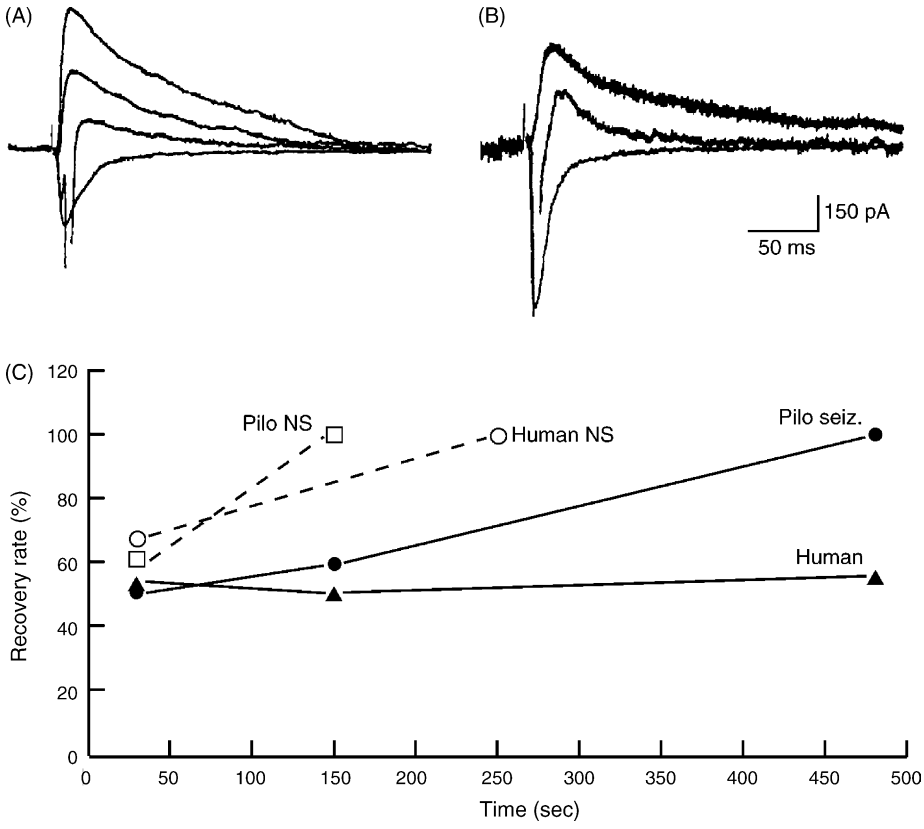

Fig. 11. Synaptic currents recorded in human epileptic and in rodent control and epileptic hippocampal neurons. (A and B) whole cell recordings of postsynaptic currents obtained from a normal rat and an epileptic human granule cell, respectively, at holding potentials of −60, −30, 0, and +20 mV (panel A) and −90, −30, and 0 mV (for panel B). Both experiments were performed in control artificial cerebrospinal fluid. The postsynaptic currents contained both ionotropic glutamate excitatory and $GABA_A$ receptor postsynaptic currents which could be separated as biphasic peaks at −30 mV because of their different reversal potentials. (C) Time course of the recovery of IPSCs after repetitive stimulation in non-sclerotic and sclerotic hippocampal tissue from MTLE patients and in pilocarpine-treated rats that presented with or without seizures. Note that the reduction of the IPSC amplitude induced by repetitive high frequency stimulation recovers to the original value within 2–4 min in the pilocarpine-treated rats presenting with no seizures (Pilo NS) and in human with non-sclerotic hippocampi (Human NS). In contrast, in pilocarpine-treated rats that experienced seizures (Pilo seiz.) and in human with sclerotic hippocampi (Human) >8 min were required for the GABA IPSCs to recover to their original amplitude. Moreover, in the case of human sclerotic hippocampi, no full recovery could be observed. Modified from Isokawa (1996), with permission.

interneurons. This nonuniform alteration of GABAergic inhibition has been shown by Wendling et al. (2002) to contribute to the transition from interictal to fast ictal activity in a computational macroscopic model of EEG activity that includes a physiologically relevant fast inhibitory feedback loop.

3.3.3. Changes in GABA receptor subunit composition

Altered $GABA_A$ receptor function in MTLE may reflect changes in $GABA_A$ receptor subunit compositions that are known to influence several functional properties such as affinity for GABA, allosteric modulation and channel biophysical characteristics (Olsen and Macdonald, 2002; Olsen et al., 2004). For instance, Loup et al. (2000) have identified upregulation of the α_2 subunit on somata and apical dendrites with reduced labeling on basal dendrites. Moreover, Palma et al. (2004, 2005a,b) have reported that human epileptic tissue samples are characterized by a different expression of several $GABA_A$ receptor subunit mRNAs when compared to autoptic non-epileptic tissue. These authors have also found that these molecular differences may be mirrored by different functional characteristics of the GABA-mediated currents recorded from *Xenopus laevis* oocytes microtransplanted with cell membranes obtained from human epileptic hippocampus/parahippocampal areas. Reverting to animal models, Houser and Esclapez (2003) have identified alterations in the $GABA_A$ receptor subunit composition that are detected in the CA1 and CA2 subfields of pilocarpine-treated rats during the chronic seizure-prone period. Similarly, significant changes in $GABA_A$ receptor subunit expression have been found in the hippocampus of kainic acid-treated animals (Friedman et al., 1994).

Linking molecular changes with functional ones, dentate granule cells from rats made epileptic by pilocarpine injection show changes in the mRNA levels of several $GABA_A$ receptor subunit genes as well as alterations in $GABA_A$ receptor function, including Zn^+ sensitivity and decreased zolpidem enhancement (Cohen et al., 2003; Fritschy et al., 1999). It has also been reported that in the kindled hippocampus, an increased GABA-receptor function can collapse because of a higher than normal sensitivity to Zn^+, an ion that plays an allosteric modulation of the $GABA_A$ receptor and that is present in high concentrations in the dentate area (Buhl et al., 1996). This means that even though there are indications of increased inhibition in the kindled dentate gyrus (increase of excitatory drive onto interneurons, decrease of presynaptic inhibition of GABA release) compensating for the increased network excitability, this is rendered sensitive to Zn^{2+} with kindling. In this way, terminals releasing Zn^{2+} during activity will obliterate this otherwise protective mechanism. Indeed, Shumate et al. (1998) have reported an enhancement of the Zn^{2+}-induced blockade of GABA current in dentate granule cells isolated from MTLE hippocampi.

Another factor in such a functional downregulation of inhibition could be alterations of delta subunits of GABA receptors. Peng et al. (2004) have also found that delta subunits—which are known to be involved in extrasynaptic tonic inhibition (Semyanov et al., 2004)—are upregulated on interneurons. With GABA spillover, this would in effect promote the silencing of inhibitory interneurons. It remains to be elucidated whether similar findings can be confirmed in human epilepsy. Therefore, in several experimental models of MTLE, there is evidence of reduced GABA-mediated inhibition that may result from plastic re-arrangements at both network and molecular level.

3.3.4. Depolarizing $GABA_A$ receptor-mediated transmission

A dysfunction of the GABAergic system of a different type has been described recently. Much like in neocortical slices from epilepsy patients (Köhling et al., 1998), also in hippocampal-subicular preparations obtained from MTLE patients spontaneous synchronous events could be observed (Cohen et al., 2002) (Fig. 12A). These discharges appeared predominantly in the subiculum (rather than in the hippocampus proper) and had variable initiation sites (Fig. 12A and B). Moreover, like the spontaneous events identified in the neocortex (see Fig. 4C), the spontaneous synchronous activity recorded in the human subiculum was also dependent on both glutamatergic and GABAergic transmission (Fig. 12C).

Not surprisingly, subicular interneurons fired during these field discharges (Fig. 13A, a). Presumed pyramidal neurons, in turn, either showed hyperpolarising responses (as in neocortical events, see Fig. 4), or indeed fired as well (Fig. 13A, panels b and c, respectively). Intriguingly, the latter subclass of pyramidal neuronal elements not only generated bursts during or even before population events but also displayed depolarizing rather than hyperpolarizing actions of GABA, and it was this subclass that thus appeared to be leading in the network-synchronized events (Cohen et al., 2002) (Figs. 12 and 13) In this context, GABA, thus, may serve a pro- rather than an antiepileptic role. Moreover, given the strategic position of the subiculum within the hippocampal–parahippocampal regions, the hyperexcitability of this structure would, unlike in the dentate region, allow for propagation of epileptiform events to other structures both in the limbic and extralimbic systems.

These findings also suggest that in the putative population of subicular ‘‘pacemaker cells,’’ intracellular Cl^- regulation has reverted to, or has been maintained at, ontogenetically juvenile stages leading to accumulation of Cl^- and thus to depolarizing actions upon $GABA_A$-receptor activation. Cohen et al. (2002) have proposed that such a depolarizing mechanism may be caused by delayed expression or down-regulation of the KCC2 transporter consequent to deafferentation from CA1 inputs that are known to be damaged in AHS (Rivera et al., 1999, 2004; Vale and Sanes, 2000). Wozny et al. (2003) have also reported that similar cellular activities can be recorded in the human subiculum in slices obtained from mildly sclerotic hippocampal tissue (Wyler scale 0–2, i.e. up to 50% cell loss; Wyler et al., 1992). However, this evidence is not sufficient to rule out the ‘‘deafferentation hypothesis’’ proposed by Cohen et al. (2002) as CA1 and other limbic structures in MTLE patients may well be hypoactive without presenting with any noticeable cell damage and since, even in the cited study, the degree of sclerosis correlated with the propensity to generate spontaneous

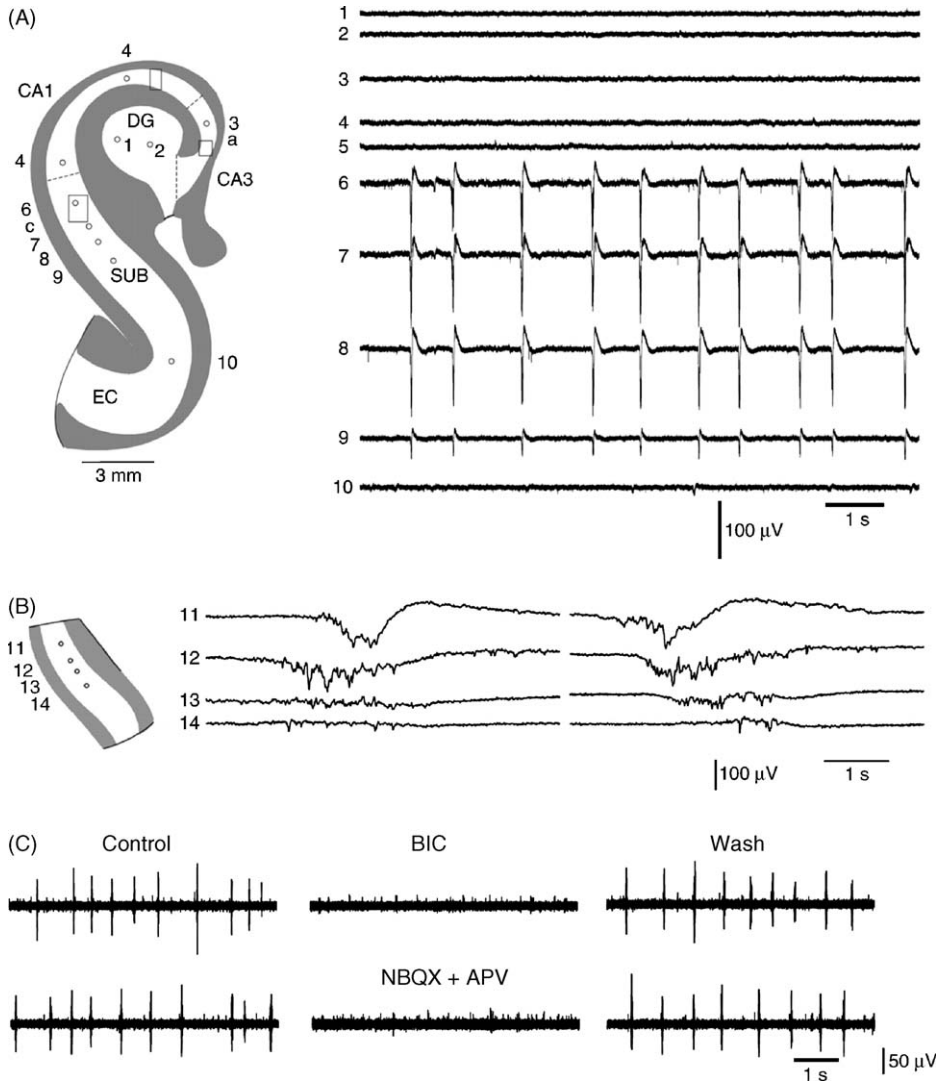

Fig. 12. Spontaneous, GABA receptor-dependent network discharges recorded in the human subiculum from patients with MTLE. (A) Spontaneous network discharges appear exclusively in the subiculum, as revealed by multielectrode recordings in positions as indicated by numbers in the diagram of a human subicular-hippocampal slice shown on the left. (B) Variable focal initiation of spontaneous discharges recorded simultaneously from different subicular sites as shown in the left diagram. (C) Spontaneous field potential discharges recorded in the human subiculum depend on both GABAergic and glutamatergic transmission, as indicated by reversible blockade using the $GABA_A$-receptor antagonist bicuculline (BIC) and the AMPA- and NMDA-receptor antagonists NBQX and APV, respectively. Modified from Cohen et al. (2002), with permission.

discharges, with mild sclerosis tissue having roughly 28% spontaneously active cells, as compared to 56% in strongly sclerotic specimens. Wozny et al. (2003) have also found that the majority of subicular cells in both sclerotic and non-sclerotic tissue were regular firing cells, which is opposite to what was reported in the rat subiculum. This and the fact that also persistent sodium currents are markedly enlarged in subicular (but not in other hippocampal regions; Vreugdenhil et al., 2004, see Section 3.2.1) indicate that the subiculum displays the most important functional changes in MTLE.

Interestingly, Khalilov et al. (2003) have found in an animal model of mirror focus—which consisted of intact and reciprocally connected hippocampi maintained in vitro—that the appearance of epileptiform discharges emerging from the mirror focus independently of discharges in the primary focus are GABA-dependent with GABA becoming depolarizing. Several in vitro studies have reported that $GABA_A$ receptor-mediated depolarizations contribute to synchronize limbic networks in several models of epileptiform discharge (Avoli et al., 1996a,b; Higashima et al., 1996; Perez-Velazquez and Carlen, 1999; Köhling et al., 2001). Moreover, such a paradoxic pro-epileptic $GABA_A$ receptor-mediated mechanism appears to play a role in human FCD (Section 5.2.2).

3.4. Other mechanisms

3.4.1. GABA transporters

Not only GABA receptors but also GABA transporters may be altered in epilepsy. Human epileptogenic tissue from MTLE patients, who were analyzed with implanted microdyalisis probes, presents reduced levels of GABA transporters (During et al., 1995). These investigators have reported that the K^+-

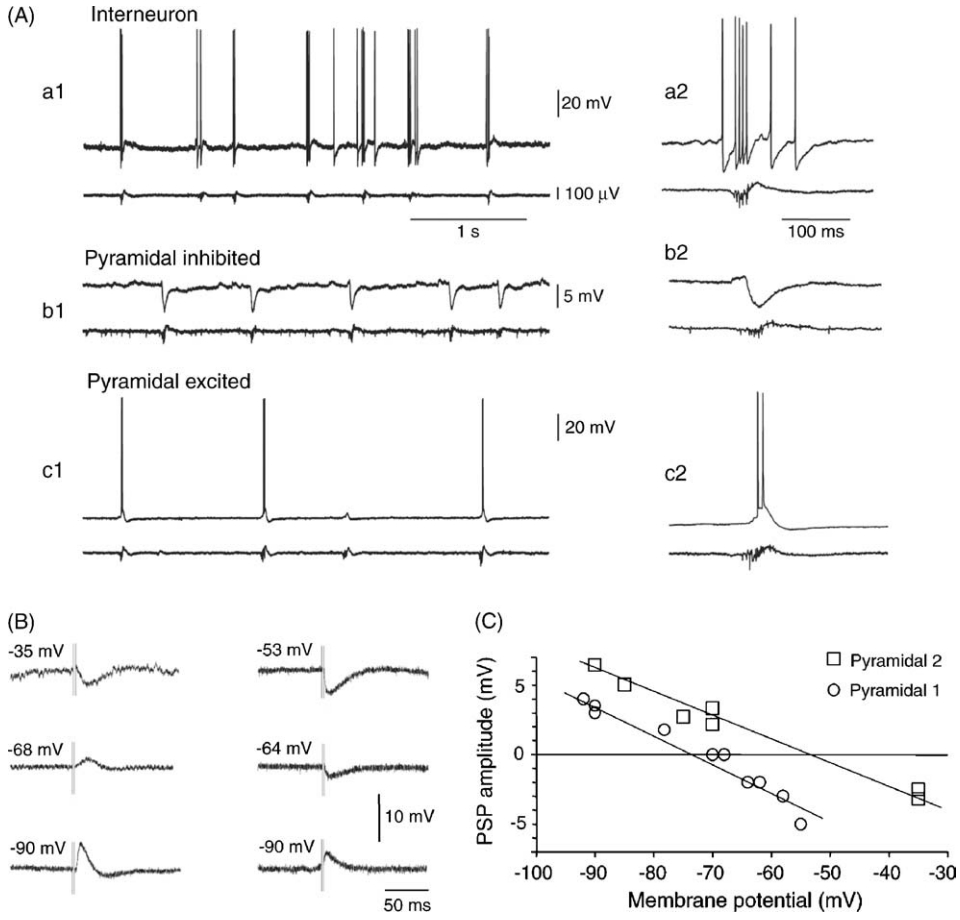

Fig. 13. Intracellular activity recorded in the human subiculum from MTLE patients during the spontaneous, GABA receptor-dependent network discharges. (A) Firing behavior of different classes of subicular neurons during spontaneous discharges. (a1) Interneuron fires during or even prior to the field discharges. (b1) Most pyramidal neurons show hyperpolarizations during the field discharges. (c1) A small fraction of pyramidal neurons generates action potentials or burst of action potentials during the field discharges. (a2–c2) Corresponding insets are illustrated at higher temporal resolution. (B and C) bursting, excited pyramids display a more positive reversal potential for GABAergic postsynaptic potentials (isolated pharmacologically) than inhibited, non-firing ones. Original recordings of GABA receptor-mediated synaptic potentials at different holding membrane potentials in bursting (left panel) and non-bursting (right panel) neurons are shown in (B). In (C), the plot showing the relationship between holding potential and GABA-receptor-mediated potential indicates a positive shift of the GABA-reversal potential by approximately 20 mV. Modified from Cohen et al. (2002), with permission.

stimulated release of GABA is increased and glutamate-induced Ca^{2+}-independent release of GABA is decreased in the epileptogenic hippocampus as compared with the controlateral non-epileptogenic hippocampus. It is, however, unclear whether these changes are the cause or the result of the epileptogenic condition.

3.4.2. Neuropeptide Y

Immunohistochemical and molecular studies have provided data indicating that neuromodulation in epileptic human hippocampus might be disturbed as well. One of the neuromodulatory substances on which attention focused recently is neuropeptide Y (NPY). NPY, apart from playing a central role in the regulation of food intake, also appears to be of central importance in the regulation of neuronal excitability and, particularly, tuning interneuron discharge propensity (Baraban and Tallent, 2004). NPY is able to decrease synaptic transmission by reducing presynaptic calcium influx (Qian et al., 1997) and can suppress epileptiform activity in vitro (Klapstein and Colmers, 1997), via Y2 receptor activation. Furthermore, Tu et al. (2005) have recently reported that tonically released, endogenous NPY may decrease excitability in recurrent mossy fibre projections in a limbic epilepsy model.

Interestingly, in hippocampal specimens with AHS, but not in those without, Y2 receptors have been found to be elevated, while Y1 receptors were downregulated, suggesting an adaptive and protective antiepileptic mechanism (Furtinger et al., 2001). Whether this relative up-regulation of Y2 receptors is sufficient to effectively control synchronization within the dentate gyrus is debatable, because Y2 receptor levels in human preparations are lower than in rodent preparations (Tu et al., 2005).

3.4.3. Gap junctions

An additional mechanism that may contribute to epileptogenesis rests on gap junctions that are increasingly recognized to play a role in synchronizing neuronal networks under physiological and pathological conditions such as epileptic seizures (Dermietzel and Spray, 1993; Bennett and Zukin, 2004; Connors and Long, 2004; Nakase and Naus, 2004). Gap junctions allow flow of electrical signals and small molecules,

including dyes, between cells thus promoting neuronal synchrony.

Procedures capable of blocking or enhancing the function of gap junctions decrease or increase epileptiform synchronization, respectively, in in vitro models of epilepsy (reviewed by Carlen et al., 2000). According to this view, elevated levels of connexin 43 mRNA have been reported in human epileptic tissue (Naus et al., 1991; Aronica et al., 2001; Fonseca et al., 2002). Connexins are the proteins that constitute gap junctions (Spray, 1996; Bruzzone and Ressot, 1997; Hormuzdi et al., 2004). Moreover, preliminary evidence obtained by studying the effects induced by gap junction decouplers on the synchronous activity generated by human neocortical slices superfused with 4-aminopyridine and glutamatergic transmission antagonists (see Section 2.4.2) suggest that interneuron activity in this preparation is synchronized via gap junctions (M. D'Antuono, J. Louvel, R. Pumain and M. Avoli, unpublished data).

3.4.4. Gene expression patterns

Recent investigations have shown that widespread changes of gene expression patterns occur in human epileptic hippocampus, some of which overlap with alterations found in the chronic MTLE condition induced by injection of pilocarpine in rats (Becker et al., 2003). These include proteins involved in cell–matrix interactions, in cell growth and differentiation, in cellular signaling, and in transcriptional regulation (Becker et al., 2003).

4. Actions of antiepileptic drugs and drug resistance in human epileptic tissue

4.1. Antiepileptic drug actions in human brain tissue

The action of new and conventional antiepileptic drugs has also been tested in human epileptic tissue. This was done both at the network level using various in vitro models of epileptiform synchronization as a screening tool for efficacy studies, and at the cellular level regarding voltage-gated currents to elucidate mechanisms of action and, as it is, therapy failure. Thus, in the Mg^{2+}-free model, carbamazepine was shown to exert only a moderate antiepileptic action, whereas vigabatrin was highly effective (Mußhoff et al., 2000). Similarly, retigabine displayed a strongly suppressive action in this and other models (Straub et al., 2001), and even melatonin, used here as an experimental antiepileptic agent, was effective in suppressing Mg^{2+}-induced epileptiform discharges (Fauteck et al., 1995).

Perhaps even more interesting than screening for antiepileptic efficacies are those investigations that have tried to elucidate why antiepileptic drugs do not work in MTLE patients. In this context, recent studies have demonstrated that therapy resistance to carbamazepine may be due to a reduced efficacy of the drug in influencing Na^+ currents particularly in AHS tissue, either by having less effect on the steady-state inactivation (Vreugdenhil et al., 1998) or by being ineffective in reducing use-dependent current reduction (Remy et al., 2003) (Fig. 14). It has also been shown that the latter mechanisms may be responsible for the reduced ability of carbamazepine to influence the epileptiform activity recorded from human brain slices superfused with Mg^{2+} free medium.

4.2. Antiepileptic drug transporters

A different, maybe additional, mechanism that may contribute to pharmacoresistance rests on the inability of the antiepileptic drugs to attain sufficient intraparenchymal concentrations. This situation, which may occur even when antiepileptic drugs reach normal serum concentrations, results from the enhanced function of drug transporters. These proteins are known to control intraparenchymal antiepileptic drug concentrations (Löscher and Potschka, 2002). Several studies have indeed demonstrated that drug transporters are upregulated in epileptic patients as well as in experimental models of epilepsy. For instance, increased MDR1 expression is seen in patients with different forms of chronic epilepsy including focal cortical dysplasia, tuberous sclerosis and brain tumors (Sisodiya et al., 2002; Sisodiya, 2003; Tishler et al., 1995; Lazarowski et al., 1999; Aronica et al., 2003a,b). Similar evidence has been obtained by studying animals presenting with limbic seizures (Rizzi et al., 2002) or genetically epilepsy-prone rats (Kwan et al., 2002).

Analogous findings have also been obtained by analyzing the antiepileptic drug transporters MRP1 (Sisodiya et al., 2001, 2002) and MRP2 (Dombrowski et al., 2001). Moreover, it has been reported in these studies that the expression of drug transporter genes in epileptic foci is present in cell types that do not usually express them. On the other hand, animals that lack drug transporters display increased intraparenchymal antiepileptic drug concentrations (Schinkel et al., 1997; Potschka et al., 2003). In keeping with this evidence, pharmacological inhibition of drug transporters alters the distribution of antiepileptic drugs in the brain (Potschka et al., 2001, 2003; Löscher and Potschka, 2002; Potschka and Loscher, 2001). Overall, these results suggest that modulating (and specifically inhibiting) the function of drug transporters in pharmacoresistant epilepsy represents an interesting clinical venue. However, it should be emphasized that this strategy by itself is unlikely to be beneficial in those epileptic patients who display altered neuronal sensitivity to antiepileptic drugs. In fact, it is unclear why pharmacoresistant epileptic patients often develop behavioral side effects such as drowsiness, suggesting that relevant CNS concentrations of antiepileptic drugs had indeed been attained in the brain.

5. Taylor's type focal cortical dysplasia

Taylor's type, focal cortical dysplasia (FCD) corresponds to a localized disruption of the normal cortical lamination with an increase in cortical thickness, the presence of balloon cells and an excess of large aberrant neurons along with glial elements that are often found in the underlying white matter (Taylor et al., 1971). Thanks to the use of MRI investigations, FCD has been more and more frequently identified in patients presenting

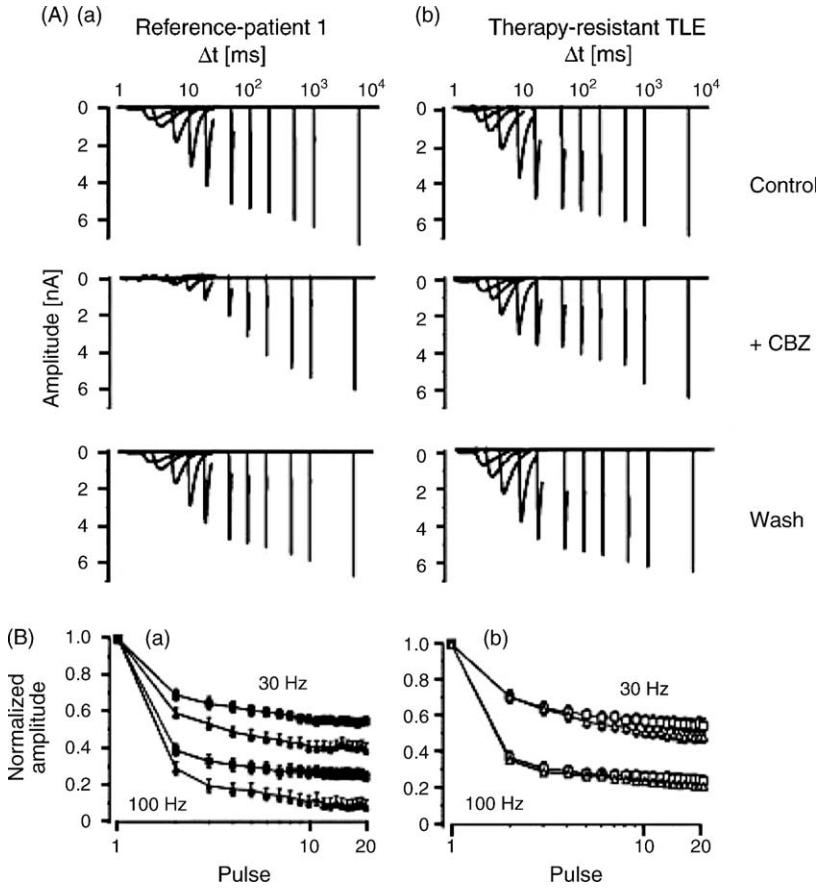

Fig. 14. Cellular bases for pharmacoresistance in MTLE patients. Reduction of carbamazepine (CBZ)-induced effects on voltage-gated Na^+ currents recorded in dentate granule cells from CBZ-resistant epileptic patients. (A) Fast recovery from inactivation. Representative family of original traces recorded under control conditions (normal medium), after application of 128 μM CBZ and after washout in dentate granule cell from a "reference" patient responding to CBZ (but not tolerating the drug and thus operated) (a) and of drug-resistant MTLE patients (b). (B) Frequency-dependent attenuation of the Na^+ currents in the absence (filled squares) and the presence of 128 μM CBZ (filled triangles) in reference patient demonstrating potentiation of frequency-dependent current reduction by CBZ (a). By contrast, CBZ loses its use-dependent block in the drug-resistant MTLE patient (b). Modified from Remy et al. (2003), with permission.

with epileptic disorders that were previously classified as cryptogenic (Bernasconi et al., 2001; Bronen et al., 1997; Guerrini et al., 1999; Tassi et al., 2002).

The intrinsic epileptogenicity of FCD tissue has been clearly characterized by Palmini et al. (1995) by employing intraoperative electrocorticography. These investigators found that continuous epileptogenic activity was most frequentlly recorded from electrodes overlying the dysplastic cortical area. More recently, a pathogenetic link to tuberous sclerosis has been postulated (Becker et al., 2002). Seizures in FCD patients are often medically intractable, which makes them candidates for neurosurgical interventions aimed at resecting the epileptogenic FCD area.

5.1. Morphological and histochemical features

Immunocytochemical analysis of surgically resected human FCD tissue has revealed an abnormal distribution of NMDA receptors (Spreafico et al., 1998). Similar alterations in the expression of glutamate receptors have been also reported by other laboratories (Kerfoot et al., 1999; Ying et al., 1999). In addition, Crino et al. (2001) have shown changes in mRNA expression in FCD tissue that are cell and receptor specific with NMDA-recetor 2B and 2C being upregulated, and NR2A being downregulated. As a consequence of the upregulation of the juvenile form of the NR2 receptor subtype, NMDA-mediated excitatory postsynaptic currents should be expected to be more pronounced (Barth and Malenka, 2001).

It was also reported in the study of Spreafico et al. (1998) that FCD tissue has a decreased number of presumptive interneurons. However, these cells appear to provide increased GABAergic innervation to principal cells (Fig. 15). These findings were later confirmed in other studies (Garbelli et al., 1999; Tassi et al., 2001, 2002, 2005). In addition, by using light and electron microscopic analysis, Alonso-Nanclares et al. (2005) have reported that giant ectopic neurons in the white matter are surrounded by hypertrophic basket formations. These terminals were positive for the Ca^{2+} binding protein parvalbumin and formed symmetrical (inhibitory) synapses with the ectopic cells. It was also found in this study that balloon cells did not establish synaptic contact, a finding that is well in agreement with data obtained by Cepeda et al. (2003). Additional abnormalities including increases in tyrosine

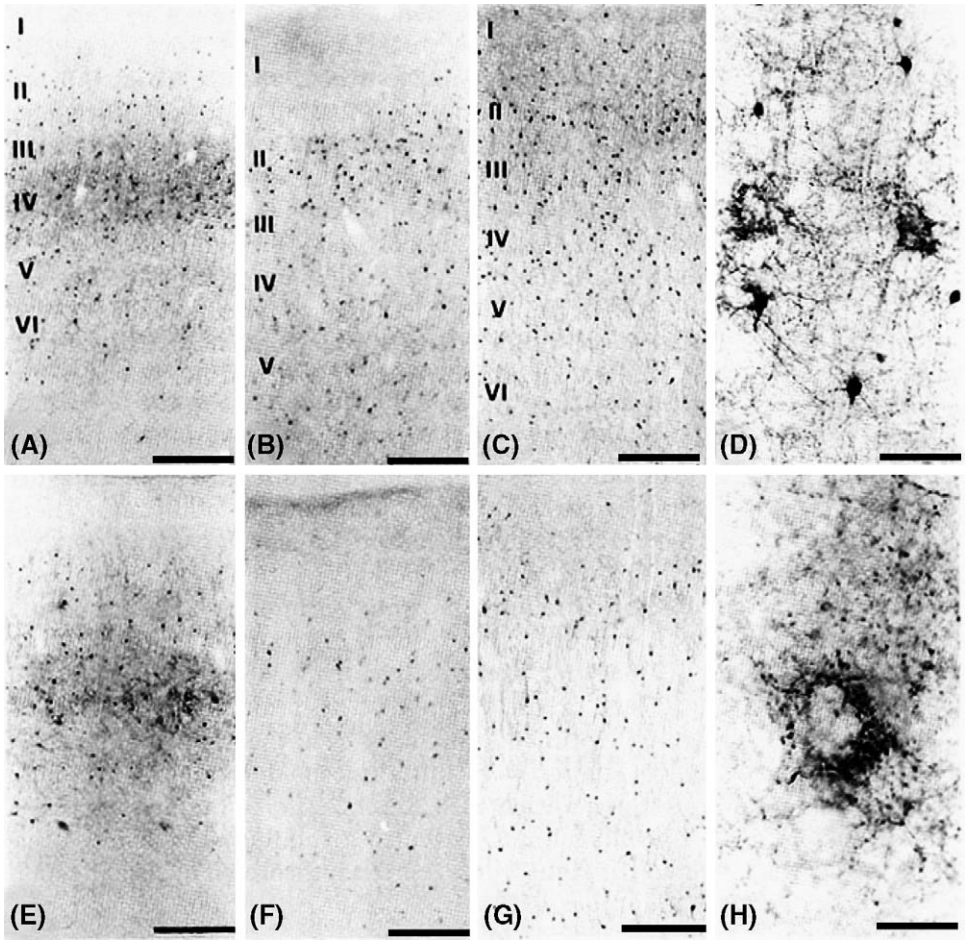

Fig. 15. Histochemical characteristics of normal and FCD tissue. Decrease of labeling for three calcium binding proteins in FCD tissue (E–G) as compared with adjacent normal cortex (A–C). Parvalbumin (A and E), calbindin D28K (B and F) and calretinin (C and G) were analyzed. Baskets of intensely parvalbulin labeled terminals surround giant pyramidal cells in the superficial layers (D) and a cell located in the white matter (H). Bars = 400 μm (A–C and E–G), 30 μm (D) and 20 μm (H). Modified from Spreafico et al. (1998), with permission.

hydroxylase activity (Trottier et al., 1994) and serotonergic hyperinnervation (Trottier et al., 1996) have been reported to occur in FCD tissue.

5.2. Functional characteristics of FCD neuronal networks

5.2.1. Hyperexcitability in FCD slices maintained in vitro

By using electrophysiological recordings in an in vitro slice preparation, we have found that FCD tissue, when treated with 4-aminopyridine, generates NMDA receptor-mediated ictal discharges along with isolated, interictal-like synchronous potentials that are mainly contributed by GABA receptor-mediated conductances (Mattia et al., 1995; Avoli et al., 1999). As reported in Section 2.4, a similar 4-aminopyridine treatment in human neocortical tissue presenting with no obvious structural abnormality induces only periodic, synchronous, interictal-like GABA receptor-mediated potentials (cf., Avoli et al., 1994) (Fig. 16). Therefore, these in vitro data support the view that epileptogenicity is a functional feature of FCD tissue.

Such a conclusion is in line with data obtained from several animal models of cortical maldevelopment in which both histochemical and more often functional disturbances of excitatory and inhibitory transmission have been identified (Benardete and Kriegstein, 2002; DeFazio and Hablitz, 2000; Gabel and Lo Turco, 2002; Hagemann et al., 2003; Jacobs et al., 1996; Luhmann and Raabe, 1996; Luhmann et al., 1998; Roper et al., 1997; Wenzel et al., 2001; Zhu and Roper, 2000). However, it must be emphasized that none of these models is characterized by histopathological patterns similar to Taylor type FCD.

Interestingly, the ictal activity induced by 4-aminopyridine in FCD slices closely resembles the electrographic activity that is recorded during pre-excision ECoG from the dysplastic lesion in these patients (Gambardella et al., 1996; Palmini et al., 1991, 1995). This pattern is believed to be a specific and sensitive indicator of FCD lesions (Gambardella et al., 1996; Dubeau et al., 1998).

It has also been reported that neurons recorded intracellularly in FCD slices superfused with normal medium have a remarkable tendency to generate all-or-none synaptic bursts (Fig. 17A); moreover, these abnormal responses are abolished by bath application of NMDA receptor antagonists (Avoli et al., 2003) (Fig. 17B). Finally, in these experiments as well as in a more extensive study (Avoli et al., 1999) we could not identify

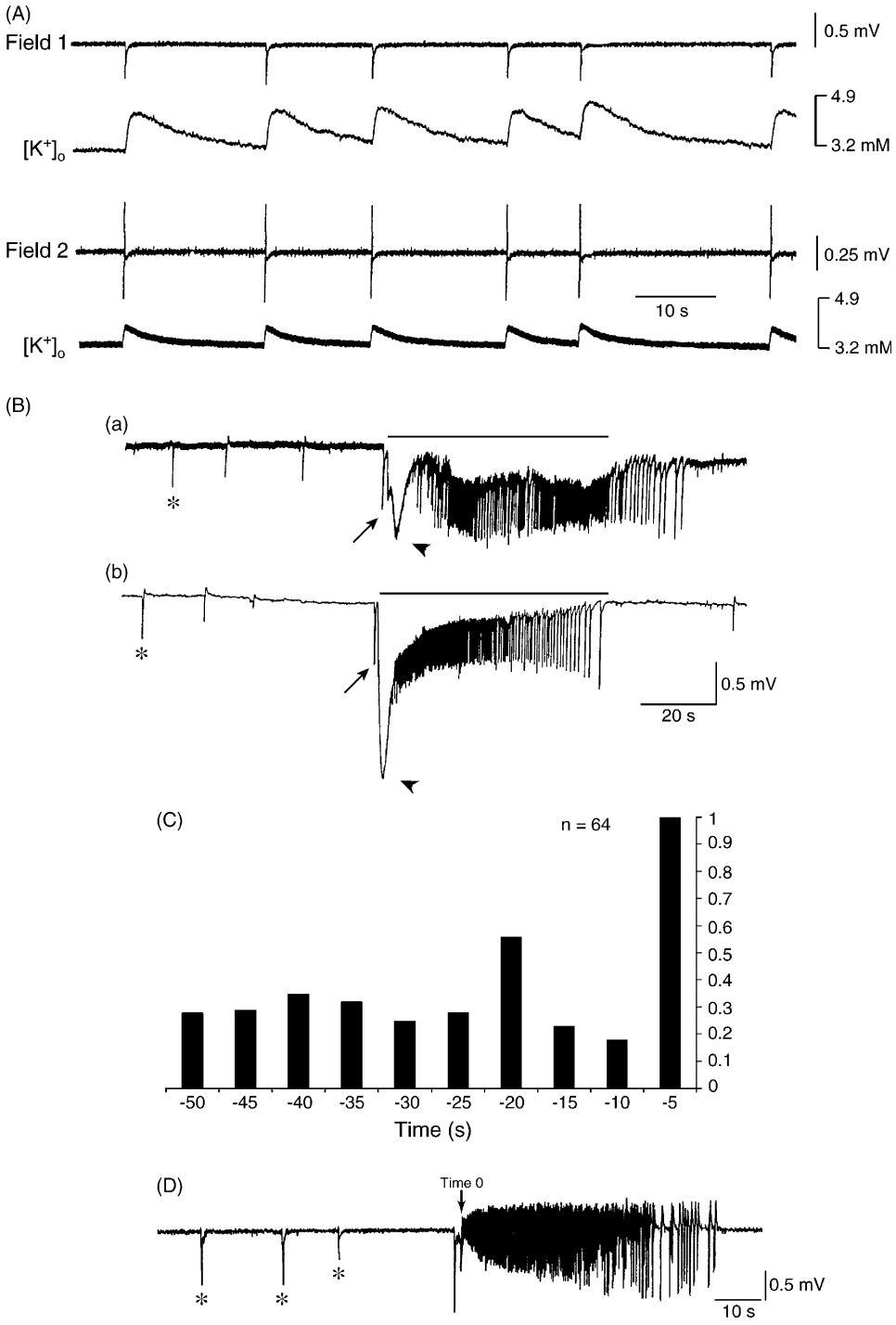

Fig. 16. Synchronous activity induced by bath application of 4-aminopyridine (4AP) in neocortical slices that were obtained from MTLE (i.e., presenting with no architectural anomaly) and FCD patients. (A) Isolated field potentials occur spontaneously in the MTLE slice analyzed with field potential and $[K^+]_o$ recordings at 1000 μm from the pia. Note that each field potential event is associated with a transient increase in $[K^+]_o$. (B) Spontaneous field potential discharges recorded in two slices (panels a and b) obtained from two FCD patients; in both cases the activity shows isolated interictal field potentials (asterisks) and sustained epileptiform events resembling ictal discharges (continuous lines). Note also that the onset of the ictal event is associated with the occurrence of a negative field potential (arrow) that is followed by a slow negative event (arrow-head) leading to ictal discharge oscillations. (C and D) temporal relation between the occurrence of slow interictal events and ictal discharge onset during 4AP application. In (C), histogram of the probability of occurrence of the interictal activity over a period of 50 s before ictal onset normalized to epoch 5 s prior to ictal event; data were obtained from 64 epochs recorded in 11 FCD slices. One of these epochs is shown in (D) where the interictal events are highlighted by asterisks. The arrow highlights the time 0, while the asterisks point at slow interictal events. From Avoli et al. (2004), with permission.

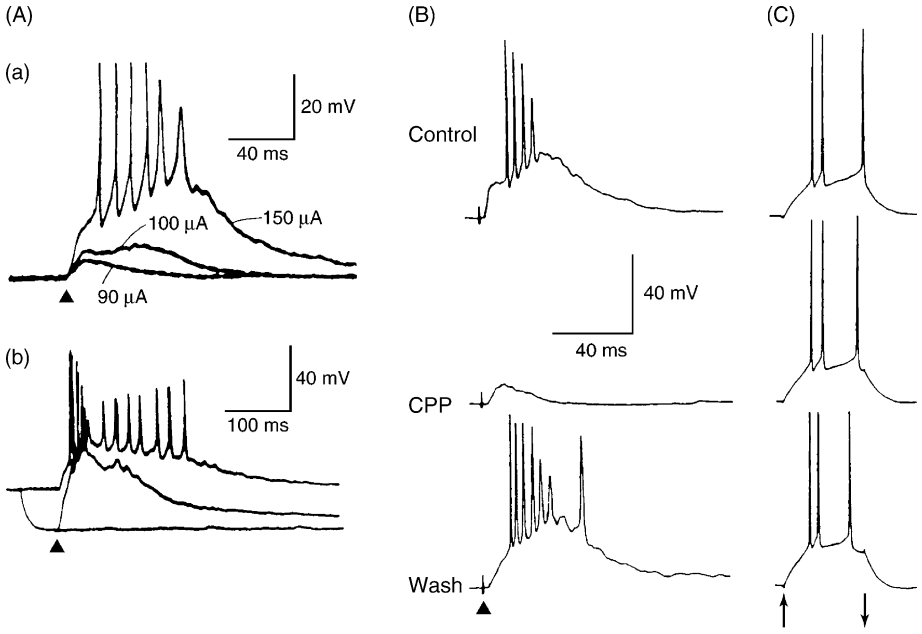

Fig. 17. Synaptic and intrinsic properties of neurons recorded in FCD slices superfused with control medium. (A) All-or-none synaptic bursts are induced by single shock stimuli; note that these responses depend on the stimulus strength (a) as well as that hyperpolarization of the membrane with injection of negative current discloses a large underlying depolarizing potential (b). (B) Abnormal stimulus-induced bursting responses are reversebly abolished by bath application of NMDA receptor antagonist CPP (10 µM). (C) Regular firing of action potential is generated by an FCD neuron during injection of depolarizing current. Modified from Avoli et al. (1995b), with permission.

any difference in the fundamental electrophysiological properties of neurons recorded in FCD slices as compared with control tissue that did not present with any obvious structural abnormality (Fig. 17C). Unfortunately, neuronal staining was not carried out in these experiments, and thus the morphology of these cells remains unknown. Nonetheless, the intracellular data obtained by studying FCD tissue in the absence of any pharmacological manipulation further support the view that network re-arrangement may lead to upregulation of NMDA receptor-mediated mechanisms in FCD.

Interestingly, Kerfoot et al. (1999) have found in FCD tissue that dysmorphic neurons, which were identified morphologically by using infrared videomicroscopy or biocytin intracellular injection, have increased immunoreactivity for several excitatory neurotransmitter receptor subunits. In addition, they show variable immunoreactivity for GABA as well as express several proteins that are normally present in immature neurons. In addition, by examining the properties of these cells, Kerfoot et al. (1999) have reported that large, pyramidal cells have voltage-gated currents larger than in normal-appearing pyramidal neurons. In contrast, in cells with atypical somatodendritic morphology (which could correspond to ''balloon'' cells) they could not record any active voltage- or ligand-gated currents; these cells, indeed, did not appear to receive any synaptic input.

More recently, Andre et al. (2004) have examined the electrophysiological responses and the NMDA receptor subunit assembly in acutely dissociated normal-appearing pyramidal and cytomegalic neurons from FCD tissue as well as in normal-appearing pyramidal neurons from non-FCD tissue. These experiments have revealed that NMDA currents recorded in most cytomegalic and in one-third of normal-appearing pyramidal neurons from FCD tissue have shown decreased Mg^{2+} sensitivity compared with non-FCD neurons. Moreover, the NR2B antagonist ifenprodil exerted effects that were less pronounced in FCD than in non-FCD neurons, thus indicating a functional loss of NR2B subunits. Finally, it has been reported that non-FCD neurons expressed NR2B subunit mRNA while one fifth of FCD pyramidal neurons lacked NR2B mRNA. Therefore, these results demonstrate the presence of NMDA receptors with altered subunit composition and Mg^{2+} sensitivity.

5.2.2. *$GABA_A$ receptor mediated mechanisms support hyperexcitability in FCD*

Epileptiform synchonization leading to in vitro ictal activity in the human FCD tissue is initiated (and presumably maintained) by a synchronizing mechanism that paradoxically relies on the activation of $GABA_A$ receptors. These findings were obtained from neocortical slices that were superfused with medium containing 4-aminopyridine in order to elicit spontaneous epileptiform discharges in vitro. As illustrated in Fig. 18A, these ictal discharges were shortly preceded by negative-going events resembling those seen in isolation during the interictal period. However, the field potentials leading to ictal discharge onset were always of larger amplitude and were often followed by a secondary, slow negative field event from which ictal oscillations emerged. It should be emphasized that the transient elevations in $[K^+]_o$ recorded in these slices during the slow 4-aminopyridine-induced interictal events attained maximal values that were often larger than those recorded during a similar type of synchronous activity in MTLE slices.

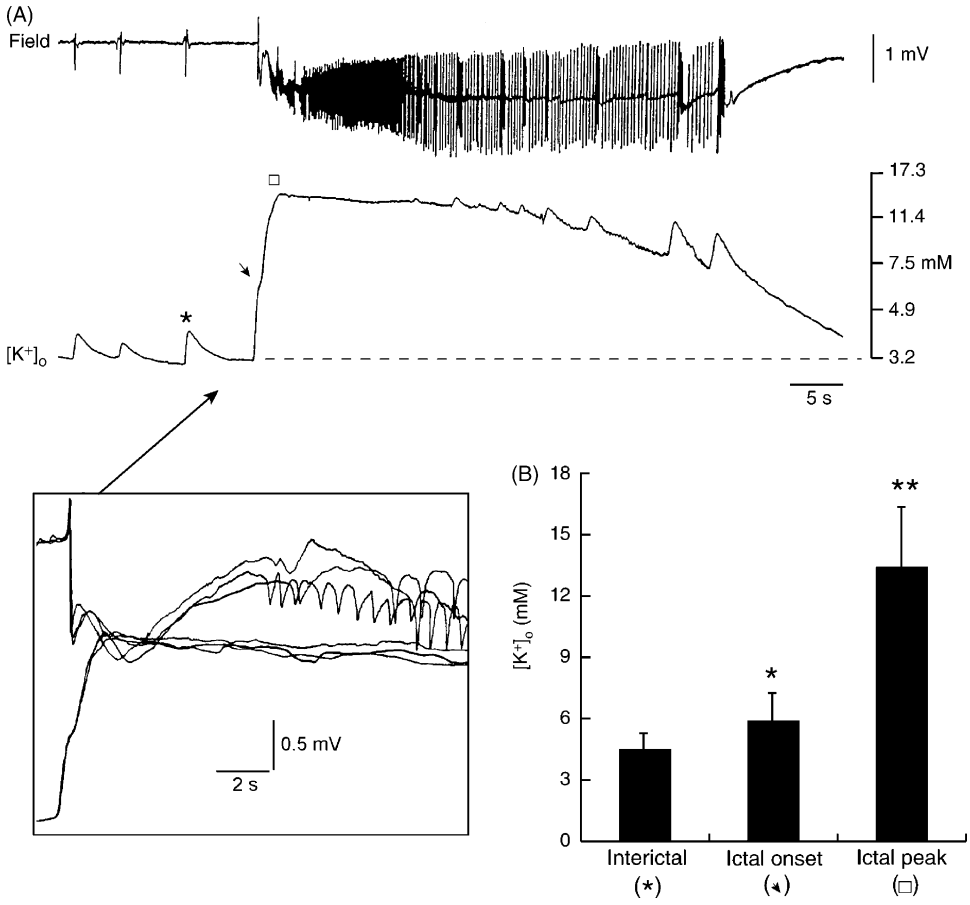

Fig. 18. Field potential activity and concomitant changes in $[K^+]_o$ induced by 4AP in FCD tissue. (A) Field potential and $[K^+]_o$ recordings obtained at 1500 μm from the pia in an FCD slice treated with 4AP-containing medium. Note that $[K^+]_o$ increases up to 4.5 mM accompany the isolated negative field events (asterisk), while an elevation up to 6.4 mM characterizes the field potential leading to the ictal discharge onset (arrow). The insert, which represents three graphically superimposed ictal onsets at faster time base, demonstrates that the initial increase in $[K^+]_o$ occurs at the same time of the initial positive-negative field event, while the slower secondary negative field event follows the peak of the elevation in $[K^+]_o$. (B) Quantitative summary of the maximal elevations in $[K^+]_o$ associated with the isolated negative-going events ($n = 44$ events from 5 slices), those occurring during the negative-going events preceding ictal discharge ($n = 12$ events from 3 slices) and during the ongoing ictal activity (identified as ictal peak; $n = 12$ events from 3 slices); single and double asterisks indicate statistical significance of $p < 0.05$ and $p < 0.02$, respectively. Modified from D'Antuono et al. (2004), with permission.

In addition, the GABA receptor-mediated potentials that shortly preceded the ictal discharge onset were characterized by rises in $[K^+]_o$ that were larger than those seen in association with similar field potentials occurring during the interictal period (Fig. 18B).

We have previously reported a similar association of large elevations in $[K^+]_o$ and ictal discharge onset in the deep layers of the entorhinal cortex (Avoli et al., 1996a; Barbarosie et al., 2002) as well as in isolated hippocampal slices obtained from young rats (Avoli et al., 1996b). Data obtained in the latter study have revealed that the occurrence of ictal activity in the CA3 area is characterized by developmental changes in GABA receptor-dependent $[K^+]_o$ homeostasis. Indeed, elevating $[K^+]_o$ can disclose seizure activity both in vivo (Zuckermann and Glaser, 1968) and in vitro (Traub and Dingledine, 1990; Traynelis and Dingledine, 1988).

The paradoxical role played by GABA receptor-mediated mechanisms in initiating ictal activity was originally reported in the CA3 subfield of young (<30-day old) rat slices treated with 4AP (Avoli et al., 1993, 1996b) and later confirmed in the adult rodent entorhinal cortex (Avoli et al., 1996a; Lopantsev and Avoli, 1998; Barbarosie et al., 2002). Moreover, the occurrence of ictal synchronization in isolated hippocampal slices treated with 4-aminopyridine depends on the maturity of the tissue (Avoli et al., 1993, 1996b), a characteristic that is mirrored by the higher propensity of young animals to generate seizures in vivo (Cavalheiro et al., 1987; Purpura, 1969). Hence, these findings suggest that the human dysplastic cortex may revert to, or rather retain, ontogenetically immature properties and is therefore susceptible to seizure generation in a way similar to the young rodent hippocampus. It should also be emphasized that the specific ability of human FCD slices to generate ictal discharges, as compared with cortical MTLE tissue, may reflect the abnormal neuronal connectivity that characterizes this type of tissue (Spreafico et al., 1998; Köhling et al., 1999).

The role of GABA receptor-mediated synchronization in initiating ictal activity in FCD tissue is further supported by pharmacological manipulations that were aimed at decreasing or enhancing the function of GABA (mainly type A) receptors. $GABA_A$ receptor antagonism or activation of μ-opioid

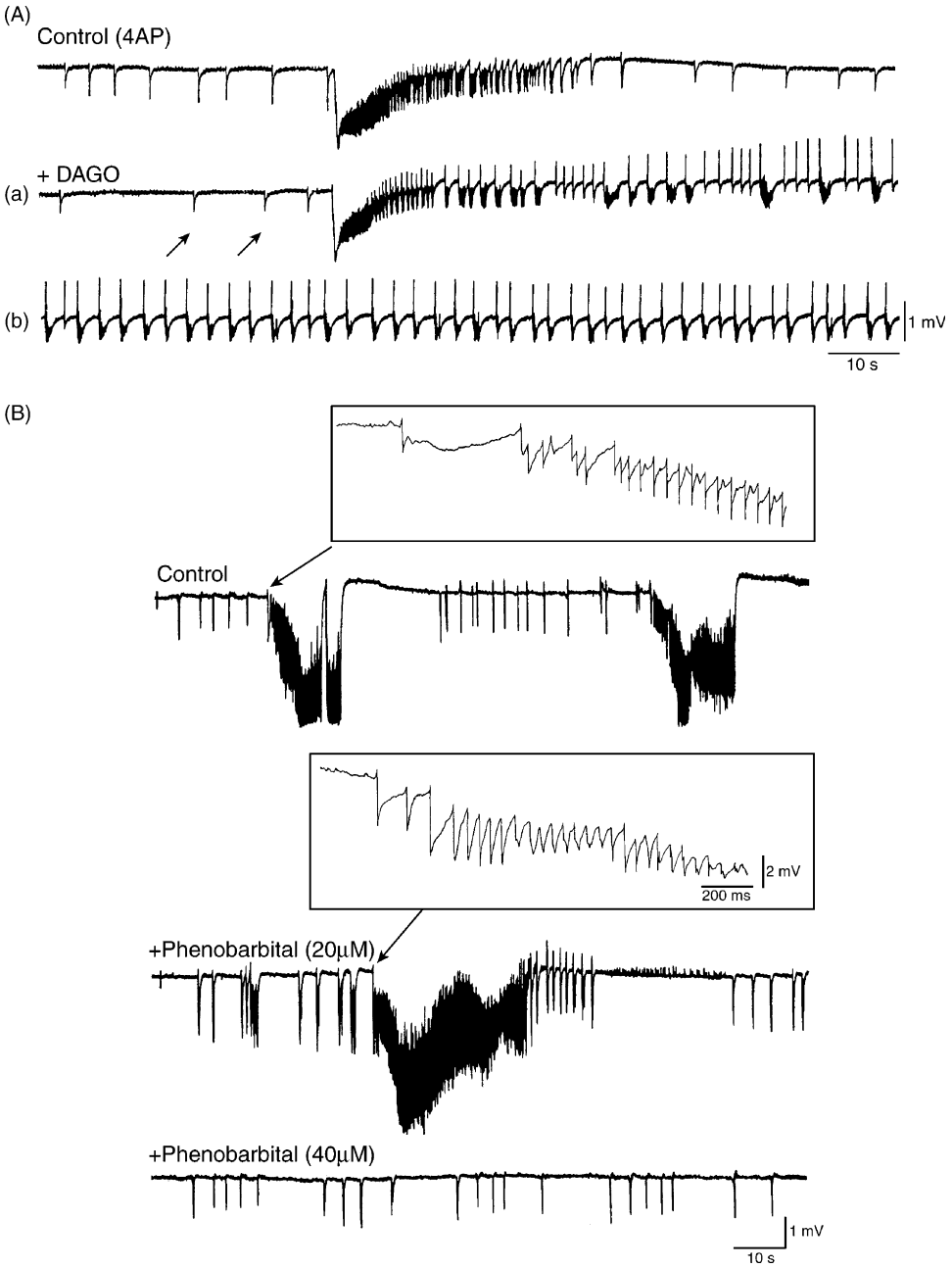

Fig. 19. Ictal discharge occurrence in FCD slices depends on and it is modulated by the function of $GABA_A$ receptors. (A) Bath application of the μ-opioid receptor agonist DAGO (10 μM) reduces the amplitude of the isolated negative field events (arrows in sample a) and transforms ictal activity into regular, robust interictal discharges (sample b). Traces identified as (a) and (b) represent a continuous recording that was started 2 min after the onset of DAGO application. (B) Bath application of phenobarbital 20 μM increases the duration of the isolated interictal field potentials and of the ictal discharges induced by 4AP in a FCD slice. Note in the expanded traces in the inserts that the effects of phenobarbital are characterized by an increase in amplitude of the 20 Hz oscillations occurring at discharge onset. Note also that a further increase of phenobarbital to 40 μM abolishes the ictal discharges and reduces the duration of the interictal events. Modified from D'Antuono et al. (2004), with permission.

receptors (which blocks the release of GABA from interneuron terminals) made ictal discharges and GABA receptor-mediated interictal events disappear (Fig. 19A). Under both conditions, FCD slices generated recurrent epileptiform activity that lacked the features of an electrographic ictal event. Conversely, potentiating $GABA_A$ receptor function with minimal concentrations of phenobarbital (Nicoll et al., 1975; Barker and McBurney, 1979) caused a prolongation of the ictal discharges along with potentiation of the slow interictal events (Fig. 19B). It has been recently shown that phenobarbital does not influence 4-aminopyridine-induced interictal activity in the dysplastic tissue analyzed in hippocampal slices obtained from rats treated with methylazoxymethanol in utero (which represents an experimental model of cortical dysplasia, even though with distinct histological differences when compared with human FCD) (Smyth et al., 2002).

5.2.3. $GABA_B$ receptor downregulation in FCD tissue

We have also found in slices obtained from FCD tissue that bath application of the $GABA_B$ receptor agonist baclofen at concentrations as low as 2 μM can abolish 4-aminopyridine-induced ictal discharges, but not the interictal events (which mainly reflect a GABA receptor-mediated mechanism) (Fig. 20A). This type of activity disappeared only with baclofen concentrations >40 μM (Fig. 20D and E). Since the effects induced by baclofen were antagonized by CGP 35348, these findings were mainly caused by the activation of $GABA_B$ receptors that are known to be located both post- and presynaptically on principal (glutamatergic) cells and interneurons (Lambert and Wilson, 1993; Misgeld et al., 1989; Newberry and Nicoll, 1984, 1985; Thompson and Gähwiler, 1992; Williams and Lacaille, 1992). Hence, the relative resistance of the slow interictal activity to baclofen may reflect a down regulation of $GABA_B$ receptors within the interneuron network in the FCD tissue.

This view is supported by the findings obtained in experiments in which we have analyzed the effects exerted

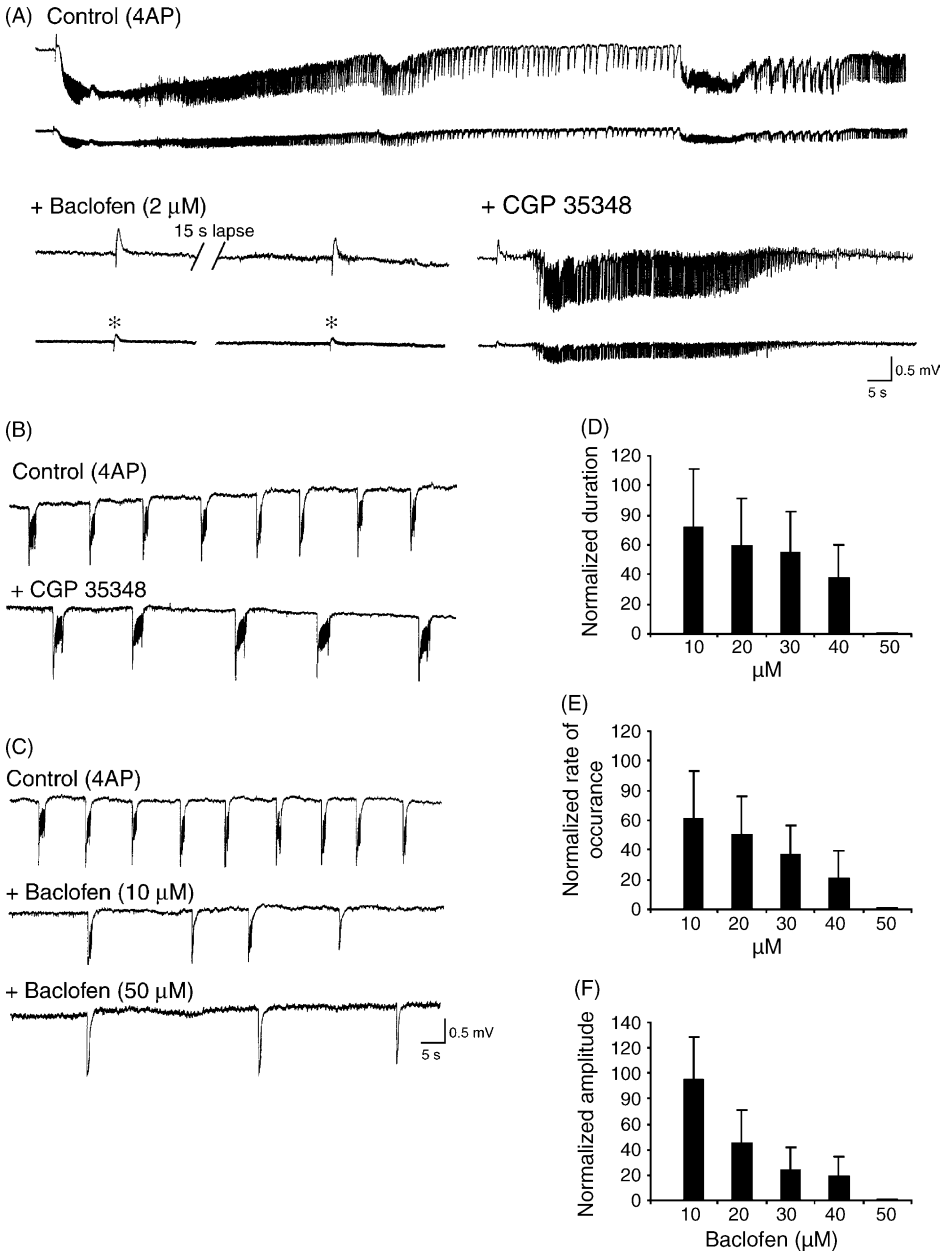

Fig. 20. Effects induced by the $GABA_B$ receptor agonist baclofen on the epileptiform activity generated by a FCD slice during 4AP application. (A) Baclofen abolishes the ictal activity at concentrations as low as 2 μM. Note that: (i) isolated interictal events occur under these experimental conditions (asterisks), and (ii) ictal discharge is restored by additional application of the $GABA_B$ receptor antagonist CGP 35348 (1 mM). (B) Effects induced by blocking the $GABA_B$ receptor with CGP 35348 (1 mM). Note that this pharmacological procedure increases the duration of the interictal events. (C) Baclofen causes a dose-dependent decrease in the duration and rate of occurrence of the interictal activity induced by 4AP. (D–F) Dose–responses of the effects induced by baclofen on the duration, rate of occurrence and amplitude of the interictal events generated by FCD slices during bath application of 4AP. Data normalized to control values obtained over a period of 10 min immediately prior to drug application. Modified from D'Antuono et al. (2004), with permission.

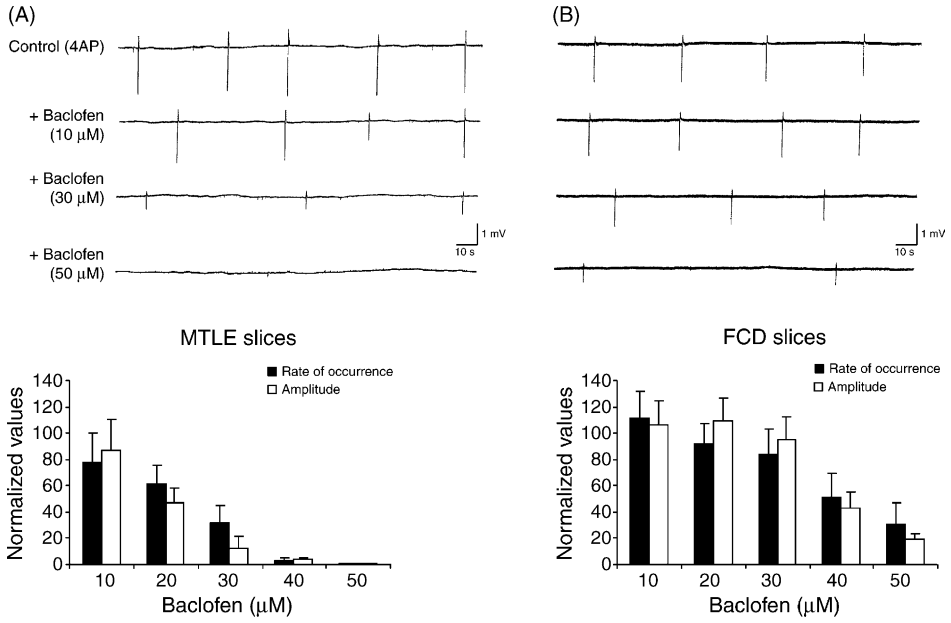

Fig. 21. $GABA_B$ receptor function is modified in FCD slices. Effects induced by the $GABA_B$ receptor agonist baclofen on the isolated field potentials recorded in MTLE (A) and FCD (B) neocortical slices superfused with medium containing 4AP and glutamatergic receptor antagonists (CNQX + CPP). Note that in both experiments $GABA_B$ receptor activation reduces and eventually abolishes these glutamatergic-independent, presumptive GABA receptor-mediated field potentials. However, the effects induced by baclofen are characterized by a higher threshold in the FCD slice. (C and D) dose–responses histograms of the effects induced by baclofen on the rate of occurrence and on the amplitude of the glutamatergic independent events generated by MTLE ($n = 4$) and FCD ($n = 5$) slices during application of medium containing 4AP + CNQX + CPP. Note that the baclofen concentration able to reduce by approx. Fifty percent of the isolated GABA receptor-mediated events is higher in the FCD slices (i.e., approximately 40 μM) as compared with the dose used in the MTLE experiments (i.e., approximately 20 μM). Data were normalized to control values obtained over a period of 10 min immediately prior to drug application. Modified from D'Antuono et al. (2004), with permission.

by baclofen on the synchronous activity recorded in FCD and MTLE slices during bath application of 4-aminopyridine and glutamatergic receptor antagonists. The synchronous potentials recorded under these experimental conditions reflect the firing of interneurons leading to GABA release and to the consequent activation of postsynaptic GABA receptors. As illustrated in Fig. 21, the half-maximal doses of baclofen required to depress the glutamatergic-independent events (and thus to inhibit the release of GABA from interneuron terminals) in FCD and MTLE slices were significantly higher in the former (i.e., 40 and 20 μM). Therefore, these data suggest that the function of $GABA_B$ receptor-mechanisms located on interneurons may be down-regulated in FCD tissue.

6. Limitations of the in vitro approaches to human tissue studies

Most of the experimental findings reviewed here rest on in vitro electrophysiological approaches. In this respect, one must consider that slice preparations involve the isolation of tissue from the widespread network system that is presumed to actively contribute to the generation of seizure activity. Even though it is remarkable how such small pieces of brain tissue can generate neuronal activity resembling electrographic seizures in vivo, this reductionistic approach must be taken into consideration when drawing conclusions that are used for formulating mechanisms of human epileptogenesis. This aspect is even more relevant when dealing with human brain tissue, as the structure that is actually responsible for seizure initiation is often unknown or not clearly defined.

One specific problem in this context is that "macroscopic" electrographic changes found in epileptic patients (i.e., EEG abnormalities) are not necessarily reflected by "microscopic" changes observed in reduced networks or even at the cellular level. In part, this may be due to the fact that while it is certainly desirable to link the tissue origin to defined sites of epileptic activity or to areas without (as determined by electrocorticography), intraoperative local EEG recordings from areas to be resected often are not performed. Moreover, when they have been, often no differences among, e.g., electrophysiological properties (Menendez de la Prida et al., 2002; Telfeian et al., 1999), histopathological findings (Marco et al., 1996) and transmitter concentration changes (Thomas et al., 2005) were found, or they did not have predictive value for cellular electrophysiology or transmitter changes (Colder et al., 1996; Kish et al., 1988; Williamson et al., 1995). This discrepancy between "microscopic" and "macroscopic" findings may be related to the fact that preoperative spiking is not correlated to postoperative outcome (and hence, epileptogenicity; Janszky et al., 2003). Alternatively, cellular alterations might best be linked to discreet network phenomena such as the spontaneous GABA-mediated potentials mentioned above, which due to the small size of the foci would go undetected in the EEG.

Another problem in interpreting "human data" is the absence of "normal" controls. Normal tissue cannot be removed for obvious ethical reasons. In addition, although

''non-epileptic'' cortical samples (e.g., those removed during surgery on deeply-lying brain tumors) have been used, it is unknown to which extent these brain specimens are ''normal''. A variety of additional strategies have been adopted to deal with the issue of controls; however, none of them may be fully adequate. For instance, several electrophysiological studies have compared human tissue that was electrographically very active (''hot'') in situ (i.e., during presurgical depth-electrode EEG recordings or during electrocorticography) with human tissue that was relatively inactive (e.g., spiking versus non-spiking cortex). However, when using this approach, it is unclear what is being compared, since two tissue samples (even though close to each other) are histologically and functionally different even under control conditions. Moreover, it is likely that even ''non-spiking'' tissue may be abnormal.

A similar strategy, which has been used when dealing with MTLE tissue, consists of comparing the same limbic area across patients by using as a basis for comparison some identifiable epilepsy marker—e.g., sclerotic versus non-sclerotic hippocampus (or lesional versus non-lesional cortex). Although, this approach may be advantageous for assessing some aspects of neuronal excitability such as synaptic plasticity, it becomes quite puzzling when used for identifying and thus formulating mechanisms that could lead to seizure generation or epileptogenesis. In fact, it may be hazardous to assume that hippocampal tissue within a temporal lobe with AHS is the site of origin of limbic seizures; therefore, the changes highlighted by this comparative approach may lead to the identification of epiphenomena rather than to the actual mechanisms of epilepsy. In addition, age, sex, age of seizure onset, duration of the seizure disorder, history of medication, etc., all are important factors in making each epileptic patient ''unique''. This aspect also contributes to another problem encountered in studying the human brain tissue, namely, the variability of the clinical phenomena that are seen among patients. These variables can be controlled in animal models. In contrast, this factor can often preclude from collecting specimens from a significant number of patients with a similar clinical disorder.

An alternative approach to the use of human control tissue rests on comparing human data with the findings identified in brain tissue obtained from animal models that mimic a similar epileptic disorder (e.g., MTLE patient specimens being compared to those from animal models such as the kainate- or the pilocarpine-induced epilepsy in rodents). However, this approach ignores species differences, including the identification of which animal brain region may correspond to a given area in the human brain. In addition, differences in time course between human epileptic disorders and animal models are likely to further increase the danger of erroneous conclusions.

Theoretically, comparisons may be less problematic when using histological or molecular approaches as these studies can also rely on the use of autoptic brain tissue. Nonetheless, also in this case one should not underestimate the human variability, even when dealing with ''control'' individuals (e.g., age, sex, history of medication, life habits, etc.). In addition, data obtained from post-mortem brain samples require careful consideration because variabilities related to the cause of death, post-mortem delay after heart arrest, autolysis during storage after death, etc., could all impact on the findings (Jones and Stavinoha, 1977; Harrison, 1999; Toyooka et al., 2002).

7. Conclusive remarks

Investigations in human epileptic tissue over the past decades have revealed a number of possible mechanisms leading to epilepsy, among them receptor re-distributions and up- or down-regulation, and functional alterations as well as seemingly paradoxical roles of GABAergic inhibition. Many of the changes found to be associated with epilepsy in human tissue could also be corroborated in animal models, with some marked exceptions regarding some properties such as spontaneous GABA-mediated discharges, depolarizing GABA responses in subicular neurons and conspicuously large persistent sodium currents, notably again in subicular neurons, to name the most prominent. This apparent redundancy in animal models and human studies may suggest human studies to be only supportive of findings one can easily obtain in experimental models. However, inverting the perspective, it may be all the more important to regularly try to confirm animal data in ''spot-check'' studies of human epileptic tissue to make sure our concepts on epilepsy still match with clinical reality.

While human studies do have their limitations regarding the availability of control tissue and the possible influence of clinical procedures (including surgery itself) on the outcome of the experiments, they are still the only way to validate animal models. Together with complementary animal data (which doubtless do and will constitute the bulk of experiments in epileptology), studies conducted on the human tissue, when carefully designed, will continue to provide us with new important information about the brain alterations associated with epilepsy.

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