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Invited review

How inhibition influences seizure propagation

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ABSTRACT

Inhibitory neuron behaviour is of fundamental importance to epileptic pathophysiology. When inhibition is compromised, such as by GABAergic blockade (Curtis et al., 1970; Connors, 1984; Traub and Miles, 1991) or by shifts in GABAergic reversal potential (Huberfeld et al., 2007), epileptiform discharges occur far more readily. Other studies have shown enhanced inhibition in vivo in the surrounding cortical territories associated with both focal pathological and physiological activity (Prince and Wilder, 1967; Dichter and Spencer, 1969a,b; Goldensohn and Salazar, 1986; Traub and Miles, 1991; Liang and Jones, 1997; Liang et al., 1998; Schwartz and Bonhoeffer, 2001). This gave rise to the concept of an "inhibitory restraint". This concept can explain the often confusing anatomical reorganizations seen in chronically epileptic brains (Sloviter, 1987; Cossart et al., 2001), indicating which changes might be pro-epileptic, and which oppose the epileptic state. It also may explain key electrophysiological features of epileptic seizures. Here we describe current knowledge about the restraint, gleaned mainly from acute pharmacological experiments in animals, both in vivo and in vitro, and speculate how this may alter our understanding of human seizure activity in clinical practice.

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

1. Introduction

One of the defining features of cortical networks is the massive amount of recurrent connections (Braitenberg and Schuz, 1998; Douglas et al., 2004). Whilst these feedback loops are presumably crucial for cortical function (Treves and Rolls, 1992; Rolls et al., 2002), they come at a high cost, since they run the risk of the network becoming locked in a cycle of recurrent excitation. To avert this, inhibitory elements must be powerful. One theory is that cortex copes with increasing excitation simply by increasing inhibition proportionately (Nelson and Turrigiano, 1998; Shu et al., 2003). Such a balancing act, though, would appear delicate, and particularly precarious when activity is high. Indeed, cortical networks seem ill served in their inhibitory capabilities. Interneurons represent just 10–20% of the total number of neurons (Peters et al., 1985), and their outputs constitute probably an even smaller percentage of the total synapses (Schuz and Palm, 1989). Yet various experimental evidence indicate that inhibition can oppose spreading activity very effectively indeed, to the extent that it may stop a seizure in its tracks. We will consider here how that is brought about, and the complementary nature of the interplay between different interneuronal populations. We will also discuss other situations where the inhibition fails, or may even promote a propagating wave. These data provide a far more nuanced view of how GABAergic interneurons influence cortical activity, and one which requires more precision in how we describe cortical activity, particularly in cases where the same term is used to describe what are clearly different network events. Finally we will consider how this may change our understanding of naturally occurring epilepsy activity in humans.

2. Spatio-temporal patterns of inhibition

There is a clear spatial arrangement of inhibitory effects in cortical networks, where focal activity is associated with suppression of activity in surrounding cortical territories. This was apparent from the very first intracellular recordings made from cortical neurons (Powell and Mountcastle, 1959). These first recordings, made in anaesthetized cats, showed that a focal cortical stimulation gave rise to pronounced inhibitory post-synaptic potentials (IPSPs) in neurons in the surrounding territory. A decade later, in 1967, Prince and Jasper showed similar lateral inhibition during interictal bursts in rat hippocampus (Prince and Wilder, 1967). Instead of focal electrical stimulation as used by

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Powell and Mountcastle, Prince and Wilder induced localized excitation pharmacologically, but the effect was the same, with pyramidal cells adjacent to the focus being bombarded with inhibitory postsynaptic currents during interictal discharges. These observations gave rise to the concept of a protective "surround inhibition".

Subsequently, other researchers have confirmed and extended these observations. Similar surround inhibition was also found in cat hippocampus following penicillin injections (Dichter and Spencer, 1969a,b), and in ferret neocortex, Schwartz and Bonhoeffer captured the effect using intrinsic optical imaging, following a focal injection of 4-aminopyridine (Schwartz and Bonhoeffer, 2001; Schwartz, 2003). These reports all describe the immediate effects of acutely induced focal activity, but such activity may also provoke chronic changes in the surround territories. Following focal tetanus injections in rats, Liang et al. showed contrasting patterns of expression of the immediate early genes, Zif-268 and c-Fos (Liang and Jones, 1997) in the focus and surround territories. They also showed a widespread increase in BDNF expression 2–3 days after the tetanus injection, but when they examined at a later time, noted that increased expression was limited to the focus, while there was a pronounced decrease in BDNF in the surrounding territories (Liang et al., 1998). Chronic models however, introduce an additional level of complexity since there are clearly both pro-epileptic and anti-epileptic changes evident, and the epilepsy phenotype is rarely stable. In contrast, the response to acute increases in activity is likely to represent an altogether more tractable set of phenomena to understand. A coherent view of this acute response to focal activity then may be used to understand exactly which chronic changes might sustain an epilepsy phenotype, and which oppose it to ameliorate the phenotype. It is thus worth striving for a full understanding of these acute models, even if we recognise that they do not fully capture the complexities of the chronic disease. The network surges occurring in acute models may indeed arise by a different mechanism to the chronic disease state, but the response to those network surges, particularly in relatively normal surrounding tissue, is likely to be comparable.

This view of focussed activity, derived from acute models of focal seizures, is clearly related to the phenomenon of topographic representations in cortical networks. It is notable then that a simple visual perceptual task aimed at eliciting surround inhibition, produces a more powerful suppression at high contrast than at low contrast (Tadin et al., 2003). Thus, even in physiological processing, one can see evidence for the dominance of inhibition over excitation. This task simply measures the duration that a small patch of moving bars needs to be presented for the observer to tell reliably whether the movement is to the right or left. For low contrast stimuli (subtle shades of grey), increasing the size of the stimulus makes it progressively easier to detect which direction it is moving. That is to say, the observer reliably identifies the direction for ever more brief presentations. For high contrast stimuli (more "black and white"), however, increasingly large stimuli are paradoxically more difficult to detect. Thus, as thalamic input to cortex rises, achieved in this study by increasing the contrast and size of the stimuli, cortical inhibition becomes increasingly dominant. A further striking finding is that schizophrenic subjects have significantly reduced suppression in this visual psychophysical test (Tadin et al., 2006). Schizophrenia is known to be associated both with visual motion disturbances which may underlie some thought disturbance symptoms, and animal models show a deficit in the function of fast-spiking interneurons. Furthermore, there is a tantalizing link between schizophrenia and epilepsy: schizophrenia dramatically increases the life-time risk of epilepsy (Chang et al., 2011), and vice versa (Qin et al., 2005), and transient psychotic episodes ("post-ictal psychosis") are a common complication of uncontrolled seizures (Slater et al., 1963).

3. Evidence of surround inhibition in propagating epileptiform events

Even when seizure activity does spread, there is compelling evidence of powerful feedforward inhibition ahead of the wavefront. For instance, Steriade, Timofeev and their colleagues have made many intracellular recordings of neocortical neurons following focal injections of GABAergic blockers to create an ictal focus, which show a very characteristic, electrophysiological pattern of recruitment to a seizure (Timofeev and Steriade, 2004). Neurons experience a period of large rhythmic depolarizations but with very little firing activity, which may last tens of seconds prior to the eventual appearance of the first paroxysmal depolarising shifts (PDSs; Fig. 1). If cells are artificially loaded with chloride through the recording electrode, thereby shifting the GABAergic reversal potential (E_{GABA}) close to 0 mV, intense PDSs are initiated much earlier in the event, indicating that the synaptic drive at this time has a very large GABAergic component (Grenier et al., 2001, 2003).

This pattern of recruitment is also reproduced in a simple, in vitro model of epileptiform activity, induced by removing Mg^{2+} ions from the bathing medium. The key thing about this model is that this pharmacological manipulation boosts excitatory neurotransmission by removing the voltage-dependent blockade of NMDA receptors, but critically leaves synaptic inhibition intact, at least initially. This creates a hyperexcitable tissue which may be used to study the cortical response to surges of activity. Interestingly, for a period of many minutes (and sometimes lasting well over an hour) after the removal of Mg^{2+} ions, one records transient (100–2000 ms) network activations, with predominantly interneuronal participation, but little pyramidal activity (unpublished observations). Eventually though, this activity evolves into propagating full ictal events, which appear to involve every neuron in the network, and characteristically show a "tonic-clonic" pattern of discharges. Another feature of these propagating ictal events is a powerful lateral inhibition: these first ictal events propagate only very slowly (<1 mm/s), much slower than events in disinhibited slices (~25–100 mm/s)(Albowitz and Kuhnt, 1993; Wadman and Gutnick, 1993; Pinto et al., 2005), and just like Steriade and colleagues' recordings, the rate limiting step appears to be the failure to recruit pyramidal cells during many repeated surges of network activity ("network crises") (Trevelyan et al., 2006, 2007a).

The level of accessibility provided by the in vitro preparation, allowed a very thorough analysis of these activity patterns, combining Ca^{2+} network imaging and multiple different types of electrophysiological recordings in up to 3 neurons, simultaneously (Trevelyan et al., 2006, 2007a,b; Trevelyan, 2009). Over many recordings, we have characterized how the synaptic input relates to the firing patterns, and also to the pattern of activity seen in other local neurons. Just like the in vivo recordings of Steriade, Timofeev and colleagues (Fig. 1A), we found that in current clamp mode, the first indication of an approaching ictal event was the start of large rhythmic depolarizations with very little firing. This pattern could be sustained for many seconds, and on occasions, failed to evolve further at all. A particularly useful recording mode was to hold pyramidal cells in voltage clamp, at about −30 mV, roughly half way between the reversal potentials for glutamate and GABA (Fig. 1B). This recording mode provides an estimate of the relative influences of excitatory and inhibitory drives. Furthermore, if one recorded pairs of layer 5 pyramidal cells during this key period, then the pattern of synaptic barrages was almost identical on to the two cells (Fig. 2A). The significance of this observation was that it