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Suppression of Neural Activity with High Frequency Stimulation

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Abstract— **Deep brain stimulation (DBS) has been shown to generate suppression of abnormal neural activity in patients with Parkinson's disease and epilepsy. High frequency stimulation is applied to the brain through depth electrodes in the range of 50 to 200 Hz. Yet the mechanisms underlying the suppression effect have not yet been elucidated. In order to study directly the effect of HFS in the brain, sinusoidal stimulation was applied in the in-vitro brain slice preparation. Sinusoidal stimulation was chosen in order to observe the activity during the stimulation by filtering the stimulation artifact.**

Sinusoidal stimulation at 50Hz applied to the CA1 region of the hippocampus was observed to block epileptiform activity in three separate models of epilepsy induced by low-calcium, high potassium and picrotoxin ($GABA_A$ blocker). Stimulation applied to the alveus showed that activity in both the cell bodies (evoked potentials) and in the axons (compound action potentials) is suppressed. The frequency range of this effect is nearly identical to that of DBS with maximum suppression effect between 50 and 200Hz. The effect could not be attributed to desynchronization or damage and was associated with increased extracellular potassium concentrations.

These data provide new insights into the effects of HFS on neuronal elements and show that HFS can block axonal activity through non-synaptic mechanisms.

Keywords—Electrical Stimulation, Suppression of neural activity, Epilepsy

I. Introduction

Although antiepileptic drugs (AEDs) can control a large majority of epileptic seizures, surgery is required to treat epilepsies refractory to conventional pharmacotherapy (Mongilner *et al.*, 2001). In many cases, however, surgery cannot be performed. Therefore, novel neurosurgical approaches, such as high frequency electrical stimulation (HFS), are being developed for the treatment of epilepsy. Preliminary studies show that HFS have met with some success (Velasco *et al.*, 2001; Vonck *et al.*, 2002). The frequencies that are effective are similar to those used in patients with Parkinson's disease. Yet, the mechanisms that underlie this effect are unknown. In particular, it would be important to know if HFS affects cell bodies, afferent and efferent axons, and axons of passage. To answer this question, several experiments have been carried out in-vitro in the hippocampal slice preparation.

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II. Methods

Extracellular recordings of field potentials will be made using glass microelectrodes (3-10 MΩ, borosilicate) filled with 150mM NaCl. Electrodes will be positioned in the CA1 stratum pyramidale and/or alvear axon field. *Artificial CSF solution:* (in mM): NaCl 124, KCl 3.75, KH_2PO4 1.25, $MgSO_4$ 2, $NaHCO_3$ 26, $CaCl_2$ 2, dextrose 10, bubbled with 95% O_2-5%CO_2

III. Results

50 Hz sinusoidal electrical fields were applied to suppress both synaptic and non-synaptic epileptiform spontaneous activity with large Ag/AgCl electrodes located on either side of the hippocampal slice. Figure 1(A) shows an example of the effect of electric fields on spontaneous low-Ca^{2+} activity in the CA1 region. Stimulation blocked bursting for the duration of the stimulus and for up to 4 minutes after termination of stimulation (Bikson et al, 2001). Stimulation was associated with a 0.5-15 mV negative shift in the field potential. These experiments show that the mechanisms underlying this effect are non-synaptic. Similar results were obtained with spontaneous epileptiform activity generated either with picrotoxin to block inhibition (Figure 1B) or high potassium concentration solution (Figure 1C).

To determine the effect of electrical stimulation on axonal conduction, electrical stimulation was applied in the alveus (pathway consisting of axons of the CA1 Cells). Activation of the pathway produces compound axon potentials as shown in Fig 2A (top left) recorded by an extracellular microelectrode placed also in the alveus. This compound axon potential was monitored at low frequency (0.5Hz). Sinusoidal high frequency was applied to a third electrode located between the stimulating and recording electrodes. High frequency stimulation (HFS) at 50Hz clearly abolished the compound action potential (Fig. 2A) which resumed after the stimulation was terminated. 100% suppression could be achieved (not shown). At 2kHz, the suppression effect disappeared (Fig 2A). The frequency dependence of this axonal suppression effect is shown in Fig 2B and is nearly identical to that reported for DBS in clinical trials.

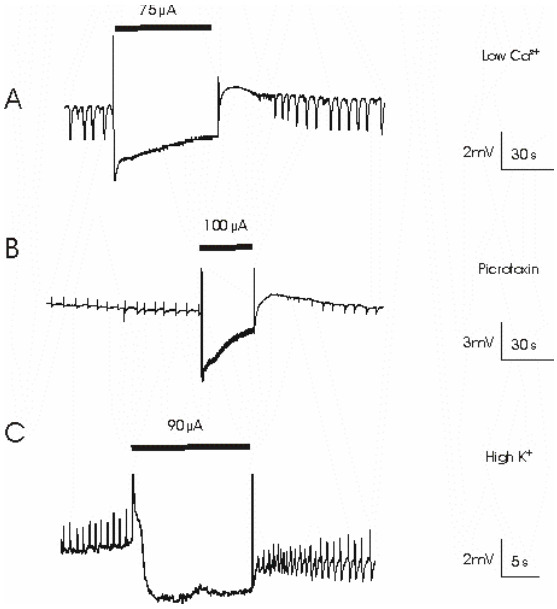

Figure 1: Effect of applied sinusoidal fields (50Hz) in spontaneous epileptiform activity generated by low-calcium solutions (A), inhibition blocker picrotoxin (B), and high potassium solutions (C). Electrical activity is suppressed in all cases during the application of the stimulation and for a few minutes following the stimulation.

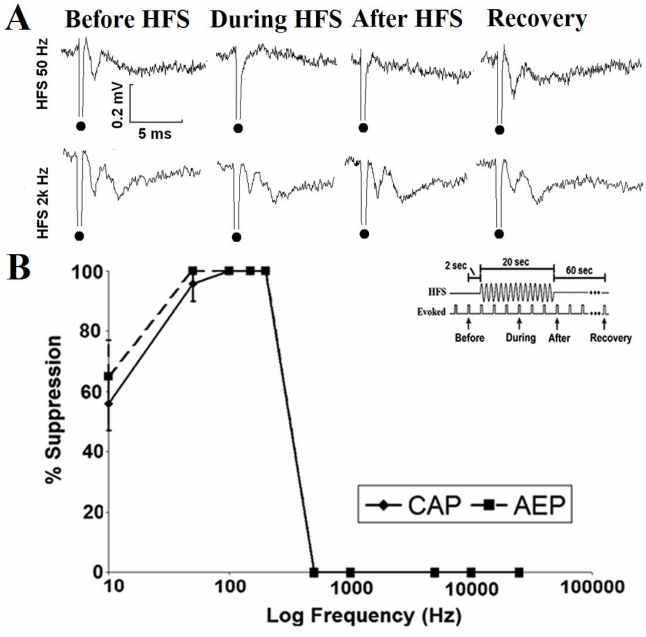

Figure 2: Effect of local sinusoidal stimulation applied through a sharp tungsten microelectrode on the compound action potential in the alveus. A; The compound action potential is suppressed at 50Hz but not at 2KHz, B: The frequency dependence of this mechanism is shown for both the compound action potential (CAP) and the antidromic CA1 evoked potential (AEP) (Jensen and Durand, 2005).

IV. DISCUSSION AND CONCLUSIONS

High frequency stimulation can generate complete suppression of electrical activity either spontaneous (Fig. 1) and evoked (Fig. 2). The suppression takes place both in the cell bodies (CA1 cells in Fig 1) and alveus axons in Fig 2. Therefore, an electrode located within the brain would suppress activity generated locally and also axons of passage. The mechanism for this suppression effect is not known. However, damage to the cells, increased inhibition, and desynchonization have been ruled out. An increase in potassium concentration has been associated with the HFS suppression effect. It is therefore likely, that, depolarization block is partially responsible for the effect. Intracellular recordings in the CA1 cells support this hypothesis (Bikson et al, 2001). However, the potassium concentration decays significantly while the suppression remains at a high level. Therefore, other mechanisms must play a role in this suppression effect. The suppression effect was shown to be localized to a region around the stimulation electrode of several hundreds of micrometers (Lian et al, 2003).

In conclusion, HFS applied globally (fields) or locally (sharp electrodes) can suppress neural activity both in axons and cells bodies in-vitro with a frequency range similar to that of DBS. The suppression is independent of duration and synaptic transmission. Therefore, the mechanisms underlying this effect could be related to those underlying DBS.

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