

EFFECTS OF WEAK ELECTRIC FIELDS ON THE ACTIVITY OF NEURONS AND NEURONAL NETWORKS

J. G. R. Jefferys, J. Deans, M. Bikson and J. Fox
Department of Neurophysiology, Division of Neuroscience
School of Medicine, University of Birmingham, B15 2TT, UK

Abstract — Electric fields applied to brain tissue will affect cellular properties. They will hyperpolarise the ends of cells closest to the positive part of the field, and depolarise ends closest to the negative. In the case of neurons this affects excitability. How these changes in transmembrane potential are distributed depends on the length constant of the neuron, and on its geometry; if the neuron is electrically compact, the change in transmembrane potential becomes an almost linear function of distance in the direction of the field. Neurons from the mammalian hippocampus, maintained in tissue slices *in vitro*, are significantly affected by fields of around $1\text{--}5\text{ V m}^{-1}$.

INTRODUCTION

It is clear that neurons respond to electrical stimulation, and that high intensity AC electrical stimulation can have dramatic effects on brain function, for example in electroconvulsive therapy. Our aim here is to consider the effect on brain function of weak AC fields at power-line frequencies (50 or 60 Hz) and below⁽¹⁾. Even when there is no direct electrical connection between an electric source and the body, electric fields can be induced in neural tissue; environmental magnetic fields can also induce electric fields in the brain. The precise relationship between electromagnetic fields in the environment and the electric fields in the body, and in particular in the brain, is complex and is considered elsewhere in this volume. Here, we review experimental investigations of the effects of applied electric fields on the acute electrophysiological activity of the brain.

DC ELECTRIC FIELDS

Several early studies showed that non-mammalian tissues were sensitive to applied weak electric fields; for instance, fields as low as 1 V m^{-1} affected the lobster stretch receptor⁽²⁾. Studies during the 1960s on mammalian brain *in vivo* showed that electric fields could modify neuronal firing and indicated the polarity of the effect^(3–5), but these phenomena were controversial⁽⁶⁾. Estimating thresholds for these effects proved complex, because of the difficulties in positioning the electrodes passing the current and hence in controlling the uniformity and direction of the induced voltage gradients. Where such thresholds were estimated, they were of the order of tens of V m^{-1} ⁽⁵⁾. These kinds of experiment also revealed interesting long-term changes in activity⁽⁷⁾, an early form of long-term potentiation, which is often seen as a model of learning and memory.

During the 1970s the brain slice preparation *in vitro*

started to be exploited in the study of the effects of applied electric fields on brain function. Slices of around 0.4 mm thick are thin enough for oxygenation of their centres, while they are thick enough to preserve much of the local neural circuitry intact. They are kept in an aqueous physiological medium so that it is very easy to place large current passing electrodes in the solution bathing the slice in such a way that the applied field is uniform, at least at a macroscopic level. Experiments on guinea pig hippocampal slices showed that electric fields of $\sim 5\text{ mV mm}^{-1}$ can modify the excitability of neurons called dentate granule cells⁽⁸⁾. The linear relationship between the applied field and the physiological response (in this case, the population spike, which estimates the numbers of neurons being made to fire) is important. It means that there is no well defined threshold for an effective electric field. The figure of 5 mV mm^{-1} quoted in this study was relatively conservative, being based on the intersection between the response to the field and two standard deviations from the mean control response, and thus is as much due to the variability of the control response as to the strength of the effect.

Similar thresholds (5 V m^{-1}) were found for DC fields applied to the CA1 region of the hippocampus⁽⁹⁾. Electric fields of this order could modulate low calcium field bursts (a kind of experimental epilepsy not dependent on synaptic transmission) in the same region^(10–12); the efficacy of this phenomenon depends on the experimental model of epilepsy and on the details of the current application. Slightly higher quasistatic fields ($15\text{--}20\text{ V m}^{-1}$) proved effective in modulating neuronal activity in slices from turtle cerebellum^(13–15).

Recently, we explored these issues in more detail on the hippocampal CA1 pyramidal neuron. We confirmed the linear relationship between applied field and effect. More importantly, we were able to measure that transmembrane potential at the cell body changed by an average of 0.12 mV for each V m^{-1} of applied field⁽¹⁶⁾. (The transmembrane potential has to be measured between the intracellular electrode and an extracellular reference

electrode in the near vicinity; normally, reference electrodes are placed some distance away in the bathing solution and would record a different potential when the electric field is applied.)

The central idea of how applied current affects neuronal activity is that it produces an extracellular voltage gradient which alters the potential difference across the membrane, with opposing polarities, at either end of the neuron^(14,17). This induced transmembrane potential change causes current to flow across the membrane and along the inside of the neuron according to the resistances presented by the membrane and the intracellular space, which determine the length constant of the neuron. Electrotonically long neurons (i.e. with a short length constant) have changes in transmembrane potential restricted to the ends of the neurons; at other locations along such neurons, the changes in potential would be equal inside and out. Electrotonically short neurons, which probably are more typical of real mammalian brain, have a transmembrane potential change that varies linearly with distance along the axis of the applied current. In real neurons, the effects of applied fields can be significantly more complex; for instance, the locations of bending and branching of dendrites and axons can have a major impact^(17,14).

Our recent experiments show that the change in transmembrane potential is not instantaneous, but has a time constant of the order of a few tens of milliseconds. This results from the capacitance of the neuronal membrane. One implication of this is that the transmembrane potential changes induced by AC fields at 50 or 60 Hz will be attenuated from those expected for DC fields.

AC ELECTRIC FIELDS

Early studies of the effects of AC fields on hippocampal slices *in vitro* found a roughly similar sensitivity to those for DC fields, i.e. $\sim 5 \text{ V m}^{-1}$ ^(9,18). More surprisingly, Bawin *et al*^(9,18) found long-term changes (>10 min) in responses following <30 s of relatively weak AC fields (as low as 0.7 V m^{-1}). These longer lasting effects were independent of the direction of the field, suggesting they did not result from membrane potential changes in the soma-dendrite complex.

The time constant we found when DC fields were switched on or off led us to expect that AC fields would

be less effective in modulating neuronal excitability. However, very small, but synchronous, effects on individual neurons may have substantial effects on the coordinated activity of large numbers of neurons within synaptic networks; indeed, it is clear that most, if not all, brain function depends on 'emergent properties' of neuronal networks. We therefore studied the effects of weak 50 Hz AC fields on coherent oscillations in the gamma (30–100 Hz) and beta (15–30 Hz) frequency bands. These oscillations have been associated with cognition^(19–21). Oscillations at these frequencies can be induced in slices by a range of chemical treatments⁽²²⁾. We used 100 nM kainic acid to induce gamma rhythms in hippocampal slices, with a peak power at ~ 30 Hz in the absence of applied current. Applied sinusoidal 50 Hz fields of $6\text{--}10 \text{ V m}^{-1}$ (peak to peak) markedly reduced the power at this frequency, and could increase the power at lower frequencies, typically at 25 Hz. The weakest effective applied sinusoidal field was 2 V m^{-1} peak to peak, which resulted in small, but statistically significant, reductions in peak power. Applied fields of 1 V m^{-1} peak to peak had no detectable effect. We have not, so far, detected long-term changes in the oscillations following application of these AC fields. The relatively low values of the fields that can modulate kainate induced gamma rhythms supports the idea that weak effects of electric fields on large numbers of neurons can alter their collective network activity. The observation that alternate cycles of the applied field tended to entrain the excitatory phase of these gamma rhythms suggests that the effect is mediated by changes in membrane potential similar to those found with DC fields.

Brain rhythms in the gamma and beta bands *in vivo* are linked to cognitive functions. However, it is a large jump from finding a measurable change in chemically induced oscillations in a piece of tissue *in vitro* to the behaviour of intact animals, and it remains to be seen whether or not these effects are harmful. At the moment we can say that 50 Hz fields of the order of 2 mV mm^{-1} in brain tissue can modulate cortical oscillations.

ACKNOWLEDGEMENTS

The authors' work is supported by the Department of Health and MRC. The National Grid plc supported the first phase of this work.

REFERENCES

1. Saunders, R. D. and Jefferys, J. G. R. *Weak electric field interactions in the central nervous system*. Health Phys. **83**(3), 366–375 (2002).
2. Terzuolo, C. A. and Bullock, T. H. *Measurement of imposed voltage gradient adequate to modulate neuronal firing*. Proc. Natl. Acad. Sci. USA **42**, 687–694 (1956).
3. Bindman, L. J., Lippold, O. J. C. and Redfearn, J. W. T. *The action of brief polarizing currents on the cerebral cortex of the rat (1) during current flow and (2) in the production of long-lasting after-effects*. J. Physiol. (Lond.) **172**, 369–382 (1964).
4. Creutzfeldt, O. D., Fromm, G. and Kapp, H. *Influences of transcortical D.C. currents on cortical neuronal activity*. Exp. Neurol. **5**, 436–452 (1962).

5. Purpura, D. P. and McMurtry, J. G. *Intracellular activities and evoked potential changes during polarization of motor cortex.* J. Neurophysiol. **28**, 166–185 (1965).
6. Purpura, D. P. *Evidence contradicting neuron sensitivity to extracellular fields.* Neurosci. Res. Prog. Bull. **12**, 143 (1974).
7. Gartside, I. B. *Mechanisms of sustained increases of firing rate of neurons in the rat cerebral cortex after polarization: reverberating circuits or modification of synaptic conductance?* Nature **220**(165), 382–383 (1968).
8. Jefferys, J. G. R. *Influence of electric fields on the excitability of granule cells in guinea-pig hippocampal slices.* J. Physiol. (Lond.) **319**, 143–152 (1981).
9. Bawin, S. M., Sheppard, A. R., Mahoney, M. D., Abu-Assal, M. and Adey, W. R. *Comparison between the effects of extracellular direct and sinusoidal currents on excitability in hippocampal slices.* Brain Res. **362**, 350–354 (1986).
10. Ghai, R. S., Bikson, M. and Durand, D. M. *Effects of applied electric fields on low-calcium epileptiform activity in the CA1 region of rat hippocampal slices.* J. Neurophysiol. **84**(1), 274–280 (2000).
11. Gluckman, B. J., Neel, E. J., Netoff, T. I., Ditto, W. L., Spano, M. L. and Schiff, S. J. *Electric field suppression of epileptiform activity in hippocampal slices.* J. Neurophysiol. **76**(6), 4202–4205 (1996).
12. Gluckman, B. J., Nguyen, H., Weinstein, S. L. and Schiff, S. J. *Adaptive electric field control of epileptic seizures.* J. Neurosci. **21**(2), 590–600 (2001).
13. Chan, C. Y. and Nicholson, C. *Modulation by applied electric fields of Purkinje and stellate cell activity in the isolated turtle cerebellum.* J. Physiol. (Lond.) **371**, 89–114 (1986).
14. Tranchina, D. and Nicholson, C. *A model for the polarization of neurons by extrinsically applied electric fields.* Biophys. J. **50**, 1139–1156 (1986).
15. Chan, C. Y., Hounsgaard, J. and Nicholson, C. *Effects of electric fields on transmembrane potential and excitability of turtle cerebellar Purkinje cells in vitro.* J. Physiol. (Lond.) **402**, 751–771 (1988).
16. Bikson, M., McIntyre, C. C., Grill, W. M., Fox, J. E. and Jefferys, J. G. R. *Effect of uniform DC electric fields on hippocampal function in vitro.* Forum Eur. Neurosci. **3**, 187.13 (2002).
17. McIntyre, C. C. and Grill, W. M. *Excitation of central nervous system neurons by nonuniform electric fields.* Biophys. J. **76**(2), 878–888 (1999).
18. Bawin, S. M., Sheppard, A. R., Mahoney, M. D. and Adey, W. R. *Influences of sinusoidal electric fields on excitability in the rat hippocampal slice.* Brain Res. **323**, 227–237 (1984).
19. Singer, W. *Time as coding space?* Curr. Opin. Neurobiol. **9**(2), 189–194 (1999).
20. Jefferys, J. G. R., Traub, R. D. and Whittington, M. A. *Neuronal networks for induced ‘40 Hz’ rhythms.* Trends Neurosci. **19**, 202–208 (1996).
21. Singer, W. and Gray, C. M. *Visual feature integration and the temporal correlation hypothesis.* Annu. Rev. Neurosci. **18**, 555–586 (1995).
22. Fisahn, A., Pike, F. G., Buhl, E. H. and Paulsen, O. *Cholinergic induction of network oscillations at 40 Hz in the hippocampus in vitro.* Nature **394**(6689), 186–189 (1998).

