Ephaptic Interactions: A Significant Mode of Communications in the Brain

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Though first postulated many decades ago, the functional significance of electric (ephaptic) interactions between neighboring nerve cells has been largely ignored. Instead, attention has been focused on chemical transmission as the generally accepted mode of cell-to-cell communication in the brain. In recent years, however, clear inhibitory or excitatory ephaptic interactions have been demonstrated in certain regions of the brain, notably in the hippocampus. Such interactions may greatly enhance synchronized firing of pyramidal cells in seizure discharges.

It may be a surprise to many readers that there was a time—within living memory—when it was not assumed that all synaptic transmission is mediated by excitatory or inhibitory chemicals. Indeed, transmission of signals between nerve cells was generally considered to be purely electrical, by current flow between active and inactive cells. Changes in excitability evoked by passive current flow in adjacent cells were described as ephaptic transmission by Arvanitaki (1) as opposed to synaptic transmission at sites of specialized junctions. Depending on the direction of predominant current flow near the sites of spike initiation, mainly excitatory or inhibitory effects could be predicted theoretically and demonstrated in experiments. It must be emphasized that ephaptic interactions are not mediated by special low resistance connections between cells (such as gap or tight junctions), and therefore they must be distinguished from other types of electrical transmission.

After the almost universal acceptance of chemical transmission as the mechanism of synaptic action, interest in electrical interactions nearly vanished. In the early 1960s, however, Furukawa and Furshpan (3) discovered an inhibitory action on Mauthner cells (in the brain stem of fish) that differed from conventional inhibitory synaptic potentials by its very brief duration and by the lack of any accompanying resistance change. It could best be explained as a passive electrical (ephaptic) phenomenon.

An important requirement for a significant ephaptic action is that the extracellular resistance, which normally provides a low resistance path for the action current generated by an action potential, should be unusually high: when this is the case, a good part of this current has to flow through neighbouring neurons, thus changing their excitability. The tight axon “cap” structure around the base of the Mauthner cell, in which many nerve endings are densely embedded, provides such a highly resistive environment. This promotes inhibitory ephaptic actions, not only between certain nerve endings and the axon hillock of the Mauthner cell but also between the Mauthner cell and smaller neurons that send processes into the axon cap (6). Having been sensitized to this kind of phenomenon, Korn subsequently detected a similar brief inhibitory action in the mammalian cerebellar cortex (2).

Until recently, excitatory ephaptic phenomena in the central nervous system received little attention, a notable exception being the convincing demonstration by Nelson (7) of a small and brief electrical interaction between spinal motoneurons. In the last year or two, however, ephaptic excitations have become very evident in the hippocampus. As early as 1964, Green had considered ephaptic interactions very likely because of the unusually dense packing of hippocampal pyramidal cells, their regular and parallel arrangement, and the scarcity of intervening glial cells. By greatly limiting interstitial current flow, these factors would maximize currents flowing at different levels into and out of adjacent neurons. Even though hippocampal slices have for some years been prodded with more microelectrodes than any other central neural structure, Green’s suggestion was long ignored. It would perhaps still be ignored, were it not for a curious observation that, in the absence of synaptic function, groups of neurons in the hippocampus tend to fire synchronously.

A major advantage of hippocampal slices is that when they are exposed to a Ca2+-free and Mg2+-enriched medium, neuronal behaviour can be studied in the absence of synaptic transmission (transmitter release requiring Ca2+ influx into nerve terminals, which is suppressed by high Mg2+). Hippocampal slices are therefore often treated in this way to eliminate synaptic action. An unexpected side effect, however, is that after a while the slices become hyperreactive. If stimulated electrically, they readily generate bursts of synchronized firing, and such paroxysmal activity may even occur “spontaneously.” But how can the firing of groups of neurons be synchronized in the absence of functional synapses?

Here was a paradoxical phenomenon, the signification of which was first pointed out in 1982 by Taylor and Dudek (8) and by Jefferys and Haas (5), working independently. Because of the scarcity of “gap” (electrotonic) junctions between pyramidal cells, these observations could be explained only by nonjunctional ephaptic interactions (or electrical...
Extracellular field effects, following Korn and Faber (6).

By recording simultaneously with intracellular and extracellular microelectrodes, Taylor and Dudek (8, 9) consistently observed markedly smaller field potentials inside than outside a resting neuron. By subtracting the external from the internal record, they demonstrated a very substantial transmembrane potential, evidently caused by the passive transmembrane current generated by action potentials in adjacent active neurons. Because this transmembrane current is depolarizing at the level of the cell bodies (Fig. 1), close to the initial segment where spikes are most readily inhibited, its effect should be to increase the excitability of the inactive cells, as was indeed demonstrated by combining such fields with subthreshold depolarizing pulses. A wider, functional relevance of this phenomenon was indicated by the demonstration of very similar ephaptic interactions in the hippocampus in situ. On the average, nearly 40% of an antidromic extracellular field appears as a depolarizing transmembrane potential so that even a small field can produce a significant increase in firing probability (10).

These ephaptic actions have some interesting functional implications, notably in promoting the synchronous firing of large groups of neurons. As more and more cells are recruited, they generate correspondingly stronger ephaptic currents: at the same time, fewer inactive cells remain, thus further reducing the external path available for current flow. The net result would be a very much steeper relationship between excitatory input and efferent response. Instead of the customary sigmoid curve, at the limit one would obtain a rectangular function, where only a minimal increase in input shifts the output from zero to maximal.

Of course, under "normal" conditions a strong inhibitory tone keeps hippocampal excitability at a low level and therefore prevents a full manifestation of the ephaptic process. But when excitability is raised, especially because of a loss of inhibitory control—for example as a result of a pathological process (as in epileptic foci) or the action of convulsant drugs (such as penicillin) that are antagonists of the main hippocampal inhibitory transmitter γ-aminobutyric acid—then the ephaptic action comes into its own. More relevant from a physiological point of view is the fact that inhibition can also be diminished by some endogenous agents, such as acetylcholine; hence activity of the septohippocampal cholinergic pathway would tend to promote synchronized hippocampal firing. Unusually favourable conditions for ephaptic excitation must account at least partly for the striking tendency of the hippocampus to generate synchronized paroxysmal firing. It would be surprising if appreciable ephaptic interactions did not occur in other regions of the central nervous system, although in few other areas is it likely to be of such major functional significance.

References