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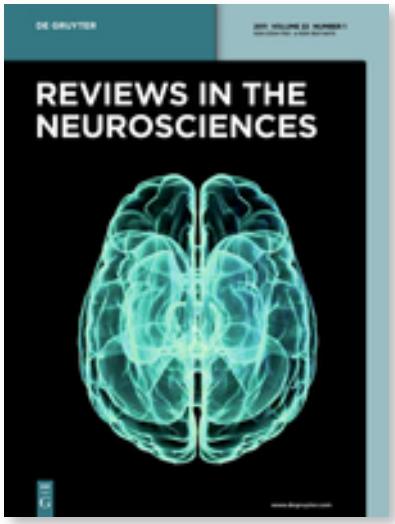

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Axonal Gap Junctions Between Principal Neurons: A Novel Source of Network Oscillations, and Perhaps Epileptogenesis

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Axonal Gap Junctions Between Principal Neurons: A Novel Source of Network Oscillations, and Perhaps Epileptogenesis

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SYNOPSIS

We hypothesized in 1998 that gap junctions might be located between the axons of principal hippocampal neurons, based on the shape of spikelets (fast prepotentials), occurring during gap junction-mediated very fast (~200 Hz) network oscillations *in vitro*. More recent electrophysiological, pharmacological and dye-coupling data indicate that axonal gap junctions exist; so far, they appear to be located about 100 µm from the soma, in CA1 pyramidal neurons. Computer modeling and theory predict that axonal gap junctions can lead to very fast network oscillations under three conditions: a) there are spontaneous axonal action potentials; b) the number of gap junctions in the network is neither too low (not less than ~1.5 per cell on average), nor too high (not more than ~3 per cell on average); c) action potentials can cross from axon to axon via gap junctions. Simulated oscillations resemble biological ones, but condition (c) remains to be demonstrated directly. Axonal network oscillations can, in turn, induce oscillatory activity in larger neuronal networks, by a variety of mechanisms. Axonal networks appear to underlie *in vivo* ripples (~200 Hz field potential oscillations superimposed on physiological sharp waves), to drive gamma (30-70 Hz) oscillations that appear in the presence of carbachol, and to initiate certain types of ictal discharge. If axonal gap junctions are important for seizure initiation in humans, there could be practical consequences for antiepileptic therapy: at least one gap junction-blocking compound, carbenoxolone, is already in clinical use (for treatment of ulcer disease), and it crosses the blood-brain barrier.

KEY WORDS

spikelet, fast prepotential, d-spike, hippocampus, electrical coupling, cortical dysplasia, ripple, seizure

SPIKELETS AND VERY FAST OSCILLATIONS

Recordings of "spikelets" or "fast prepotentials" - potentials resembling small action potentials, a few mV in amplitude - in the somata of hippocampal neurons go back 40 years. Spencer and Kandel /66/ observed them as spontaneous events in cat hippocampal neurons *in vivo*. Spencer and Kandel discussed the possibility that fast prepotentials might arise in the axon and conduct decrementally to the soma, as was suggested earlier to occur in feline spinal motorneurons, when antidromic spikes "blocked" in the axon, not too far from the soma /15/; they preferred, however, the

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