

Fast Oscillations and Epilepsy

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Very fast oscillations, 80 Hz and greater (designated here VFOs or "ripples") have been observed in the hippocampus and neocortex, under a variety of conditions that are summarized briefly later. VFOs may be of relevance for normal brain function (1–4) and could also be of relevance in the initiation of focal epileptic seizures (5,6). To determine whether such relevance indeed exists, an understanding of the cellular mechanisms of VFOs is essential. For purposes of this commentary, I shall assume that all forms of VFOs are governed by a few common basic underlying principles. Future experimental data may show that assumption to be false, but for now, the assumption at least allows the formulation of straightforward hypotheses that could stimulate experiments.

Consider those conditions under which VFOs have been observed. The conditions may be divided into two categories: *first* are conditions in which the local field potentials associated with the ripples are small, say less than 0.2 mV. Principal neurons under such conditions are presumed to be not particularly depolarized. *Second* are conditions in which ripples are superimposed on larger field potentials, or on significant intracellular depolarizations.

In the first category (low amplitude of the background), we have the following sorts of VFOs: (a) VFOs occurring spontaneously in hippocampal slices bathed in 32 mM bicarbonate and/or in low $[Ca^{2+}]_o$ media, at frequencies of about 200 Hz (7,8). These sorts of ripples are found intracellularly in pyramidal cells, but not in interneurons. The ripples do not require chemical synaptic transmission, but respond to gap-junction blockers (including halothane) and pH changes in such a way as to suggest that gap junction-mediated electrical coupling is critical (7). The gap-junctional protein mediating the coupling seems not to be connexin36, as the oscillations are present in connexin36 knockout mice (8). Oscillations take the form of small population spikes, of maximal amplitude in principal cell layers. The shape of presumed coupling potentials—spikelets, or fast prepotentials—suggested the hypothesis that electrical

coupling took place between principal cell axons, as the rise times and decay times of the spikelets appeared too fast to be mediated by somatic or dendritic coupling (see also later); (b) VFOs occurring either spontaneously, or after tetanic stimulation, in hippocampal slices bathed in TMA (tetramethylamine), a compound expected to alkalinize the medium and to open gap junctions (6). The frequency of these oscillations was about 100 Hz. If the VFOs were elicited by tetanic stimulation, then an electrographic seizure-like discharge would typically follow the VFO; (c) run of VFOs may precede the onset of a focal seizure in certain patients, including children with focal cortical dysplasias, at frequencies in the neighborhood of 100 Hz (5,6). The cellular correlates of this type of oscillation are not known, nor is the relation, if any, to pH of the cerebrospinal fluid (CSF).

In the *second* category are examples of VFOs superimposed on a transient excitatory event. One can subdivide this category accordingly as the transient excitation is considered to be a physiologic event (a, b, or c, later), or an epileptiform burst (d or e, later). Thus, we have (a) ripples at about 200 Hz, superimposed on physiologic sharp waves in the hippocampus *in vivo*, especially CA1 (1,2); similar events have been observed in mouse hippocampus *in vitro* (9). *In vivo* ripples are suppressed by halothane, although the sharp waves persist (2). *In vivo* ripples occur in the awake state and during anesthesia. Fast-spiking interneuron action potentials are entrained to the ripple, as are the (less frequent) action potentials of principal cells. Inhibitory postsynaptic potentials (IPSPs) occur at ripple frequency in principal cells (2); (b) ripples at 80–200 Hz occur in the neocortex of cats during the slow (0.5–1.0 Hz) sleep rhythm, during the phase of the rhythm when cells are depolarized (10). Such ripples do not require that the animal be anesthetized; however, they are blocked by halothane, as are hippocampal *in vivo* ripples. Again, fast-spiking putative interneurons are often fire phase-locked to the ripple; and principal neurons exhibit ripple-frequency IPSPs; (c) ripples (>200 Hz, but most reliably, >400 Hz) are superimposed on neocortical somatosensory potentials evoked by vibrissae stimulation in rats (3,4), or median nerve stimulation in humans (11). Yet again, in the rat, fast-spiking putative interneurons are entrained to the VFO. Nevertheless, epipial application of bicuculline does not abolish the rippling; instead, it *prolongs* the VFO, with negligible alteration of amplitude or frequency (12). The vibrissae-evoked ripples are blocked by halothane (4); (d) In a variety of experimental epilepsy models (13–15), VFOs (~200–600 Hz) can occur superimposed on a synchronized burst. In some of the

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Epilepsy Currents, Vol. 3, No. 3 (May/June) 2003 pp. 77–79

Blackwell Publishing, Inc.

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models (13,14), γ -aminobutyric acid (GABA)_A receptors have been blocked. In the kainate acid lesion model used by Bragin et al. (15), subsequent addition of bicuculline did not block the VFOs; instead, it enlarged the tissue volume in which VFOs could be recorded; (e) VFOs have been recorded superimposed on epileptic burst complexes in humans (6), at frequencies of 110 to 130 Hz.

If it is really true that a common principle runs through all of these examples of VFOs, then the principle cannot depend on fast synaptic inhibition, as many of the examples involve a situation in which GABA_A receptors have been blocked. Indeed, one wonders if synaptic transmission can be involved at all, at least in a primary way: excitatory postsynaptic currents (EPSCs) on pyramidal neurons have relaxation time constants of a few milliseconds, rather long for an oscillation that can exhibit a period of less than 2 ms. (Of course, synaptic transmission could be involved in a secondary way, if depolarization of neurons sets the stage for, or unmasks, a VFO.)

One mechanism that could, in principle, explain VFOs involves networks of principal neurons, interconnected by gap junctions between their axons [reviewed in (16)]. Arguments supporting this mechanism include these:

1. VFOs must be generated by principal neurons, as they persist (in many of the experimental models) during disinhibition. VFOs can also be associated with population spikes characteristic of the tightly synchronized firing of principal neurons (7).
2. VFOs can occur in cases in which all chemical synaptic transmission has been suppressed (7).
3. Pharmacologic blockade of gap junctions, albeit not obtainable “cleanly,” suppresses VFOs. Although electrical coupling between interneurons exists (17,18), no apparent way exists that such coupling could explain VFOs. That leaves electrical coupling between principal cells.
4. Convincing evidence is lacking for electrical coupling between principal cell somata and dendrites, in mature hippocampus and cortex.
5. Experimental evidence exists for axonal gap junctions between principal hippocampal neurons (19).
6. Modeling of axonally coupled pairs of pyramidal neurons, and of large networks, shows that one can replicate experimentally observed spikelets, and also very fast network oscillations, with minimal assumptions. This replication works under three experimentally relevant conditions: (a) all synaptic transmission is blocked, or (b) pyramidal cells synaptically excite each other, or (c) both excitatory and inhibitory

chemical synapses exist between principal cells and interneurons (7,19–21). Condition (a) corresponds to one of the cases in Draguhn et al. (7), low $[Ca^{2+}]_o$ media; condition (b) corresponds to cases in which epileptic bursts occur in disinhibited tissue; condition (c) corresponds to the case of in vivo hippocampal ripples.

7. Modeling also explains why, if the ripple is not excessively fast, one can observe trains of IPSPs at, say, 200 Hz in principal cells (21). The output of the principal cell axonal plexus is a coherent VFO that can induce coherent fast firing in pools of interneurons; the synaptic output of such pools would then induce coherent IPSPs in principal cells. Conversely, as the VFO is not (we propose) actually generated in the interneurons (but rather in the principal cell axonal plexus), the VFO can persist after IPSPs are blocked.

Unfortunately, modeling has not replicated 500 Hz or greater oscillations, of the sort observed in somatosensory cortex, and sometimes in hippocampus and parahippocampal areas (11,12,15). Although space does not permit a detailed analysis of how a network of axonally coupled neurons produces a particular frequency of oscillation, it is possible to list some of the relevant variables (20). Such variables include (a) the density of connections, with higher connectivity leading to faster frequencies; (b) the rate at which axons are stimulated by some external influence, the network frequency tending to increase with this rate; and (c) the time it takes for an action potential in one axon to induce an action potential in a coupled axon (“crossing time”), the frequency going inversely with the crossing time. The crossing time will be sensitive to the conductance of the gap junction, the local input resistance of the axon, the existence of nearby membrane shunts, and the density and voltage-dependent properties of the axonal sodium channels. It is quite possible that the properties of axons themselves, and of putative axonal gap junctions, are different in neocortex from those in CA1 or CA3 hippocampal pyramidal neurons. Indeed, multiple networks of axonally interconnected neocortical cell populations could exist (e.g., superficial pyramids, layer 4 spiny stellate cells, deep pyramids), each with a characteristic network oscillation frequency.

In summary, VFOs are present in several experimental/clinical paradigms, and appear related to the initiation and expression of both normal and pathologic synchronized bursts. A hypothesis exists concerning how VFOs are generated that is reasonable, so far as it goes, but that requires very extensive (and probably difficult) experimental work to test. Most important is to determine whether axonal gap junctions exist at all in the neocortex.

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