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Can a Synaptic Signal Arise from Noise?

The spontaneous fusion of vesicles at nerve terminals produces random miniature postsynaptic potentials (quantal responses) that are thought to have little functional significance. In this issue of *Neuron*, Sharma and Vijayaraghavan provide evidence that exogenous signals can accelerate and synchronize the occurrence of quanta strongly enough to activate postsynaptic neurons in what may be a new way to transfer information across synapses.

It was over 50 years ago that Paul Fatt and Bernard Katz (Fatt and Katz, 1950, 1952) first observed the random release of transmitter packages, which they called "quanta," at the frog neuromuscular junction. Originally mistaken for the footsteps of A.V. Hill, who was wont in those days to pace the corridors of University College London, quanta were too large to reflect leakage of single molecules of acetylcholine, and local nerve terminal spikes were proposed. It didn't take long for Fatt and Katz (1953) to recognize that the electrical events they recorded from muscle fibers corresponded to the spontaneous release of multimolecular packets of transmitter, independent of presynaptic electrical activity. Once synaptic vesicles were described using the electron microscope, it was natural to suppose that these were the packets of transmitter-comprising quanta (Castillo and Katz, 1955). Quantal responses were a naturally occurring synaptic noise, which subsequently proved quite valuable in analyzing mechanisms of transmitter release at synapses. These miniature endplate potentials (mEPPs), or miniature excitatory or inhibitory synaptic potentials (mEPSPs or mIPSPs) as they are called when they are recorded from central neuronal synapses, provided a marvelously useful tool for probing synaptic function. They formed the foundation for a lively cottage industry of "quantal analysis" that has occupied synaptic biophysicists for decades and continues to this time, even after the death last month of its esteemed discoverer (Heuser, 2003).

The functional relevance of these "minis," as they are affectionately called by most neurobiologists, has remained obscure—so obscure, in fact, that usually relevance is denied. It is widely thought that minis are merely an aspect of the way synapses happen to work. This notion is challenged by a paper in this issue of *Neuron* by Sharma and Vijayaraghavan (2003). Their work shows that mini frequency can be accelerated sufficiently that the resulting postsynaptic depolarization can evoke a quite vigorous burst of action potentials. The agent triggering this response was nicotine, acting on presynaptic nicotinic acetylcholine receptors (nAChRs) in mossy fiber terminals onto hippocampal CA3 pyramidal neurons. This appears to be an example where the noise of minis has generated a meaningful neuronal signal.

Presynaptic excitatory effects of nicotine involving presynaptic $[Ca^{2+}]_i$ were first shown at interpeduncular nucleus synapses by McGehee et al. (1995) and at mossy fiber synapses by Gray et al. (1996). The study by Sharma and Vijayaraghavan reports four important results: (1) nicotine dramatically increases the frequency of occurrence of miniature excitatory postsynaptic currents (mEPSCs) recorded under voltage clamp from postynaptic neurons, (2) a new class of very large mEPSCs appears, (3) both effects depend upon Ca^{2+} influx through nAChRs and Ca^{2+}-induced Ca^{2+} release (CICR) from ryanodine-sensitive intracellular Ca^{2+} stores, and (4) the high-frequency barrage of mEPSCs—including large mEPSCs—depolarizes pyramidal cells sufficiently to induce intense firing, transmitting a "signal" across the synapse.

Perhaps the most remarkable finding relates to the nicotinic enhancement of the release of very large mEPSCs, up to 200 pA or 3 times the largest minis seen under control conditions. Henze et al. (2002) have described occasional even larger "giant" minis (up to 1.7 nA), which are probably due to the release of giant vesicles. The giant minis are unaffected by changes in external $[Ca^{2+}]$, unlike the large minis studied by Sharma and Vijayaraghavan (2003), suggesting that the two are distinct. An important question is whether the large minis Sharma and Vijayaraghavan observe are indeed multiquantal, as they do not show some features characteristic of multiquantal release at other synapses, including the telltale periodic peaks in amplitude histograms previously described in the multiquantal mEPSCs in cerebellar mossy fiber to granule cell synapses (Wall and Usowicz, 1998) and periodic notches on their rising phase. They do, however, show the dependence on CICR of mIPSCs recorded from Purkinje cells (Llano et al., 2000). The strongest evidence presented for multiquantal minis is a correlation between amplitude and rise time that might reflect near coherence of quantal units. Alternative explanations for this correlation might be postsynaptic receptor saturation, or spillover to adjacent postsynaptic densities, by large uniquantal minis. However, the "giant" minis should be even more blunted by such saturation, or broadened by spillover, which seems not to be the case (Henze et al., 2002), making these alternative explanations less likely. Further experiments that would strengthen the case for multiquantal

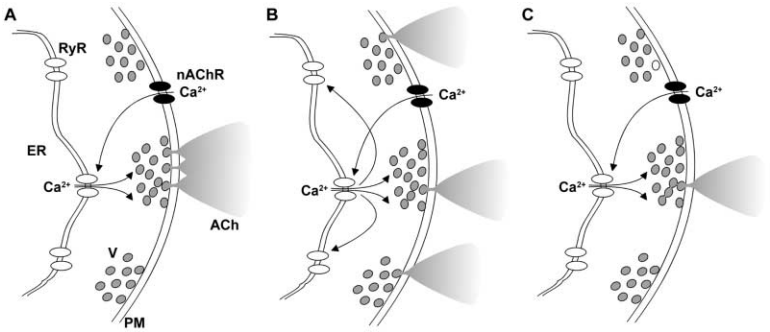

Figure 1. Schematic of Three Possible Origins of Multiquantal Minis

(A) Multiple vesicle fusions at one active zone.
(B) Synchronous release from neighboring active zones.
(C) Compound vesicle fusion.
Abbreviations: Ca^{2+}, calcium ions; ER, endoplasmic reticulum; RyR, ryanodine receptor; PM, plasma membrane; nAChR, nicotinic acetylcholine receptor; V, vesicles; ACh, acetylcholine.

minis include a demonstration that they can be desynchronized into their component parts, for example by low temperature, or that they are resistant to the stimulatory action of sucrose, which should act downstream of any synchronizing process.

How can this spontaneous synchronization of quantal elements come about? One could imagine that a very local rise in $[Ca^{2+}]_i$ due to CICR activates multiple vesicular fusions at one release site (Figure 1A), but Sharma and Vijayaraghavan argue against this because of the apparent imperfect synchrony in the longer rise times of large minis. They propose a somewhat less localized $[Ca^{2+}]_i$ rise activating several neighboring active zones nearly simultaneously (Figure 1B). A third possibility might be compound exocytosis (Parsons and Sterling, 2003), caused by the high $[Ca^{2+}]_i$ levels reached at the back of active zones distant from the plasmalemma and its Ca^{2+} channels (Figure 1C). Distinguishing these alternatives will no doubt be the subject of further work on this synapse. Recording the local $[Ca^{2+}]_i$ blips that are inferred to underlie large minis, perhaps by use of fast confocal scanning microscopy or two-photon scanning microscopy (Emptage et al., 2001; Llano et al., 2000), and correlating them with the occurrence of large minis might provide further mechanistic insight into how they arise.

Beyond mechanism lies the further question of function. Sharma and Vijayaraghavan showed that enhancement of mini frequency, and apparent synchronization, can together have a strong effect on a postsynaptic cell, driving it to fire a prolonged high-frequency burst in response to focal application of 20 μM nicotine. It will be important to determine whether a presynaptic action of acetylcholine in exciting synaptic transmission occurs with endogenous cholinergic input. It will be also be interesting to find out whether nicotine levels occurring in smokers have similar effects and whether this contributes to nicotine toxicity. If such a mechanism for generating a meaningful synaptic signal out of quantal noise can be shown to occur in vivo in a physiologically relevant context, it will provide an important addition to the repertoire of mechanisms of neuronal plasticity.

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Ocular Dominance Plasticity in Mature Mice

Ocular dominance plasticity, classically thought to be restricted to an early critical period, is now described by Sawtell et al. in fully adult mice. Adult plasticity, like critical period plasticity, requires cortical NMDA receptors but involves different functional changes in cortical circuits.

Much of our understanding of how sensory experience shapes circuit function derives from the study of ocular dominance in primary visual cortex (V1). Ocular dominance is the relative response of a neuron to visual stimulation of the right versus the left eye. As first shown in the cat and monkey, closing one eye for a brief period (monocular deprivation, MD) causes a lasting shift in ocular dominance toward the open eye (Hubel, 1982). In these classic experiments, plasticity occurred only when MD was begun during a narrow age range in the