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TECHNICAL COMMENTS

Long-Term Potentiation in the CA1 Hippocampus

Polarized debate continues regarding the locus of the modification responsible for the enhancement of synaptic transmission during long-term potentiation (LTP) in CA1 hippocampus, a widely studied cellular model of learning and memory. Two recent papers (*1*, *2*) have shed light using techniques in which only one or a few axons are stimulated. In this way, transmission may be characterized not only by the mean amplitude of the response (as usual), but also by identifying failures (responses with zero amplitude) and successes of transmission. With LTP, these researchers observe a change in the rate of successes, but no change in the mean amplitude of successes (the "potency"). They argue that such an observation is only compatible with an increased probability of transmitter release, indicating a presynaptic mechanism. They note that postsynaptic changes such as addition of receptors at a transmitting synapse or addition of new synapses (which would occasionally produce simultaneous release at the new and old synapses) would increase potency. However, if LTP is a result of the addition of new synapses [possibly by AMPAfication of pure NMDA synapses (*3*, *4*) or by splitting of existing synapses (*5*)] will the potency necessarily change?

With Monte Carlo simulations of various models, we found that if new synapses recruited during LTP have a smaller response (quantal size, q) than previously existing synapses, the potency need not change (Fig. 1). Intuitively, if a new synapse recruited with LTP has a smaller q, then when the new synapse acts alone, the potency will be decreased; when the old and new synapses act together, the potency will be increased. These effects can cancel each other out, keeping the potency constant. We have considered analytically what requirements are placed on newly transmitting synapses so as to keep the potency constant.

As a simple case, consider one synapse before LTP transmitting with probability of release $p1$, and mean quantal size 1. Let the new synapse added with LTP have a probability of release $p2$ and mean quantal size $q2$. Then,

mean amplitude of transmission before LTP $\equiv$ Mb $= p1$,

mean amplitude of transmission after LTP $\equiv$ Ma $= p1 + p2q2$,

potency before LTP $\equiv$ Pb $=$ Mb/$p1$, and

potency after LTP $\equiv$ Pa $=$ Ma/$\{1 - [(1 - p1)(1 - p2)]\}$.

If we require that Pa $= P$b and solve for $q2$, we obtain: $q2 = 1 - p1$.

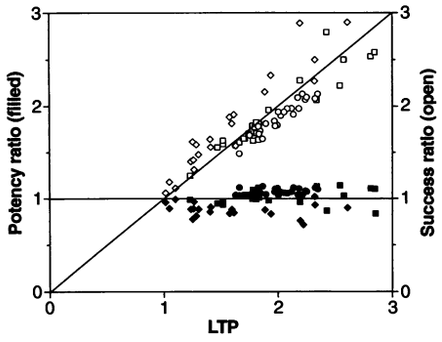

Fig. 1. Changes in potency and success ratio for Monte Carlo simulations of three scenarios in which LTP is produced by adding synapses. For each scenario, 25 experiments each consisting of 250 trials before and after LTP were simulated. Plotted are the ratio of the mean potency before and after LTP (filled symbols) and the ratio of the success probability (fraction of trials with response amplitude >0, open symbols). For each experiment a new set of parameters was chosen randomly from a uniform distribution of specified range (hereafter denoted [min to max]). Circles: one synapse is augmented by a second ($q1 = 1$, $p1$ in [0.15 to 0.45]). Squares: splitting of one synapse ($q = 1$, p in [0.15 to 0.45]) into two ($q1$ and $q2$ in [0.65 to 0.95], $p1$ and $p2$ in [0.15 to 0.45]). Diamonds: addition of synapses under assumption of Poisson statistics (initial population $q1 = 1$, m1 in [0.16 to 0.6], added population $q2$ in [0.55 to 0.85], m2 in [0.16 to 0.6]).

This anlaysis leads us to the puzzling requirement that the response of a new synapse is dependent on the release probability of a previously existing synapse. However, this unsavory demand is not stringent: If we allow for reasonable experimental error in measuring potency, then $q2$ can range considerably (Fig. 2). Similar results are obtained with more general cases (Binomial or Poisson release).

The observation that potency does not change during LTP is not universal, as examples showing changes in potency have been published with minimal stimulation (*3*, *6*) and cell pair recordings (*7*). In our hands, in 6 of 12 experiments with failure rates greater or equal to 50% potency changed more than 20% with pairing-induced LTP (*8*). From the above analysis, we conclude that even in those cases where potency does not change, the underlying mechanism could be addition of new synapses.

A corollary of this result is that manipulations such as paired-pulse facilitation or changes in extracellular calcium may not change potency even if multiple synapses are stimulated, provided these manipulations preferentially act on synapses which have a smaller quantal size. Thus, constant potency during presynaptic perturbations does not necessarily imply stimulation of a

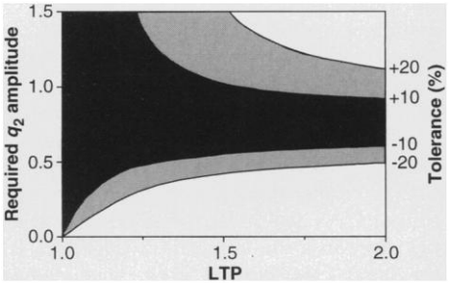

Fig. 2. Requirements on a new synapse to maintain constant potency. A single synapse ($q1 = 1$, $p1 = 0.25$) is augmented by a second synapse to produce LTP. The postsynaptic amplitude $q2$ necessary to maintain potency constant to within a given tolerance and the amount of LTP resulting were computed as functions of $p2$. Tolerances of ±10% and ±20% are shown. Constant potency was more difficult to satisfy with larger LTP (and also with larger initial $p1$, not shown).

single synapse. This reinforces the view (9) that the simple relations of quantal analysis do not necessarily hold in heterogeneous populations such as those found in the central nervous system.

Addition of synapses with lower quantal size will, however, change the amplitude distribution of nonfailure responses, which was not observed in the above studies (*1*, *2*). Nevertheless, detecting this change in distribution may be difficult given the nonstationary nature of quantal size [especially early in a recording (*10*)], the difficulty of distinguishing failures from small responses, and the problem of estimating higher moments from small sample sizes. Furthermore, other similar scenarios, like a simultaneous increase of small and decrease of large synapses during LTP, can produce large potentiation with no change in potency or response variance.

These electrophysiological studies have propelled the study of central transmission to a new level of analytical scrutiny. Nevertheless, it is a sobering thought that electrophysiology alone is largely blind to the anatomical, biochemical, and cell biological processes that will ultimately play major roles in our understanding of LTP.

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Response: Malinow and Mainen have raised an interesting theoretical point regarding quantal analysis of synaptic transmission and LTP. We (*1*) and Stevens and Wang (*2*, *3*) studied excitatory synaptic transmission and LTP in the hippocampus between single presynaptic CA3 pyramidal neurons and single postsynaptic CA1 pyramidal neurons. The synaptic responses could be divided into successes and failures, based on whether or not a given presynaptic stimulus was able to cause release of transmitter and produce an excitatory postsynaptic current (EPSC) response. We found that EPSC amplitude histograms could be fit by the sum of two Gaussian functions, one corresponding to the failures (mean at 0 pA) and one corresponding to the successes (mean at around −4 pA) of release, supporting the view that there was but a single site of release. Induction of LTP was associated with an increase in the fraction of successes, with no change in the position or shape of the failure and success peaks in the EPSC amplitude histogram. The most straightforward interpretation of these findings is that LTP, under the conditions of our experiments, results from an increase in the probability of transmitter release with no change in postsynaptic sensitivity to transmitter and no addition of new release sites (otherwise the success peak would change its position and shape). Stevens and Wang (*2*) also reported a decrease in the fraction of failures following LTP, with no change in the mean size of the successful EPSCs (which they termed potency), also consistent with an increase in probability of release.

However, Malinow and Zainen show that it might be theoretically possible to add new synapses following LTP without altering the mean size of the successful EPSCs (potency). They argue that this condition will be met as long as the quantal amplitude of the newly added synapse is smaller than the quantal amplitude of the initial synapse and obeys the following relation: $q2 = (1 - p1)$, where $q2$ is the ratio of the quantal amplitude of the new synapse divided by the quantal amplitude of the old synapse and $p1$ is the probability of release at the old synapse. The reason why "potency" remains unchanged following LTP in this hypothetical case is that even though some EPSCs will be larger than the initial EPSC (due to simultaneous successes at both new and original synapses) some EPSCs will have the same amplitude as the original EPSC (due to a simultaneous success at the original synapse and a failure at the new synapse) and some EPSCs will be smaller than the original EPSC (due to a failure at the original synapse and a success at the new synapse).

In our opinion this hypothesis has two serious flaws. First, it requires that the quan-

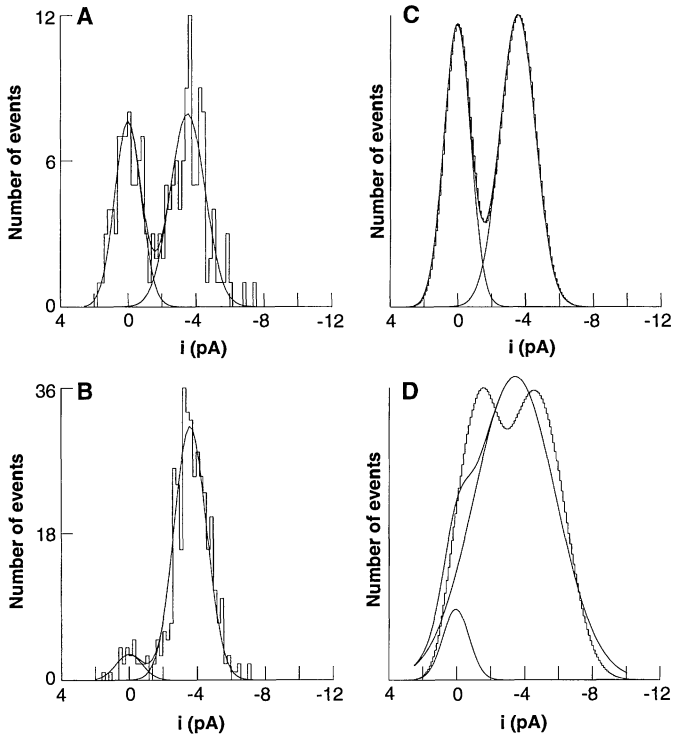

Fig. 1. Experimental and theoretical EPSC amplitude histograms before and after LTP. (**A**) Data from experiment shown in figure 5A of (*1*). Control histogram fitted by sum of two Gaussians, one with a mean of 0.04 pA and SD of 0.78 pA (failures) and one with a mean of −3.56 pA and SD of 1.03 pA (success peak). Probability of release (obtained from area under success peak) was 0.58. (**B**) Histogram obtained after induction of LTP was fitted by sum of two Gaussian functions nearly identical to those used to fit control data. Success peak had a mean and SD = −3.65 pA and 0.94 pA, respectively. Failure peak mean and SD = 0.05 pA and 0.73 pA, respectively. Probability of release was 0.92. Failure peak Gaussian functions were always constrained so that their mean and SD were equal to Gaussian fits to background noise. (**C**) EPSC histograms for control conditions and (**D**) after LTP calculated from model of Malinow and Mainen. Control histogram was obtained from the two Gaussian functions fit to our experimental control histogram. LTP histogram was calculated from the model assuming that a new synapse was added with a quantal amplitude given by $q2 = 0.42$, based on our measurement that $p1 = 0.58$. From the enhancement of the ensemble-averaged EPSC after LTP, the probability of release at the new synapse was constrained to be equal to 0.8. SD for the new synapse EPSC was set equal to that at the original synapse. It was assumed that when both inputs are active, nonbackground noise variances will be added. Predicted histogram (stepped curve) was then fit by the sum of two Gaussian functions (smooth curves). Gaussian curve for the failures peak was constrained so that its mean and SD were equal to baseline noise (as was done for experimental histograms). Predicted histogram cannot be fit by the two Gaussian components; the SD of the success peak is more than twofold larger than the SD of the pre-LTP success peak.

tal amplitude at the new synapse added after LTP be determined by the initial probability of release ($p1$) at the original synapse [due to the constraint that $q2 = (1 - p1)$]. Because the initial probability of release can vary greatly at different synapses, the model must postulate an unprecedented and unknown mechanism which couples postsynaptic properties at the new synapse to presynaptic properties at the old synapse. Second, and more important, the model predicts significant changes in the shape of the EPSC amplitude histogram following LTP, which we do not observe experimentally (Fig. 1) (*1*). The predicted change in shape of the EPSC histogram is a result of the following: Before LTP, successes of transmission only result from release at the original synapse (whose quantal amplitude = a). After induction of LTP, there are now two release sites, the original site (whose quantal amplitude = a) and the new site (whose quantal amplitude = $q2 \times a$). Successes of transmission after LTP can now fall into one of three categories: Those due to release from the new synapse alone (EPSC amplitude = $q2 \times a$), those due to release from the original synapse alone (EPSC amplitude = a), and those due to release from both synapses simultaneously (EPSC amplitude = $a + q2 \times a$). The contribution of the three classes of successful events to the EPSC amplitude histogram leads to the appearance of new peaks or to a broadening and shifting in the position of the two original peaks (whether or not new distinct peaks can be detected depends on the standard deviation of the various peaks).

As we do not observe changes in the shape of the EPSC amplitude histogram following LTP, we thus stand by our original conclusion. Under our experimental conditions, LTP results from an increase in probability of transmitter release with no change in quantal amplitude and no addition of new sites of synaptic transmission. However, because our data are restricted to the first 30 to 40 min after induction of LTP, it is possible that other changes may occur at later times.

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Estimating Geologic Age from Cosmogenic Nuclides: An Update

We and others have used in situ–produced cosmogenic nuclides to estimate exposure ages of geomorphic surfaces such as moraines and alluvial fans (*1*). Every study published to date has calculated exposure ages using temporally averaged production rates commonly acknowledging but then disregarding variations in production rates caused by a variable geomagnetic field.

In order to improve the accuracy of exposure age estimates, we have recently developed a model which allows cosmogenic exposure ages to be calibrated for changing geomagnetic field strength (*2*). The model incorporates published paleomagnetic field strength records (*3*), field strength/rigidity relationships (*4*), and accepted altitude/latitude corrections (*5*) excluding the contribution of muons to ^{26}Al and ^{10}Be production (*6*). In calibrating, we assume that the current geographic latitude of a site represents its average geomagnetic latitude over the duration of cosmic-ray exposure. The model indicates that production rate response to changing field strength is a nonlinear function of altitude, latitude, and exposure duration. Geomagnetically modulated production rate changes and age inaccuracies are greatest at high altitudes and low latitudes.

Applying our model to existing data reconciles three apparently disparate production rate estimates for ^{26}Al and ^{10}Be (*4*, *7*), generally increases calculated exposure ages, and appears to confirm recently published data suggesting that a glacial advance in the Rocky Mountains may have occurred during Younger Dryas time (*8*). To demonstrate how the model changes exposure ages, we have recalculated recently published ages (*1*) for alluvial fan boulders (*9*).

Our model and relevant documentation are publicly available (*10*) and will be updated in the near future to include additional nuclides and paleomagnetic intensity records.

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Pliocene Extinction of Antarctic Pectinid Mollusks

The report by Edward J. Petuch (*1*) about a two-stage Pliocene-Pleistocene mass extinction that decreased the diversity of stenothermal molluscan genera in Florida raises the question of where the climatic cooling events propagated. It is accepted that the Northern Hemisphere ice sheets began developing at the end of the Pliocene (*2*), but their feedback and late Neogene connection with changes in the Antarctic ice sheets (*3*) have not been resolved. Southern Ocean molluscan extinctions, however, provide evidence that an environmental threshold was reached at the end of the Pliocene around Antarctica. Throughout most of the Cenozoic, pectinid bivalve genera (primarily *Chlamys*) inhabited coastal environments around the continent as indicated by extensive deposits from the Eocene (*4*), Oligocene (*5*), and Pliocene (*6*). These Paleogene-Neogene pectinids had large (>5 cm) thick shells, which indicate that calcium carbonate precipitation was enhanced for early Cenozoic bivalves as compared to that for subsequent cold-water pelecypods in the Southern Ocean, 70% of which are smaller than 1 cm today (*7*). Large thick-shelled pectinid bivalves became extinct in the Southern Ocean during the Pliocene, perhaps in conjunction with the spread and first appearance of cold-water *Chlamys* species in New Zealand (*8*). After the Pliocene, large wafer-thin–shelled *Adamussium colbecki* emerged into coastal environments from the deep sea around Antarctica (*9*), where it originated during the Oligocene (*10*). This endemic monospecific genus, with its circumpolar distribution (*11*), has been the only pectinid in Antarctic coastal areas during the Quaternary. The marked diversity decrease among Pectinidae in Antarctic coastal environ-