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Persistent increase of hippocampal presynaptic axon excitability after repetitive electrical stimulation: Dependence on *N*-methyl-D-aspartate receptor activity, nitric-oxide synthase, and temperature

(quantal analysis/long-term potentiation/neurophysiology)

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ABSTRACT **The electrical excitability of Schaffer collateral axons and/or terminals was studied in hippocampal slices by monitoring single, CA3 pyramidal neurons activated antidromically from CA1 stratum radiatum. At 22°C, weak, repetitive stimulation with as few as 10 impulses at 2 Hz led to a robust lowering of the antidromic activation threshold that lasted >30 min. The effect was completely absent at 32°C and was blocked by both the *N*-methyl-D-aspartate receptor antagonist, 2-amino-5-phosphonovalerate and the inhibitor of nitric-oxide synthase, L-nitroarginine methyl ester. Such threshold lowering would alter the variance of synaptic responses from axons stimulated in the variable excitation region of their input–output functions. These results thus raise important doubts about the interpretation of experiments in which the so-called minimal-stimulation method has been used at reduced temperature to infer changes in quantal transmission during hippocampal long-term potentiation. In the present experiments, no changes were observed in the estimate of excitatory postsynaptic potential quantal content in long-term potentiation experiments at either temperature, which could not be accounted for by an artifactual, temperature-dependent change in the responsiveness of presynaptic axons.**

Changes in synaptic response fluctuation have been used to make inferences about the possible pre- or postsynaptic locus of hippocampal long-term potentiation (LTP) expression. Using similar methods of analysis, different groups have suggested either an increased number of transmitter quanta released per impulse, an increase in the size of individual quantal components, or both (1–8). Although the appropriateness of standard methods of quantal analysis at these synapses (9) is controversial, these methods do give the expected answer when either the size of quantal components is reduced by postsynaptic receptor antagonism (5) or excitatory postsynaptic potential (epsp) quantal content is increased during short-term synaptic facilitation (2). Hence, it is likely that the explanation for the variable results lies elsewhere. A second controversy pertains to the putative role of NO and other agents (e.g., CO) as retrograde messengers. Under some conditions, *N*-methyl-D-aspartate (NMDA)-receptor-dependent NO release apparently induces an increase in the evoked release of transmitter from presynaptic terminals (10–14). Again, the role of NO synthesis or release in the induction of LTP appears to depend considerably upon experimental conditions (15, 16).

One variable of possible importance is the experimental temperature (1). For example, most of the experiments of Bekkers and Stevens (4) and of Malinow and Tsien (6) were done at room temperature, and the predominant effect during LTP was an increase in the estimate of quantal content. In contrast, at 32°C, Foster and McNaughton (2) observed only an increase in the estimate of quantal size.

Most of the foregoing experiments were conducted with weak electrical stimulation, under the assumptions that only one, or at most a few presynaptic fibers are activated (17) and that activation is reliable and consistent throughout the experiment. Certain paradoxical results of our attempts to detect an increased quantal content after LTP induction at reduced temperature have led us to reexamine these assumptions, which are crucial to the interpretation of such studies, because any change in the reliability of excitation of presynaptic axons would be spuriously interpreted as a change in epsp failures and/or in the coefficient of variation of the epsp.

MATERIALS AND METHODS

Hippocampal slices (2) from Sprague–Dawley rats (3–5 weeks of age) were maintained in a moist air (95% O_2/5% CO_2)-interface chamber, superfused continuously (1–2 ml/min) with artificial cerebrospinal fluid (119 mM NaCl/2.5 mM KCl/1.3 mM $MgSO_4$/2.5 mM $CaCl_2$/26 mM $NaHCO_3$/1.0 mM KH_2PO_4/11 mM dextrose).

Two sets of experiments are described. (*i*) Either intracellular recordings were obtained from CA1 pyramidal cells using conventional, current-clamp recording, or evoked synaptic-field potentials were recorded from stratum radiatum. Stimulation in all experiments was via platinum iridium microwires, using constant-current, diphasic pulses (200 μsec). For intracellular studies, the method of "minimal" stimulation was used (2, 4, 6, 17). The stimulus intensity was increased gradually from zero until a nonzero average epsp was obtained, using on-line signal averaging of 25–50 sweeps. Under these conditions, frequent apparent response failures are observed (e.g., Fig. 1*A*). As in prior studies (6) LTP was induced by using weak stimulation at 2 Hz, paired with depolarizing current pulses applied through the microelectrode (18). Quantal parameters were estimated by using both the method of failures and noise-deconvolution (19–22), as described (2). These analyses produce estimates of quantal content m and quantal size q, based on certain statistical assumptions. Whether or not these assumptions are adequately met and whether or not LTP is due to changes in actual quantal release are not at issue in the present report. What is at issue is the possible nonsynaptic source of

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Abbreviations: NMDA, *N*-methyl-D-aspartate; LTP, long-term potentiation; PTP, posttetanic potentiation; epsp, excitatory postsynaptic potential.

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stimulus-induced changes in these parameters. Accordingly, the terms *m* and *q* are used to refer to the analysis results, not necessarily to true quantal-release parameters. As both methods yielded consistent results, only the noise-deconvolution data are presented (Fig. 1 *B* and *C*). All data were included in the analysis, as preselection of data sets exhibiting large changes in the mean epsp can lead to spurious conclusions regarding stimulation-dependent elevations of quantal content (2). Field potentials were elicited by stimulation at intensities high enough to produce about a one-half maximal-field epsp in the stratum radiatum, and LTP was elicited by the cooperativity method (23), in which many afferents are stimulated simultaneously at high frequency.

(*ii*) The second series of experiments assessed possible effects of repeated stimulation on the local excitability of Schaffer collateral axons and/or terminals. Antidromic spikes were recorded extracellularly, using conventional, tungsten microelectrodes (2–5 MΩ), in single CA3 pyramidal cells projecting to CA1 (Fig. 3*A*). A stimulating electrode in CA1 stratum radiatum was positioned to evoke antidromic action potentials with minimum currents. Antidromic spikes were identified by their constant (±200 μsec) latency over a range of stimulus intensities. During repetitive stimulation at 2 Hz, stimulus intensity was increased to a level sufficient to insure >95% antidromic firing at low frequency. Because of the steepness of the excitation function of individual axons (see Fig. 1 *C* and *D*) this typically required increases of only a few microamperes. In some preliminary studies, repetitive (2 Hz) stimulation was applied with no change in the stimulus intensity, and essentially the same results.

RESULTS

In the first intracellular recording study, LTP was compared at 33°C (n = 17) and 22°C (n = 11) by using the minimal-stimulation method (Fig. 1 *A–C*). For LTP induction, 0.5–1.0 nA of depolarizing current was applied during a low-frequency tetanus (40 impulses at 2 Hz). To avoid the possibility that failure to detect a change in quantal parameters might be attributable to failure of adequate stimulation, the stimulus intensity was increased during 2-Hz stimulation, to insure faithful activation of the presynaptic fibers. This procedure evoked an intracellular population epsp of 2–3 mV. Many previous studies have shown that the presynaptic-fiber potential follows moderate stimulus frequencies at such stimulus levels with little or no detectable decrement. LTP, measured between 20 and 40 min after induction, was >2-fold greater at 22°C than at 33°C ($P < 0.05$; Fig. 1*D*). As reported (2), at 33°C all of the LTP was accounted for by an increase in *q*. There was no significant increase in *m*. At 22°C, however, the additional LTP above the 33°C condition was accounted for by an increased *m*; the growth in *q* was almost identical at the two temperatures.

A second intracellular experiment was conducted at 22°C, again using minimal stimulation. Apart from verifying the foregoing temperature effect on LTP, the main objective was to determine whether weak stimulation at 2 Hz, without applied postsynaptic current, could produce a long-lasting change in synaptic responses. For example, in invertebrate neurons, nonassociative posttetanic potentiation (PTP) exhibits an abrupt increase in its persistence at a critical temperature ≈10°C below acclimatization temperature (24). Thus, it was possible that the increase in *m* in LTP experiments at 22°C reflects prolonged PTP, rather than LTP. Experiments were done at 22°C in which 40-pulse, 2-Hz stimulus trains were delivered either with (n = 26) or without (n = 17) concurrent, depolarizing current. Again, to insure faithful activation of the presynaptic fibers, the stimulus intensity was increased during 2-Hz stimulation to a level sufficient to produce a 2- to 3-mV intracellular epsp. At 22°C,

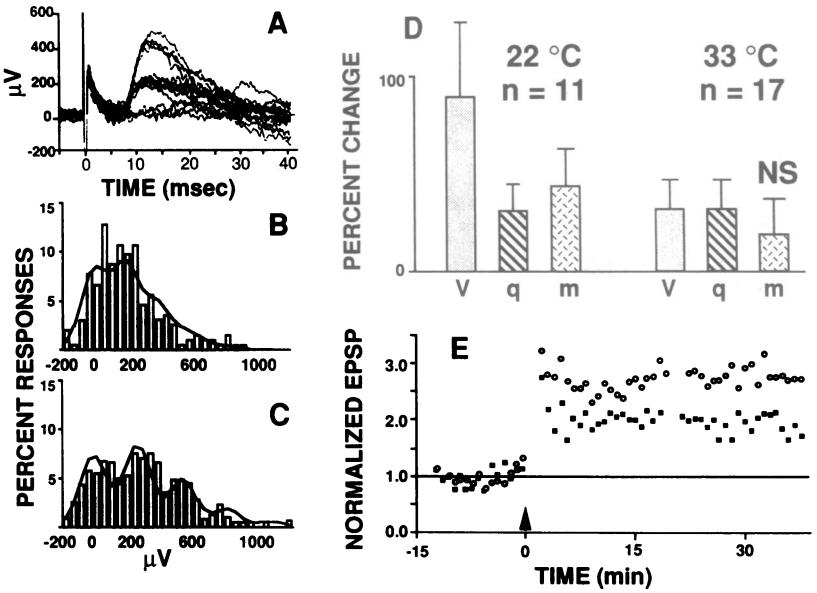

FIG. 1. (*A*) Apparent failures and fluctuations in unitary epsps recorded intracellularly in one CA1 cell in response to 20 consecutive weak Schaffer collateral stimuli. Unitary epsp amplitudes were measured as the difference between the mean voltage for 1.5 msec before stimulus onset and the mean voltage for 1 msec surrounding the peak average epsp. The same analysis was used for "noise-only" records collected before each response, in which stimuli were omitted. Frequency distributions for response amplitudes (bars) recorded from a different cell than *A*, for the 200 responses preceding *B*, and 400 responses after *C* pairing 2-Hz stimulation with postsynaptic depolarization. A nonlinear optimization procedure was used to find mean quantal content (*m*) and quantal amplitude (*q*) estimates that best fit (line) the observed distributions of response and noise (2). (*D*) The effect of bath temperature on the enhancement of mean epsp (*V*) and estimated quantal parameters *m* and *q* after "minimal" stimulation with 40 pulses at 2 Hz and concurrent postsynaptic depolarization. At 22°C, a large increase in *V* was accounted for by statistically significant ($P < 0.05$) increases in both *m* and *q*. At 33°C, the substantially smaller epsp enhancement was entirely accounted for by an increased *q*. The small change in *m* was not statistically significant (NS). (*E*) Changes in mean epsp amplitude (at 22°C) after 2-Hz stimulation with concurrent depolarization (○) and without it (■). Gaps in the data at the beginning of recording and at ≈20 min after 2-Hz stimulation reflect the period in which "minimal" stimulation was replaced with population stimulation (see text). The corresponding data are shown in Fig. 2*C*.

pairing repetitive stimulation with depolarizing current again produced a large, persistent increase in the "minimal" epsp, substantially more than in previous studies at 33°C (2); however, there was also a significant increase after stimulation without depolarizing current (Fig. 1*E*). With depolarizing current, the increased epsp was accompanied by changes in both *q* and *m*, whereas only *m* increased significantly when depolarizing current was omitted.

The increase in *m*, in the absence of depolarizing current, suggested a temperature-dependent increase in the persistence of presynaptic PTP, as seen in other preparations (24). This hypothesis turned out to be incorrect, however (Fig. 2). If there is an increased persistence in PTP at 22°C, even with the relatively mild stimulation parameters used in the preceding experiment, then standard, high-frequency stimulation (e.g., two trains of 1 sec at 100 Hz, separated by 20 sec) should produce a much greater epsp elevation at 22°C than at 32°C. To test this, field epsps were recorded in CA1. Using moderately intense Schaffer collateral stimulation, there was, indeed, a mild elevation and prolongation (from ≈1 min to ≈2 min) of short-term PTP after the tetanus; however, this could not account for the prolonged elevation in *m* seen in the preceding experiment (Fig. 2*A*). Moreover, LTP magnitudes were the same at 22°C and 32°C. A second series of field-potential studies at 22°C compared the effects of 40 pulses at

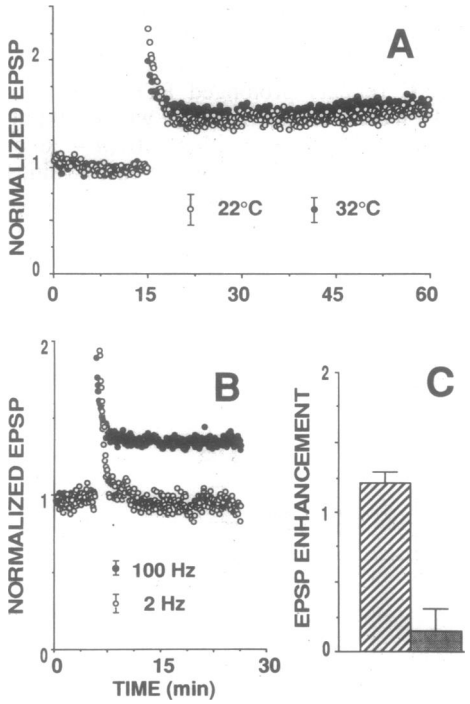

FIG. 2. (*A*) Lack of a temperature effect on LTP of CA1 synaptic field potentials (22°C, $n = 10$; 32°C, $n = 8$), induced by two 100-sec tetani at 100 Hz, with 20 sec between trains. There was a moderate increase, at 22°C, in short-term PTP during the first 2–3 min; however, there was no difference in LTP ($P > 0.05$). (*B*) Comparison of the effects of high-frequency (100 Hz for 1 sec, twice) and low-frequency (2 Hz, 40 pulses) tetani on CA1 synaptic field potentials. As in *A* robust LTP was seen with high frequency ($P < 0.001$). In contrast to the case in which minimal stimulation and intracellular recording were used at 22°C (Fig. 1*E*), low-frequency tetani led to PTP only ($P < 0.0001$ for 2 Hz vs. 100 Hz). There was no LTP ($P > 0.05$). (*C*) Data from the same experiment as in Fig. 1*E*. Stimulus intensity was increased before, during, and 20 min after 2-Hz stimulation at 22°C, to elicit intracellular, population epsps of ≈2- to 3-mV in amplitude. As in *B* there was no persistent LTP of the population responses (stippled bar) in the absence of concurrent postsynaptic depolarization, in spite of the apparent LTP of the "unitary" responses (hatched bar) evoked with minimal stimulation ($P < 0.05$).

2 Hz to the effects of high-frequency stimulation. Although 2-Hz stimulation did lead to some PTP, there was no LTP (Fig. 2*B*). Finally, the effects of 2-Hz stimulation on 2- to 3-mV population epsps were assessed by using intracellular recording with or without concurrent depolarization. These data were collected at 22°C during the same experiments illustrated in Fig. 1*E*. Before 2-Hz stimulation, during it, and again at 20 min after it, the stimulus intensity was increased by a fixed amount sufficient to evoke 2- to 3-mV epsps during baseline, and 10 responses were collected before returning the stimulus to the "minimal" level. Although there was ≈100% enhancement of the minimal response in the absence of concurrent depolarization and about a 200% enhancement when depolarization was applied (Fig. 1*E*), the intracellular population responses showed no increase without depolarization, and only ≈120% enhancement with depolarization (Fig. 2*C*).

We were thus faced with several apparently conflicting results. By using minimal stimulation, there was a substantial elevation of the magnitude of LTP at 22°C. This involved an increase in both *q* and *m*. The effect on *m*, however, was independent of whether depolarizing current was applied during afferent stimulation. At higher temperature, there was less LTP, and only *q* increased significantly. In contrast, when large populations of synapses were recorded from, there was no persistent epsp enhancement in the absence of either concurrent depolarization or high-frequency stimulation, and there was no difference between the magnitudes of LTP after high-frequency stimulation at 22°C or 32°C. Why should the mechanism of LTP expression depend so critically on the temperature at which it was induced and why should weak stimulation lead to an apparently nonassociative LTP, whereas stronger stimulation had no such effect? More puzzling, how could the same moderate stimulation produce changes in "minimal" epsps obtained with weak stimulation and not change the population epsp obtained with stronger stimulation?

These questions led us to reexamine the fundamental assumptions underlying the use of the minimal stimulation method. It had been reported (2) that at 32°C, the quantal parameters obtained with this method were reasonably consistent with those obtained from dual recording experiments, in which the firing of single CA3 cells that were presynaptic to CA1 cells was monitored directly. It was possible, however, that at 22°C, the electrical excitability of Schaffer collateral axons might be less stable.

To test this hypothesis, extracellular spikes were recorded from single CA3 pyramidal cells while stimulating their axons antidromically from CA1 stratum radiatum (Fig. 3) with the same sort of weak stimuli used in the minimal stimulation protocol. The probability of antidromic activation as a function of stimulus intensity rose from zero to one over a narrow range of intensities (Fig. 3 *C* and *D*). In preliminary studies at 22°C, relative excitability sometimes increased appreciably with stimulation at 2 Hz, with no change in stimulus intensity. The effects of stimulus trains of 40 pulses at 2 Hz were tested systematically at both 22°C and 32°C. Test stimuli were delivered at 0.2 Hz, as previously, and the stimulus was adjusted for ≈30–40% "success" in antidromic activation. Stimulus intensity was increased slightly (≈10%) during 2-Hz stimulation, so that the antidromic response followed the stimulation reliably. Before the start of each experiment, the stability of antidromic activation was assessed by counting the number of "successes" in consecutive blocks of 50 trials. Sometimes, this number changed over the initial few blocks, even when stimulating at 0.2 Hz. When this occurred, the stimulus intensity was adjusted, and testing was resumed until the response appeared stable. To control for possible further drift in excitability, at both temperatures, experiments were

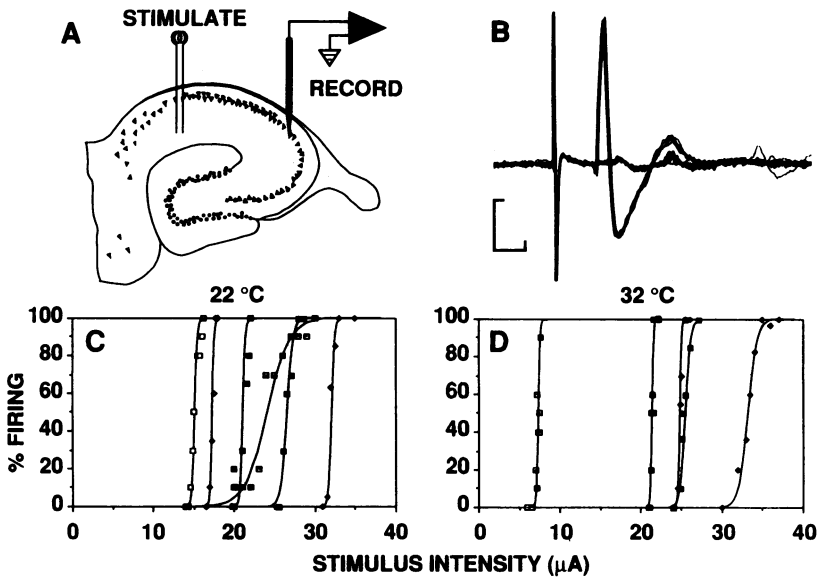

FIG. 3. Recording configuration (*A*) and typical responses (*B*) for experiments involving antidromic activation of CA3 neurons from CA1 using minimal stimulation in stratum radiatum. Criteria for antidromic activation were the presence of minimal latency-variation, in spite of stimulus-intensity changes, and a sharp threshold function (calibration, 1 msec, 200 μV). (*C* and *D*) Representative threshold functions for antidromic units recorded at 22°C and 32°C. Typically, the firing probabilities varied from ≈0.1 to ≈0.9 over 0.5–2.0 μA. There were no major effects of temperature on the slopes of the threshold functions.

conducted in which only low-frequency test stimuli were delivered. There was a large, persistent increase in reliability of antidromic excitation after 2-Hz stimulation at 22°C, but not at 32°C. Control responses were stable at both temperatures (Fig. 4*A*). There was a reciprocal relationship between the elevation in firing probability (at 22°C) and the initial probability during the baseline period (Fig. 4*B*).

Additional experiments were conducted at 22°C in which the number of pulses at 2 Hz was successively doubled, from 10 to 80, or the stimulus frequency during 20-pulse trains was varied from 2 to 50 Hz. For variations in pulse number, the maximum elevation in excitability was observed at 40 pulses (Fig. 5*A*); however, the slightly lower effect at 80 pulses was not significantly different from the effect of 40 pulses. For stimulus-frequency variation, the relative elevation of firing probability declined with stimulus frequency (Fig. 5*B*). This

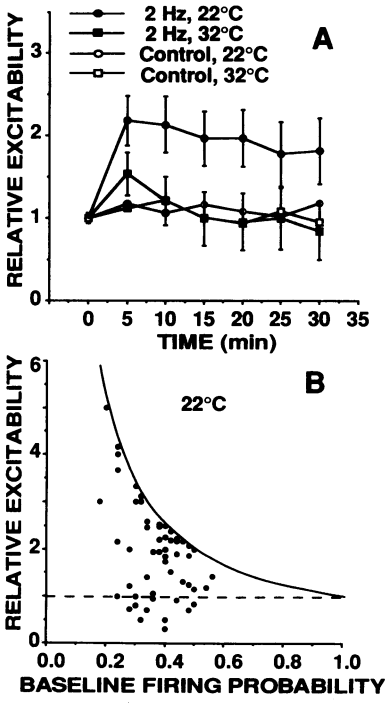

FIG. 4. (*A*) The effects of 40-pulse, 2-Hz stimulation on subsequent CA3 antidromic response probability at 22°C (●; 14 cells from seven rats) and 32°C (■; 13 cells from six rats). The 0.2-Hz, control conditions (17 cells from seven rats) are shown with open symbols (○, □). In all cases, the baseline stimulus was adjusted to a firing probability of 0.3–0.4. Repetitive stimulation caused a large, prolonged elevation of antidromic firing probability at 22°C ($P < 0.001$). At 32°C there was a small, transient effect only ($P > 0.05$). (*B*) The relative elevation of firing probability at 22°C was reciprocally related to the initial firing probability during baseline. ——, Maximum possible elevation for given initial values.

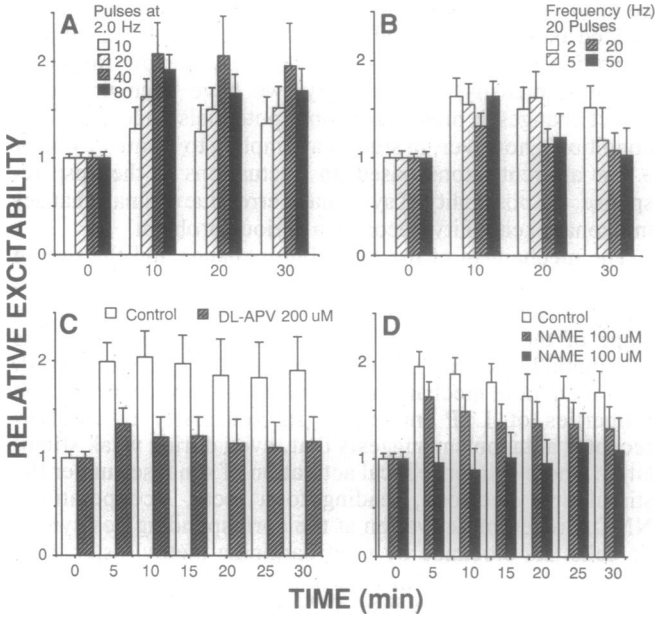

FIG. 5. (*A*) Antidromic firing probability was elevated in a stimulus-dependent manner, when the number of pulses was varied from 10 to 80 during 2-Hz stimulation at 22°C (57 cells from 23 rats). The difference between 40 and 80 pulses was not statistically significant, probably reflecting a ceiling effect. (*B*) The persistent elevation of antidromic firing probability decreased with increased stimulus frequency during stimulus trains of 20 pulses delivered at various frequencies (47 cells from 20 rats). This effect was due to an increase in refractoriness of the axons during the repetitive stimulation at higher frequencies. (*C*) Stimulus-dependent increase in axonal excitability at 22°C was completely blocked by the NMDA-receptor antagonist DL-2-amino-5-phosphonovalerate at 200 μM (29 cells from 12 rats; $P < 0.05$), a concentration that blocks both LTP and the apparent increase in quantal release that accompanies it under some conditions (4, 6). (*D*) Increase in axonal excitability at 22°C was blocked by the nitric oxide synthase antagonist L-nitroarginine methyl ester (NAME; 74 cells from 30 rats; $P < 0.05$).

result was due to increased refractoriness of the fibers at increased frequency.

For this stimulus-dependent excitability change to be a potential factor in the interpretation of earlier studies on quantal release, it would have to exhibit sensitivity to the same pharmacological manipulations as the "LTP" seen in those studies. Accordingly, experiments were conducted at 22°C, in which the bath contained antagonists of either NMDA receptors (DL-2-amino-5-phosphovalerate, 200 μM) or nitric oxide synthase (L-nitroarginine methyl ester, 100 or 200 μM). These concentrations block LTP under similar conditions. The increase in axonal excitability after 2-Hz stimulation (40 pulses) at 22°C was almost completely blocked by both DL-2-amino-5-phosphovalerate (Fig. 5*C*) and L-nitroarginine methyl ester at the higher dose and was partly blocked by the intermediate dose of L-nitroarginine methyl ester (Fig. 5*D*).

DISCUSSION

Two main conclusions follow from the present results. (*i*) Under some experimental conditions, even moderate electrical stimulation in the terminal field of Schaffer collateral axons causes a persistent, localized increase in the electrical excitability of presynaptic axons and/or synaptic varicosities. This result cannot be explained by alterations in antidromic invasion of the soma, as 100% reliable antidromic responses could be obtained at slightly higher intensities, with no change in conduction latency. Temperature is a major factor in this effect. The excitability change is extremely small, from the point of view of population studies in which the bulk of the excited axons are activated well above their regions of variable excitation (which extend over only very narrow ranges of stimulus intensity). Accordingly, we have been unable to detect changes in presynaptic fiber potentials under the same conditions; however, in studies attempting to stimulate one or a few afferent axons based on fluctuations in the epsp response, the possibility of systematic error due to small changes in axonal excitability becomes a serious problem.

The mechanism of the excitability change and the reason for its restriction to conditions of reduced temperature are unclear. A possible explanation might have been that the slope of the threshold function at lower temperature was substantially steeper; however, this result was not observed. The induction mechanism appears to share some of the properties of LTP induction. Its sensitivity to NMDA-receptor antagonism suggests that, even during weak stimulation, there is intense local activation of synapses under the stimulating electrode, leading to a local, "cooperative" NMDA-receptor activation at the corresponding postsynaptic cells. Its blockade by L-nitroarginine methyl ester, suggests that the excitability change involves an NMDA-receptor-dependent release of NO from postsynaptic neurons, as has been inferred in other studies. Like the NO-dependent increases in synaptic efficacy *per se* (14, 15), the present excitability change is, at least under the conditions of these experiments, markedly dependent on the temperature of the experimental preparation. The apparent increase in transmitter release seen under some conditions after pairing of postsynaptic depolarization with orthodromic synaptic activation could, in fact, be mediated by increased terminal excitability and a consequent, more efficient invasion of the action potential into the presynaptic terminal zones. Enhanced spread of depolarization in presynaptic axons may also provide a possible explanation for the reported spread of LTP via the stimulated axon to other postsynaptic neurons within the immediate vicinity of LTP induced with the pairing method (25).

(*ii*) Under our experimental conditions, however, we do not find evidence for increased transmitter release that cannot be accounted for by an elevation of the firing probability of the presynaptic axons. This result does not mean that previous reports of increased quantal release at reduced temperatures are *necessarily* contaminated by the same potential artifact. Subtle differences in experimental conditions may have made those studies immune from this problem; however, the present results do warrant the suggestion that a substantial part of the previously reported change in *m* may have been artifactual and that this should be reinvestigated. Certainly, the inverse relationship shown in Fig. 4*B* could explain the reported inverse relationship between the initial value of *m* and its apparent increase after stimulation (26).

Although excitability change was not observed at 32°C, until its properties are better understood, it should not be excluded as a possible factor in apparent changes in presynaptic release under other conditions, even at physiological temperatures. Finally, it should be emphasized that experiments in which no changes in quantal release parameters are detected by the classical methods (i.e., coefficient of variation, failures, noise deconvolution) are probably not subject to altered presynaptic excitability. As pointed out by Faber and Korn (9), alterations in the faithfulness of axonal excitation, such as those shown here, necessarily lead to spurious estimates of quantal release changes with such methods.

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