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LONG-TERM POTENTIATION AND DEPRESSION OF SYNAPTIC RESPONSES IN THE RAT HIPPOCAMPUS: LOCALIZATION AND FREQUENCY DEPENDENCY

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SUMMARY

1. The consequences of repetitive activation of excitatory synaptic inputs to the CA1 pyramidal cells of rat hippocampus have been studied using *in vitro* techniques.

2. Single stimulation trains of 100 pulses at rates of 5–100/sec resulted in potentiation of population spike amplitudes lasting the duration of a 5 min test period in thirty-four out of thirty-five cases. Trains of 100 pulses delivered at 1/sec resulted in depression of the stimulated pathway in ten out of twelve experiments.

3. Responses to test stimulation of other excitatory inputs to the same cell population were depressed following conditioning trains at frequencies in the range 1–100/sec. Depression was seen both in the population spike amplitude (reflecting synchronous cell discharge) as well as the extracellularly recorded population e.p.s.p., and appeared to be maximal at lower frequencies.

4. Trains of antidromic stimulation of the CA1 cell population produced subsequent decreases in synaptically evoked responses, indicating that repetitive firing of pyramidal neurones or interneurones do not cause potentiation, but may be involved in heterosynaptic depression.

5. The results suggest that potentiation and heterosynaptic depression arise from different mechanisms, and that potentiation is confined to the set of terminals activated by a conditioning train, whereas the depression is generalized to the whole neurone.

INTRODUCTION

Hippocampal neurones have firing patterns which range across a broad frequency spectrum; changes in these patterns presumably reflect various short-term operations being carried out by the neural circuitries of the functioning hippocampus. Recent work on the longer-term consequences of repetitive electrical stimulation of hippocampal pathways suggests that such patterns of activity might play another type of role, namely that of modulating the strength or efficacy of synaptic connexions. Relatively brief trains of stimulation to any of several fibre projections in hippocampus have been found to produce a long-lasting increase in the responses of that projection's target cells to subsequent single pulse activation (Alger & Teyler, 1976). Long-term potentiation, this prolonged increase in synaptically evoked responses seen in several hippocampal pathways following repetitive stimulation, is somewhat unique

when compared to the post-tetanic potentiation seen at the neuromuscular junction or in invertebrates, in that once instituted, it is of extremely long duration, lasting as long as days or weeks, and possessing little if any decremental character (Bliss & Lømo, 1973; Bliss & Gardner-Medwin, 1973; Douglas & Goddard, 1975). A second process, a reduced sensitivity of the target cells to their remaining afferents, following repetitive stimulation in hippocampus, has recently been demonstrated (Lynch, Dunwiddie & Gribkoff, 1977). This heterosynaptic depression does not appear to be as long-lasting as LTP, but it persists for at least 15 min, and can effect a sizeable reduction in the responses generated in non-tetanized pathways.

The present experiments were designed to provide information about two aspects of long-lasting synaptic change in hippocampus. First, the possibility was being examined that the various frequencies of repetitive discharge found in hippocampus might be consistently related to one or both of these forms of synaptic plasticity. Therefore a systematical investigation was carried out of the effects induced by brief trains of repetitive stimulation at differing frequencies upon subsequent responses recorded from the cell layer to single pulse activation of homo- and heterosynaptic pathways. It was hoped that data of this sort might also be useful in uncovering the events which trigger the mechanisms underlying long term synaptic changes in hippocampus. A secondary aim of these experiments was to study the effects of these trains on other types of responses (e.g. dendritic field potentials and antidromic field potentials) in order to test various hypotheses regarding the nature of these processes.

METHODS

The experiments were conducted using *in vitro* hippocampal slice preparations. 40–100 day-old rats were decapitated and the hippocampi dissected free while chilling the brain in 4 °C medium consisting of NaCl, 124 mM; KCl, 4·9 mM; KH_2PO_4, 1·2 mM; $MgSO_4$, 1·3 mM; $CaCl_2$, 3·1 mM; $NaHCO_3$, 25·6 mM; glucose, 10 mM; which was pregassed with 95 % O_2 + 5 % CO_2. Slices 600 μm thick were cut from the mid-septo-temporal regions of both hippocampi, perpendicularly to the long axis of this structure, with a Sorvall tissue chopper, then placed on nylon nets in a recording chamber of our own design (Spencer, Gribkoff, Cotman & Lynch, 1976). The chamber was kept at 33–35 °C, 95 % O_2 + 5 % CO_2 was bubbled through the water bath surrounding the chamber, and the fluid level was maintained at or just below the upper surface of the slice. In order to minimize differences between slices from various preparations comparisons between frequencies were made on sets of slices taken from the same hippocampus, with minimal time between experiments.

Bipolar stimulation was delivered either through 300 μm concentric stainless steel, or two-strand twisted 62 μm nichrome wire electrodes which were visually located in afferent fibre pathways under transillumination of the slice. Stimuli were biphasic 0·1 msec pulses of 2–20 V. Stimulating electrodes were lowered into the slice until potentials of maximum amplitude were obtained from a particular recording site, and the voltage was then set so as to evoke a 0·5–1 mV population spike. Recording was done with 1–5 MΩ glass micro-electrodes filled with 2 M-NaCl which were also placed under visual guidance. In most cases, two responses evoked 5 sec apart were averaged with a Nuclear Chicago CAT at 1 min intervals to test the effects of repetitive stimulation; testing with more stimuli or at more frequent intervals was avoided due to the sensitivity of this preparation even to low frequency (less than 1/sec) stimulation. When two or more pathways were being tested simultaneously, responses were evoked alternately from the various pathways at 5 sec intervals and averaged in pairs at minute intervals. Occasionally responses were photographed directly from the oscilloscope face or were recorded with a U.V. chart recorder in order to analyse individual responses. The amplitude of the population spike was taken as the average of the differences between the spike peak negativity and the preceding and following positivities. Measurements were made at five 1 min intervals prior to the condition-

ing stimulation, which consisted of trains of 100 pulses at frequencies of 1, 5, 15, 33, or 100/sec. Following the train responses were tested as before at five 1 min intervals, and differences were assessed with two-tailed *t* tests on the five pre- vs. five post-stimulation responses.

Three essentially distinct synaptic pathways to the CA1 pyramidal cells were used in these experiments as illustrated in Fig. 1. Stimulation of stratum oriens evokes a monosynaptic response via primarily commissural fibres and their terminals in the basal dendrites of the CA1 cells (BC), which is independent of the apical dendritic response to Schaffer collateral and commissural fibres (O-SC) evoked by stimulation in stratum radiatum at the CA2–CA1 border (Andersen, Sundberg, Sveen & Wigstrom, 1977; Lynch *et al.* 1977). Stimulation near the

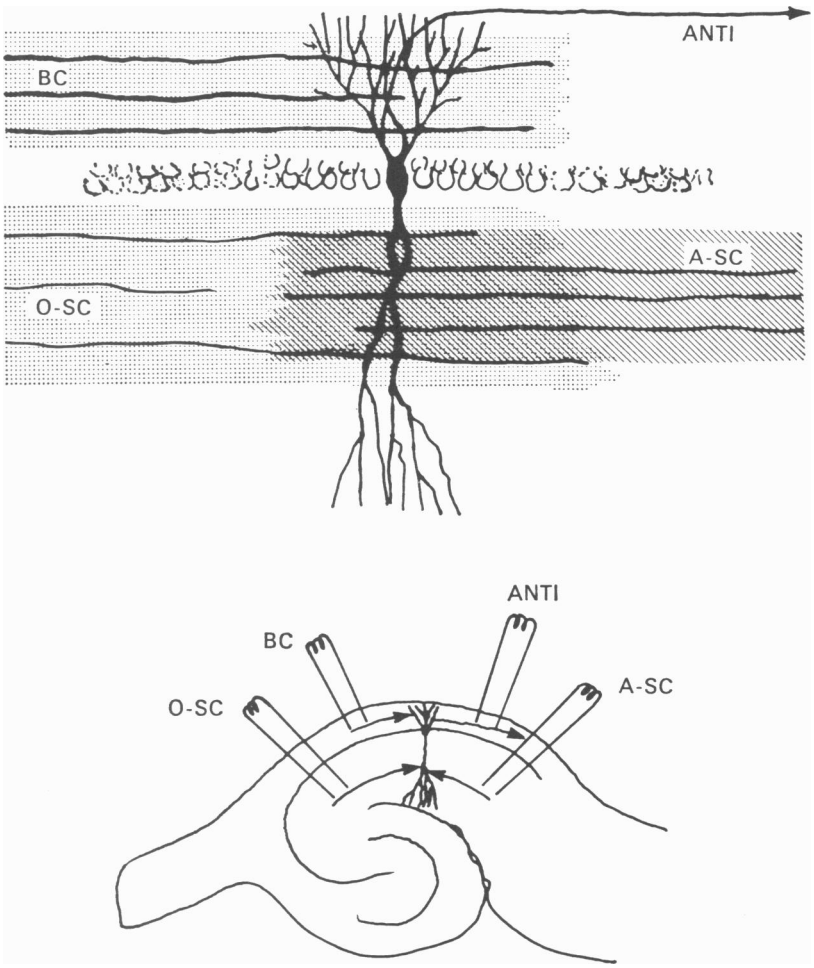

Fig. 1. Schematic representation of the stimulation sites used in these experiments. Stimulating electrodes were located in Schaffer and commissural fibres near the CA2–CA1 border (O-SC), near the subicular margin of the CA1 field (A-SC), in stratum oriens activating primarily commissural fibres (BC), and on the efferent fibres of CA1 pyramidal cells (ANTI). The three synaptic pathways rarely extended over the complete medio-lateral range of the slice, but were usually truncated in preparation, as represented in the upper half of the figure. Outside the central area of overlap (darker shading) responses could be seen to stimulation via one but not both of the Schaffer-commissural electrodes.

CA1–subicular border evokes a nearly identical response from a different subpopulation of Schaffer and commissural fibres activated in the antidromic sense. Andersen & Lømo (1966) have demonstrated the ability of these *en passage* contacts with the apical dendrites to be activated by stimulation either in the orthodromic (O-SC) or antidromic (A-SC) direction. Since the zone of viability of these slices is 100–200 μm in thickness (based both on electrophysiological measurements and on electron microscopy of slices), it is unlikely that individual fibres run the entire distance between the CA3 and subicular border stimulating sites, which were separated by 2–2·5 mm. This was confirmed using physiological techniques to further differentiate between them. Stimulation of Schaffer fibres near the subicular margin rarely generated a discernible response in CA3, and no response to orthodromic activation of these fibres could be detected when recording at the subicular border stimulation site. Since stimulation of each of these pathways with pulse pairs separated by 20 msec–1 sec produces a characteristic facilitation of the second response, we tested the capability of a conditioning pulse delivered via one input to facilitate test stimuli to other pathways. Paired-pulse facilitation was never observed between those inputs (BC and A-SC, and BC and O-SC) which have previously been shown to be independent (Alger & Teyler, 1977), and results for O-SC and A-SC stimulation showed the same pattern of depression. Paired-pulse facilitation was never observed with any combination of inputs on twenty-one different slices; such facilitation would have been expected if a significant fraction of the fibres stimulated by the first pulse were common to the second electrode as well. When O-SC and A-SC pathways were activated simultaneously, the resulting dendritic e.p.s.p. was 80–90 % of the algebraic sum of the two responses, again suggesting that the inputs were largely independent. Finally, during high frequency stimulation of any test projection, stimulation of a second pathway evoked normal and usually facilitated responses, although the stimulated afferent was completely suppressed. The conditioning and testing inputs were randomly selected from the three pathways but since no significant differences were seen with any combinations of stimulation, the results were grouped for subsequent analysis.

Attempts were made to monitor the presynaptic compound action potential reported by Andersen *et al.* (1977). However, these potentials proved difficult to detect (see Fig. 8) except with larger stimulating voltages than those used in our experiments or when synaptic potentials were eliminated by calcium-free media. (These potentials are apparently not seen *in vivo* with similar types of stimulation (*cf.* Andersen, 1960, Fig. 2)). Since it has been reported that these potentials apparently do not vary systematically following repetitive stimulation (Andersen *et al.* 1977) and there is no change in the electrical threshold for evoking post-synaptic responses (Bliss & Gardner-Medwin, 1973) or in the antidromic field potential generated by the Schaffer stimulation recorded in the CA3 region (Schwartzkroin & Wester, 1975), it was assumed that alterations in the presynaptic volley were not responsible for the types of changes observed in this study.

RESULTS

Effect of repetitive stimulation on the stimulated pathway

Repetitive synaptic activation at a wide range of frequencies induced stable changes consistent across each of the three synaptic populations. Repeated testing under the control conditions used in this experiment (2 stimuli/min) resulted in no long-term changes in the amplitude of the evoked response. Stimulation trains at the lowest frequency employed (1/sec for 100 sec) resulted in a significant depression of population spike amplitudes for the duration of the 5 min test period in ten out of twelve slices. Most of the slices in this group showed some initial frequency potentiation during the trains, whilst decreasing responses were usually obtained in the later parts of the trains.

At frequencies above 1/sec, trains of 100 stimuli induced long-term potentiation in thirty-four out of thirty-five cases with a trend toward a greater degree of potentiation at the higher frequencies (Fig. 2). The greatest differences were found between stimulation at 5/sec, which produced minimal potentiation as a rule (population

spike range = 80–168% of control levels) and at 15, 33 and 100/sec which in nearly every case produced potentiation exceeding 200% of control levels.

Long-term potentiation appeared to be unrelated to the types of changes seen in the response during the conditioning train, since both frequency potentiation and depression were observed during repetitive stimulation. Responses followed well and usually showed frequency potentiation at frequencies of 5–33/sec, but 100/sec trains resulted in a rapid decrement in the response within 4–5 impulses (see Fig. 3), as has been reported by others (Schwartzkroin & Wester, 1975).

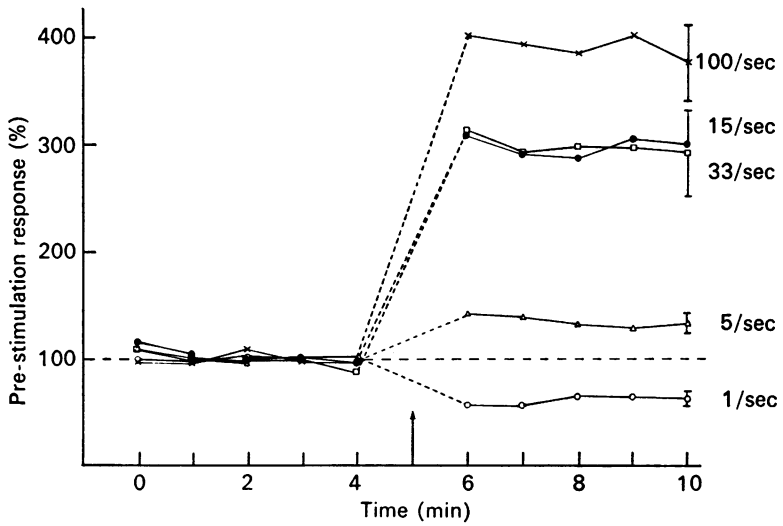

Fig. 2. Effects of trains of 100 pulses on the amplitude of the population spike of subsequent responses evoked from the stimulated pathway. Conditioning trains were begun at 5 min, and the first test response taken 1 min after the termination of each train. The points are averages for twelve slices (at 1 and 100/sec), eight slices (at 5 and 33/sec) or seven slices (at 15/sec). Bars indicate standard error of the mean. Note the consistent depression established by 1/sec trains, as opposed to the potentiation following trains at all other frequencies.

Only a few of the slices described in these experiments were tested for longer than 5 min, since the return to control levels occurred gradually if at all. In a previously published experiment (Lynch *et al.* 1977), seventeen slices were stimulated with 15/sec trains for 15 sec, and the average degree of potentiation was maintained at 390% after 5 min and 332% after 15 min. Two examples from the present experiment further illustrate the longevity of the potentiation (Fig. 4).

In many cases particularly with high frequencies, facilitated responses were seen immediately following the stimulation train; with 100/sec trains, which resulted in depression during the train, potentiated responses could often be evoked within 20–30 msec after the termination of the train (see Fig. 3). In other cases, long-term potentiation was preceded by a 10–30 sec period of depression before augmentation to increased levels. Within the first minute the potentiated response would decrease somewhat, but from 1 to 5 min the decrement was usually small or non-existent (Fig. 2).

Effects of repetitive stimulation on heterosynaptic inputs

Following repetitive stimulation of one synaptic input to a population of cells at frequencies of 1–100/sec, other excitatory inputs to the same group of cells almost without exception manifested diminished responses (see Fig. 5). As was discussed above, stimulation at 1/sec for 100 sec produced a homosynaptic as well

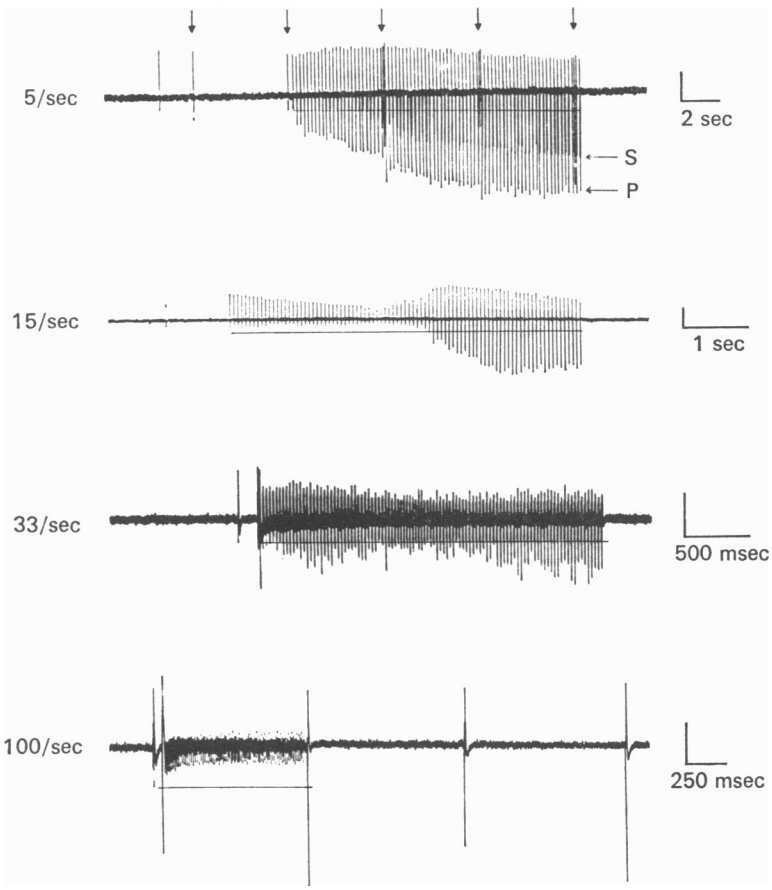

Fig. 3. Frequency facilitation and depression seen at several frequencies. In each case, the solid line below the trace indicates the population spike amplitude of control responses prior to the beginning of the train. All conditioning trains were delivered via orthodromic Schaffer-commissural stimulation. The uppermost trace illustrates facilitation of another input (BC, indicated by arrows) during the conditioning train and the development of a secondary population spike (S) in addition to the primary spike (P) during the train. The 15/sec train demonstrated the delayed facilitation observed at this frequency, whereas 33/sec produces relatively little facilitation. The initial response of the 100/sec train was increased by nearly 100 % by a stimulus delivered through the same electrode 70 msec prior to the train; by the second response of the train the amplitude had dropped below control levels. However, a test response following the cessation of the train by 30 msec was greatly facilitated, as were subsequent test responses. (The vertical bar in each record represents 1 mV; some records were retouched to facilitate reproduction. In this and in all subsequent records upwards direction corresponds to positive polarity).

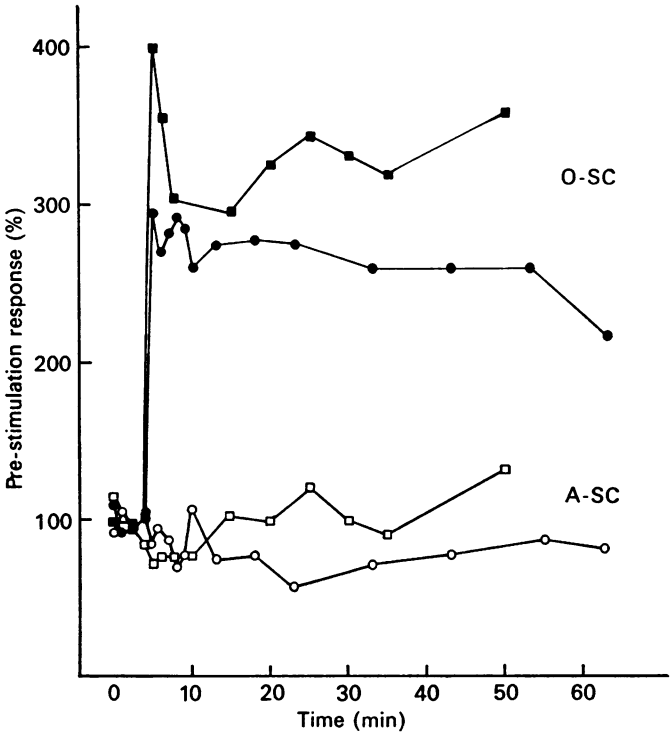

Fig. 4. Long-term effects of conditioning stimuli on population spike amplitude in stimulated (O-SC) and unstimulated (A-SC) pathways. Data from one slice are indicated by open and filled circles, from another by squares. Both heterosynaptic pathways showed short-term depressions, but only one remained depressed for the duration of the 60 min post-test. All points represent averages of four responses.

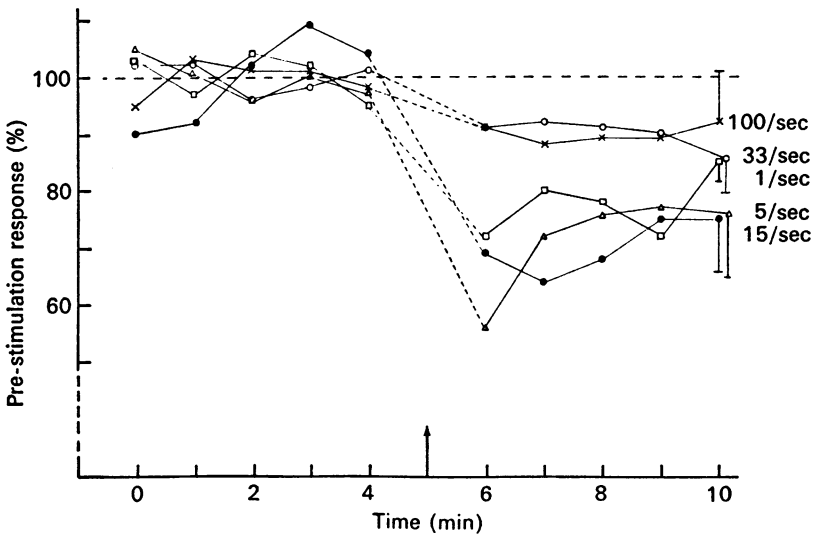

Fig. 5. Effects of stimulation at different rates on the population spike amplitude of test responses evoked via unstimulated pathways; □, 1/sec; △, 5/sec; ●, 15/sec; ○, 33/sec, × 100/sec. (Same group of slices as described in Fig. 2.) Note that the higher frequencies (100/sec and 33/sec) appear to show somewhat less depression than the three lower ones. Bars indicate standard error of the mean.

as heterosynaptic depression, although the heterosynaptic effect was of lesser magnitude. Within the range of frequencies which produced potentiation of the homosynaptic pathway (5–100/sec) there appeared to be a slight trend towards less heterosynaptic depression at higher frequencies. This can be seen not only in the average degree of depression, which appears to decrease with higher frequencies, but also in the percentage of slices which demonstrated the effect. As shown in Fig. 6,

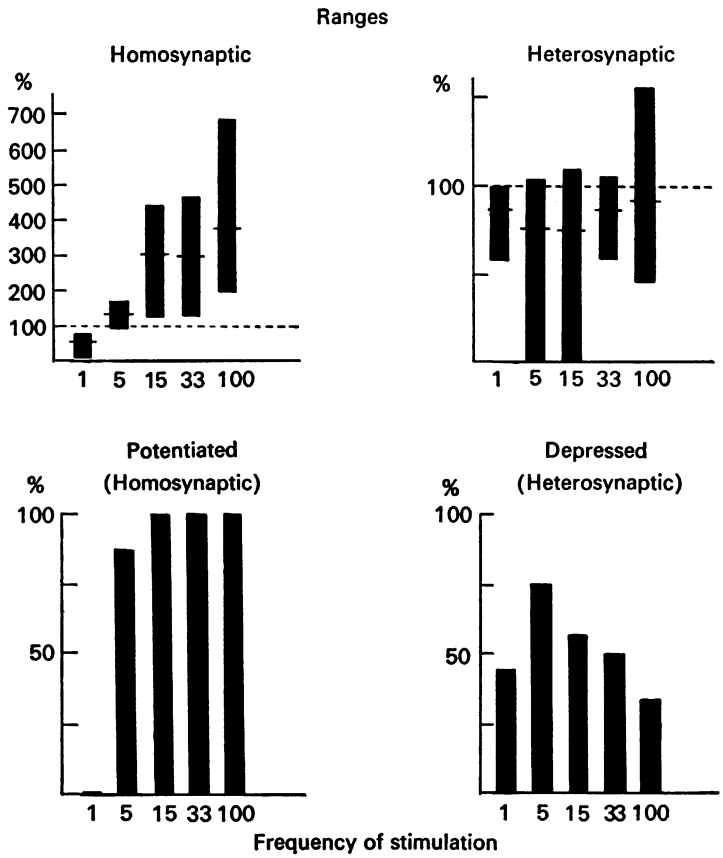

Fig. 6. The upper half of the figure illustrates the ranges of population spike responses to test stimuli 5 min following the conditioning trains. (Bars indicate means.) The lower half of the figure illustrates the percentage of slices reaching a criterion level of potentiation or depression in the two conditions (criterion was a two-tailed t test on the five pre-test vs. five post-test response measures, $P < 0{\cdot}05$). Data came from thirty-five slices, seven at each frequency. Note that even though the mean level of potentiation could be quite low (e.g. 5/sec), the effect itself was still fairly reliable (six of seven slices). In the heterosynaptic pathways, those frequencies which produced the maximal depression (complete suppression of population spike) had the highest probability of meeting the criterion for these effects.

the number of slices which did not meet the criterion for significant heterosynaptic depression increased with increasing frequency. If records were taken from all three pathways, concurrent depressions were evoked in all non-stimulated pathways and with similar time courses (see Fig. 7), regardless of whether the test inputs were in

the apical or basal dendritic region; previously potentiated pathways were also seen to be depressed.

As was reported above, depression can be seen in the conditioning pathway with stimulation which induces little or no potentiation (e.g. low frequency stimulation trains). On occasions, particularly with low voltage stimulation, depression of the conditioning pathway is also seen at frequencies which normally produce potentiation. When seen under either of these conditions, the depression effect is usually maximal in the conditioning pathway.

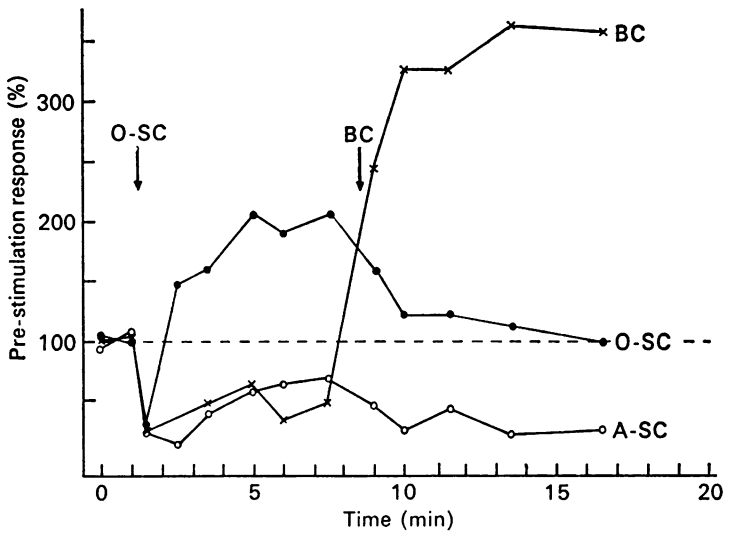

Fig. 7. Potentiation and heterosynaptic depression tested simultaneously in all three pathways of a single slice. Depression of the population spike amplitude to inputs terminating in both the basal (BC) and apical (A-SC) dendritic fields are quite similar following a conditioning train to the O-SC pathway (15/sec for 15 sec) indicated by arrow). Similar parallels are seen in the depression of the previously potentiated (O-SC) and depressed (A-SC) responses upon BC stimulation. Note also the transient depression of the conditioned pathway 30 sec following the train to the O-SC input, before its increase to potentiated levels.

Effects of antidromic and low voltage stimulation trains

In an effort to determine which aspects of stimulation were responsible for heterosynaptic depression, two other types of stimulation were used. In one series of experiments, low voltage stimulation of CA1 axons in the alveus near the subiculum was used to evoke antidromic responses from the pyramidal cells. When the stimulation voltage was adjusted so as to produce a 1–2 mV antidromic field potential in the CA1 cell layer, stimulation at frequencies appropriate for heterosynaptic depression rarely produced significant depression of synaptically evoked responses. However, since the synaptic (but not antidromic) stimulation trains often showed a high degree of facilitation during the train, experiments were done using larger antidromic responses which would more closely approximate the degree of activation associated with synaptic trains. Twenty-five slices were stimulated with antidromic trains of 100 pulses, mostly at 15/sec (fifteen slices), the rest at 1, 5, 33 and 100/sec. The

average synaptic response 1 min following the trains was 75% of the amplitude during a 5 min pre-test, and returned to 83% of control after 5 min. However, at these higher stimulation voltages an apparently synaptically evoked population spike could occasionally be observed as well (eight out of twenty-five slices). This response, which is presumably due to activation of primarily commissural fibres and terminals in a manner analogous to the 'antidromic' Schaffer commissural response,

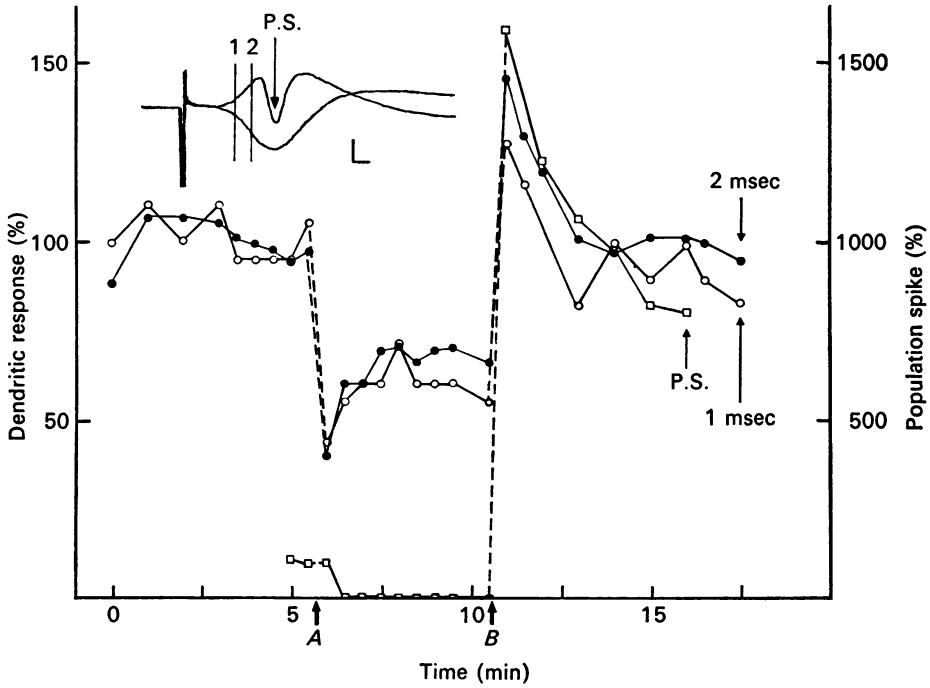

Fig. 8. Changes in dendritic potentials following homo- and heterosynaptic conditioning trains. Parallel changes were observed in the dendritic e.p.s.p. measured 1 msec (open circles) and 2 msec (filled circles) after the onset of the response, as well as in the amplitude of the population spike (P.S., open squares). Note that the scale for the population spike is larger by an order of magnitude. All responses were measured simultaneously to test stimulation of the O-SC pathway following stimulation of the A-SC pathway (*A*) and the O-SC input (*B*). Insert illustrates the recordings made simultaneously from the cell layer (upper) and dendritic zone (lower) and the points at which the dendritic potential was measured. Calibration marks indicate 1 mV, 1 msec.

demonstrated frequency facilitation at frequencies of 5–33/sec (which was not observed in the antidromic component of the response), and occasionally showed long-term potentiation. Thus, although some slices showed no depression following antidromic trains, the general trend was a depression similar in many respects to that occurring with synaptic stimulation. However, because of the possibility that these effects are due to synaptic excitation of the same cells, conclusions as to the role of cell firing in heterosynaptic depression remain uncertain.

Effects of repetitive activation on extracellular dendritic e.p.s.p.s

Recordings made in the regions of synaptic termination show a negativity which is considered to be the extracellular reflexion of the intracellular e.p.s.p. (Andersen, 1960). As can be seen in Fig. 8 both heterosynaptic depression and long-term potentiation are reflected in changes seen in the extracellular e.p.s.p.s which parallel

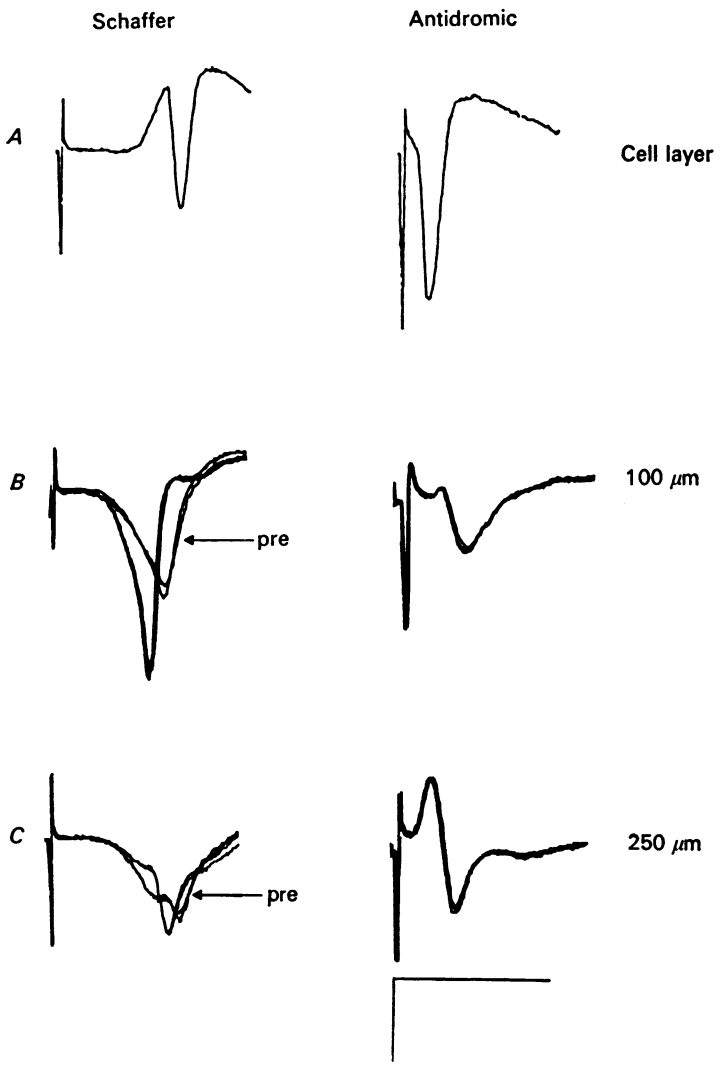

Fig. 9. Responses to Schaffer (O-SC) and antidromic stimulation. *A*, typical responses recorded from the cell layer with both types of stimulation (average of two responses). *B*, potentials recorded 100 μm from the cell layer and *C* at 250 μm. Two responses evoked prior to conditioning stimulation (pre) are superimposed on two responses evoked 2 min following a 15 Hz, 15 sec train to the O-SC electrode. Antidromic responses prior to and following conditioning stimulation superimposed nearly exactly when recorded both at 100 μm and 250 μm whereas dendritic e.p.s.p.s were easily distinguished. (Calibration bars indicate 5 msec and 2 mV; 1·33 mV for upper two rows. Each pair of records was obtained from different slices).

those seen in the population spike, although of considerably lower amplitude. These changes were seen regardless of whether the dendritic potentials were measured to peak negativity or 1 msec after their onset. Since the latter measure precludes polysynaptic influences, any role of interneurones in these effects would be expected to be minimal. The ability of the extracellularly recorded potential to reflect the e.p.s.p. accurately should not be accepted uncritically, since changes in the cable properties of dendritic elements or in the extracellular space might affect the amplitude of recorded potentials. This possibility was tested by measuring the amplitude of responses evoked by antidromic stimulation of the CA1 neurones recorded at several points in the dendritic field before and after conditioning stimulation delivered to afferents which terminate in the same dendritic zone. As can be seen from Fig. 9, no changes were seen in the amplitude of antidromic potentials recorded from areas which *did* show changes in dendritic e.p.s.p.s to synaptic stimulation, suggesting that the passive electrical properties of dendrites are unchanged by stimulation which induces both long-term potentiation and heterosynaptic depression.

DISCUSSION

The results of these experiments demonstrate that long-term potentiation is but one consequence of repetitive activation of synaptic populations in the hippocampus. By testing several inputs concurrently it was seen that over a wide range of frequencies, repetitive stimulation induced a generalized decrease in responsivity to excitatory inputs not only on the same dendrites, but on others several hundred microns removed and on the opposite side of the pyramidal cell layer. The long-term potentiation phenomenon was found to be superimposed on this generalized depression and appeared to be restricted almost solely to the specific set of synapses activated by the conditioning stimulation.

Several independent lines of evidence support the concept of this generalized depression. As was shown here, inputs to any dendritic zone of the same cell population all reflect similar types of depression. Two stimulating electrodes in CA3 separated by 100 μm orthogonally to the direction of the Schaffer fibres can demonstrate heterosynaptic depression as well; only in cases where both electrodes were placed along the trajectory of the same group of fibres was cross-potentiation seen, and even then, to a lesser degree in the test input as compared to the conditioning input. Further evidence suggesting a generalized reduction in sensitivity is that of Lynch, Gribkoff & Deadwyler (1976) in which the sensitivity of pyramidal cells to iontophoretically applied glutamic acid was reduced following stimulation producing potentiation. Furthermore, this depression was also generalized to the entire neurone, in that there was a reduction in sensitivity to glutamic acid applied to either the basal or apical dendrites upon stimulation of the Schaffer pathway. It would appear that this reduction in sensitivity is more clearly related to the heterosynaptic depression effect than to long-term potentiation as was originally suggested.

Several mechanisms could be suggested to underlie heterosynaptic depression on the basis of these experiments. Since the dendritic e.p.s.p. is depressed as early as 1 msec after its onset, it is clear that feed-back inhibition can be excluded as a candidate. Presynaptic inhibition is unlikely because of the paucity of axo-axonic

contacts in this area on the hippocampus (Lynch, G. S., unpublished observations) and because stimulation in one pathway would be unlikely to activate terminal elements in the opposing dendritic field. The problems discussed above regarding antidromic activation of the CA1 pyramidal cells make it unclear whether repetitive cell firing or perhaps tonic effects of feed-back interneurones due to repetitive activation are perhaps involved.

The fact that depression was brought about by low frequency stimulation suggests that depression and potentiation are not necessarily linked since the latter effect is rarely seen at these frequencies. Taken together, the evidence points to the conclusion that repetitive activation *per se* is the adequate stimulus for eliciting depression. This observation, combined with the generalized post-synaptic nature of the phenomenon, may indicate that it is caused by some secondary effect of synaptic transmission on the basic biochemistry of the target cell population. It has been shown elsewhere that certain populations of hippocampal afferents release adenosine or one of its derivatives during synaptic transmission, and this is rapidly sequestered by post-synaptic cells (Schubert, Lee, West, Deadwyler & Lynch, 1976). In view of the potency of adenosine in regulating cyclic nucleotides and the evidence implicating these latter compounds in depression of cell firing in several systems (Siggins, Hoffer & Bloom, 1971; Segal & Bloom, 1974) it is possible that this trans-synaptic transport may be involved in heterosynaptic depression. Alternatively, generalized changes in the extracellular ionic environment brought about by repetitive stimulation might play a role. It has been shown that synaptic activity in hippocampus causes an increase in the concentration of extracellular potassium (Fritz & Gardner-Medwin, 1976) and it is conceivable that this might act to cause local changes in either terminals or post-synaptic elements.

With regard to potentiation, several aspects of synaptic responses (paired-pulse facilitation, frequency facilitation and/or depression during the conditioning train) have all been investigated to see whether any of these might be used as predictors of long-term potentiation (Dunwiddie, T. & Lynch, G., unpublished observations), but no single one of these measures appears to reflect accurately the degree to which a given slice will potentiate under a given set of conditions. It would appear that the frequency-related events associated with stimulus trains are not involved in any obvious way with the potentiation process, in as much as no distinguishing characteristic can be found common to all slices which potentiate. However, the fact that high frequency stimulation elicited potentiation which was as strong as or stronger than that found with lower frequencies indicates that the degree of post-synaptic response is not a key variable, since transmission is greatly reduced after the first few pulses given at this rate. It is unclear from these experiments whether higher frequencies *per se* induced more potentiation than lower ones, or whether the greater depression produced by lower frequencies may have acted to offset essentially similar degrees of potentiation.

The present results also help to confine the possible loci for long-term potentiation. The experiments in which the dendritic zone receiving the potentiating train was also the target for the test afferent (i.e. with A-SC and O-SC stimulation) strongly suggest that local dendritic changes could not be responsible for the effect, although it could not be demonstrated that the conditioning and test inputs impinged upon the same

dendritic segments. In this regard, the demonstration that antidromic responses recorded from dendritic regions are unchanged by conditioning trains provides further evidence that neither long-term potentiation nor heterosynaptic depression are accompanied by substantial changes in the electrotonic properties of these regions. In summary, these findings strongly suggest that the potentiation effect must be located within the terminal, spine, or in the synapse itself.

The implications which these two opposing processes of potentiation and depression have for hippocampal function are considerably broader than those of potentiation alone. If potentiation is a process which in one form or another is thought to cause enduring increases in synaptic potency in the behaving organism, then symmetry would suggest a corresponding process which might effect a reduction in the sensitivity of other synaptic pathways as a consequence of repetitive activation. Thus, it can be seen that heterosynaptic depression could serve at least two functions. It would serve as a process which acts as a counterbalance to potentiation, and thus prevent a situation in which every input to a target cell population was maximally potentiated, a situation in which the plasticity of the cells would be effectively reduced to zero. At the same time it might act to amplify the effects of potentiating one input to a neurone by reducing the potency of inputs along others. Thus, a single conditioning volley would alter the consequences of subsequent impulses not only by directly increasing the synaptic 'signal' generated by the set of synapses, but by reducing the 'noise' being concurrently produced a long other pathways and lessening the probability of a given cell firing in response to extraneous inputs. Intracellular recordings from the CA1 pyramidal cells (Deadwyler, S. A., Dunwiddie, T. V. & Lynch, G., in preparation) substantiate the fact that these effects are likely to be taking place at the level of the individual neurone, and are not restricted to differing populations of cells.

Since various conditioning frequencies apparently induce differing degrees of long-term potentiation and heterosynaptic depression, this would suggest that inputs to the hippocampus may invoke variant effects even through the same synapses by a type of frequency coding. The frequency which induced maximal suppression of other inputs in this experiment (5/sec), is quite close to the normal theta frequency, and various groups of cells have been reported to fire at this frequency during periods of theta activity (Ranck, 1975). Such patterns of input would be expected to cause a generalized reduction in sensitivity throughout the stimulated population of cells, with the exception of those synapses being directly activated. On the other hand, the bursting patterns of dentate and pyramidal cells occur at frequencies quite close to the 100/sec used here to elicit maximal potentiation. Although much longer trains were used standardly in these experiments, under some conditions as few as 6 pulses at 100/sec can produce potentiation lasting at least 15 min (Dunwiddie, T. V., unpublished observation).

Thus, the process of heterosynaptic depression can act to highlight the increase in sensitivity of certain synapses by suppressing others, whilst the frequency characteristics of these two processes may serve to allow different types of information to imprint their own 'signatures' on post-synaptic neurones by means of different frequencies of activation.

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