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POST-TETANIC POTENTIATION AND FACILITATION OF SYNAPTIC POTENTIALS EVOKED IN CAT SPINAL MOTONEURONES

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SUMMARY

1. Excitatory post-synaptic potentials (e.p.s.p.s) were evoked in spinal α-motoneurones of the cat by impulses in single group Ia nerve fibres.

2. The average peak amplitude of some of these e.p.s.p.s was increased by a conditioning tetanus. The maximum increase observed was 54% of the control amplitude.

3. The average peak amplitude of some e.p.s.p.s was increased by a single conditioning stimulus which preceded the test stimulus by 1 or 2 msec. The maximum increase observed was 28% of the control amplitude.

4. The ability of e.p.s.p.s to potentiate following a tetanus was correlated with their ability to be facilitated by a single conditioning stimulus.

5. If an e.p.s.p. could be facilitated prior to a tetanus, the amount of facilitation was reduced after the tetanus, with all facilitation being abolished when post-tetanic potentiation was maximal.

6. The fluctuations of an e.p.s.p. were analysed before and after a tetanus. The peak amplitudes that an e.p.s.p. fluctuated between while potentiated did not gradually diminish as the effects of the tetanus disappeared. Post-tetanic potentiation, when it occurred, was accompanied by a decrease in the probability of occurrence of components with smaller peak amplitudes and an increase in the probability of occurrence of components with larger peak amplitudes.

7. These results are consistent with the suggestion that the magnitude of the synaptic potential generated at a single bouton does not vary from trial to trial (Jack, Redman & Wong, 1981*a*). Nor does the amplitude of this potential vary following a single conditioning stimulus or a tetanus. Post-tetanic potentiation and facilitation result from a decrease in the probability of failure to release transmitter following the conditioning stimuli.

INTRODUCTION

In the previous paper (Jack, Redman & Wong, 1981*a*) it was proposed that the synaptic potential generated by a single bouton of a group Ia afferent fibre occurs in an all-or-nothing manner. To account for this, as well as other observations, it was proposed that at each bouton a quantum of transmitter is sufficient to saturate all receptors within diffusional reach of the release site. It was also proposed that the

probability of failure to release transmitter at a bouton is not the same for each bouton and that fluctuations in a synaptic potential arise when this form of transmission is applied to all the boutons making up the termination of a single afferent fibre.

The detailed mechanisms of synaptic transmission can be examined by procedures which alter the size of synaptic potentials evoked via the group Ia pathway. Synaptic transmission can be increased by the effects of a prior tetanus, causing post-tetanic potentiation (p.t.p.) of the excitatory post-synaptic potential (e.p.s.p.) and by the effect of a single conditioning stimulus, causing facilitation of the test e.p.s.p. (Curtis & Eccles, 1960; Kuno, 1964). In this paper we show that both p.t.p. and facilitation occur in single-fibre e.p.s.p.s, but not always. When an e.p.s.p. is potentiated by a tetanus, in contrast to observations made at the skeletal neuromuscular junction (Landau, Smolinsky & Lass, 1973) the facilitating effect of a prior stimulus is removed or reduced. This result, and the analysis of fluctuations in potentiated e.p.s.p.s, supports our view that a single bouton normally behaves in an all-or-nothing manner. With this mode of transmission at a single bouton facilitation and p.t.p. can occur by a decrease in the probability of failure at all or some of the boutons involved in transmission (Redman, Wong & Hirst, 1978).

METHODS

The recording methods and the techniques used for the isolation of a single group I a fibre input have been described previously (Jack *et al.* 1981*a*).

In each of the experiments described in this paper a common stimulating regime and data collection procedure were used. The appropriate peripheral nerve was stimulated at the start of each sequence with a single shock, and again after 170 msec by a pair of shocks separated by 1 or 2 msec. 170 msec later, a membrane potential record in the absence of stimulation was collected. Each record was digitized and stored on disk for subsequent analysis. This sequence was repeated at 0·5 sec intervals until 400 sequences had been recorded. In each experiment the stimulus strength was adjusted to be 3 times the threshold value for the I a fibre to ensure that the fibre was stimulated during and after the tetanus when its threshold may have been elevated.

A tetanus (200 Hz for 20 sec) was then delivered to the nerve containing the sensory fibre; no data were collected during this period. Following the tetanus an interval of 5 sec was allowed to elapse so as to avoid possible complication by post-tetanic depression (Curtis & Eccles, 1960). The same sequence of stimuli as described for the collection of control data was then repeated, usually for 200 sequences. As before, individual sweeps were stored on disk. The entire sequence of a tetanus and data collection were repeated for a minimum of six tetani, allowing 5 min between each tetanus.

The amounts of facilitation and post-tetanic facilitation were determined later. Data gathered at a known time after a tetanus were separated into a noise recording, a single e.p.s.p. recording and a paired e.p.s.p. recording. This procedure was repeated for each data collection after each tetanus. Thus data collected at the same time after a series of tetani could be added together to give an average amplitude of each of the three data records. It was impractical to make measurements from the averaged e.p.s.p. obtained in a single short period of time after the tetani because of the poor signal-to-noise conditions. Rather, data obtained during intervals varying from 10 to 30 sec obtained at known times after the tetani were lumped together. Post-tetanic potentiation and facilitation were calculated as the increase in peak amplitude over that of the control e.p.s.p., expressed as a percentage of control.

RESULTS

Post-tetanic potentiation

The effect of a preceding tetanus (200 Hz for 20 sec) on the amplitude of e.p.s.p.s was examined in seventeen experiments. A proportion (five out of seventeen) failed to show an appreciable potentiation (i.e. an increase of 5 % or greater than control). The failure of some e.p.s.p.s to facilitate was also noted by Kuno (1964). In the remaining twelve experiments post-tetanic potentiation ranged from 7 % to an extreme value of 54 %. An example is shown in Fig. 1. The average peak potentiation from all experiments was 19 % ; no examples of post-tetanic depression were detected.

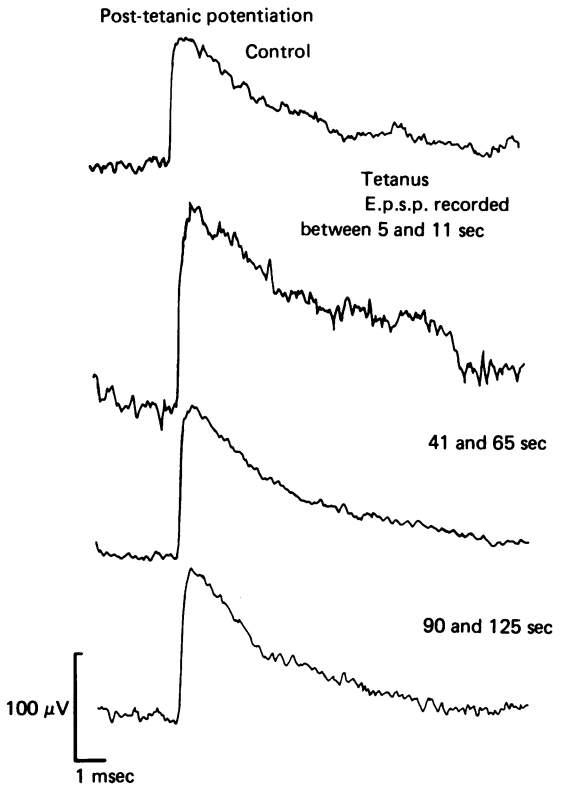

Fig. 1. Effect of a tetanus on the amplitude of an e.p.s.p. The control response (average of 400 sweeps) is shown at the top. This is followed by grouped data acquired from periods following ten tetani, the periods illustrated being 5–11 sec after tetanus, 41–65 sec after tetanus and 90–125 sec after tetanus. It can be seen that the e.p.s.p. increased in amplitude shortly after the tetanus and rapidly returned to its control value. The calibration bars apply to each record.

After the initial potentiation the mean amplitude of the e.p.s.p. returned to control values within 90 sec (Fig. 2). Both the amount of p.t.p. and the time period over which p.t.p. occurred are considerably less than that reported for composite e.p.s.p.s recorded from similar motoneurones (Curtis & Eccles, 1960). In a number of our experiments, the recordings of Ia e.p.s.p.s were complicated by the presence of

e.p.s.p.s which occurred after a longer latency ($\approx$ 2 msec) than the Ia e.p.s.p. These 'late' e.p.s.p.s were initiated by the higher stimulus strengths used to ensure stimulation of the Ia fibres after a tetanus. Although the dorsal root fibres which remained intact contained only single Ia fibres from each peripheral nerve used they also contained a number of higher threshold more slowly conducting afferent fibres. Presumably the late e.p.s.p. reflects recruitment of polysynaptic excitatory pathways. Many of these e.p.s.p.s were dramatically increased in amplitude following a tetanus;

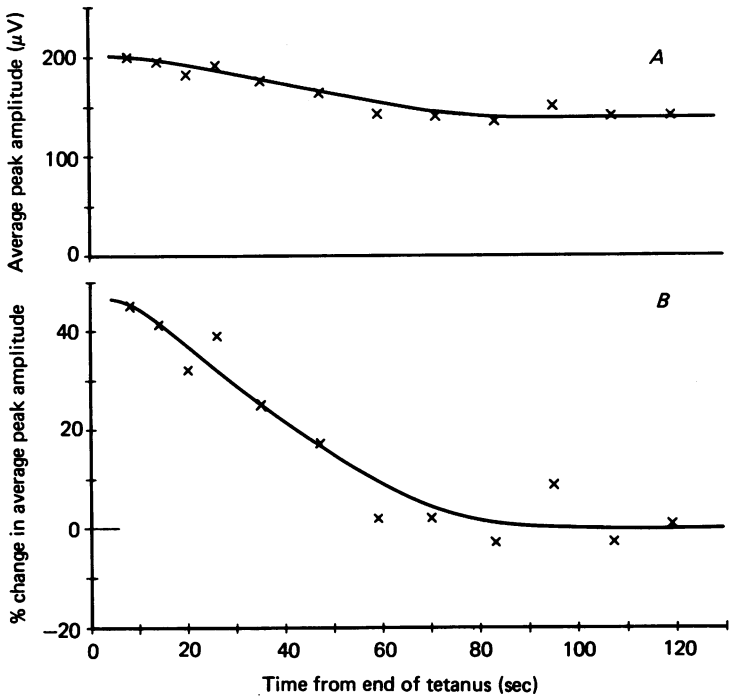

Fig. 2. *A* shows the peak amplitude of the e.p.s.p. illustrated in Fig. 1 at different times after the tetanus. The points are averages using all the responses recorded in the interval between two adjacent points for ten successive tetani. *B* is the same result as shown in *A*, but the post-tetanic potentiation is calculated as the percentage change in control amplitude.

their return to control values was somewhat slower than that of the Ia e.p.s.p.s. A part of the discrepancy between our results from single Ia e.p.s.p.s and data obtained from composite e.p.s.p.s may reflect contamination by the latter potentials. A small polysynaptic component would not be noticed in a composite e.p.s.p. supposedly generated only at group Ia synapses on the motoneurone. A composite Ia e.p.s.p. can contain unitary components which have times to peak greater than 2 msec (Burke, 1967).

Facilitation

The e.p.s.p. initiated by a pair of stimuli (separation 1 or 2 msec) was recorded from the same seventeen neurones following stimulation of the same nerve used for the

post-tetanic response. Again, in only a proportion of neurones was the amplitude of the second e.p.s.p. increased by prior stimulation; that is, on four occasions facilitation was not detected. In the cells where facilitation did occur the amplitude of the second e.p.s.p. was increased by between 10 and 31 % of the control value (an example is shown in Fig. 3). On one occasion (not included in the population of seventeen), the second of a pair of e.p.s.p.s was depressed in amplitude (by 30 % of its control value). The time course of decay of facilitation was not examined in these experiments.

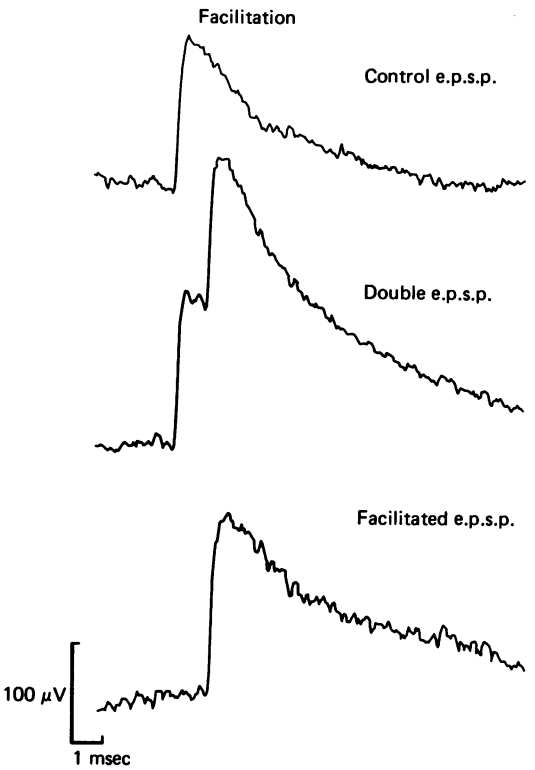

Fig. 3. Effect of paired stimuli on the amplitude of e.p.s.p.s. The average amplitude of 400 e.p.s.p.s is shown in the upper record. The average of a similar number of responses evoked by pairs of stimuli, separated by 1 msec, is shown in the middle record. The amplitude of the second of the pair of e.p.s.p.s is shown in the lower records. This was obtained by subtracting the upper record from the middle record. It can be seen that the amplitude of the second e.p.s.p. was slightly increased. Calibrations apply to each record.

Again these values for facilitation (mean 11 %) are less than values obtained from experiments on composite e.p.s.p.s (Curtis & Eccles, 1960) but are similar to the values reported by Kuno (1964) for unitary e.p.s.p.s.

Interaction between post-tetanic potentiation and facilitation

The relationship between peak potentiation and facilitation for the seventeen pairs of data is shown in Fig. 4. The e.p.s.p.s which showed the larger percentages of p.t.p. also gave evidence of their ability to facilitate. A test for a correlation between

facilitation and potentiation using a simple linear test showed that the correlation was only significant at the 10% level.

Our hypothesis for the mechanisms underlying facilitation and p.t.p. is that these phenomena occur primarily by a decrease in the probability of failure at some boutons which before the conditioning stimulus did not always release transmitter. In the generation of some e.p.s.p.s, the probability of releasing at least one unit of transmitter from a single bouton is one and this is not altered by the conditioning

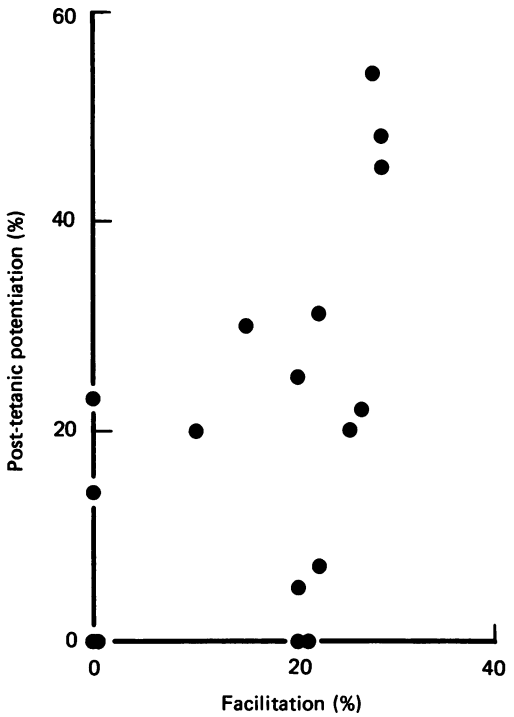

Fig. 4. Relationship between post-tetanic potentiation and facilitation of e.p.s.p.s. Each point shows the relationship between post-tetanic potentiation and facilitation of the same unitary e.p.s.p.; both are expressed as percentage increase over control. It can be seen that there is a tendency for an e.p.s.p. which shows facilitation also to show post-tetanic potentiation.

stimulus. Under these circumstances, the maximum conditioning which could be achieved would be to raise the probability to one of releasing transmitter at those boutons where this was not so before conditioning. If this were achieved by the tetanus no facilitation would occur during the period of p.t.p. and the two phenomena would be interdependent. If the release of one unit of transmitter at a single bouton was insufficient to saturate all post-synaptic receptors, maximum conditioning might not be achieved by the tetanus and less interdependence would be expected.

We examined the effects of a preceding tetanus on the ability of an e.p.s.p. to facilitate for each of the seventeen e.p.s.p.s studied (see Methods). In each case where an e.p.s.p. facilitated prior to the tetanus, the e.p.s.p. did not facilitate after the tetanus. An example is shown in Fig. 5. Before the tetanus, the second of the pair

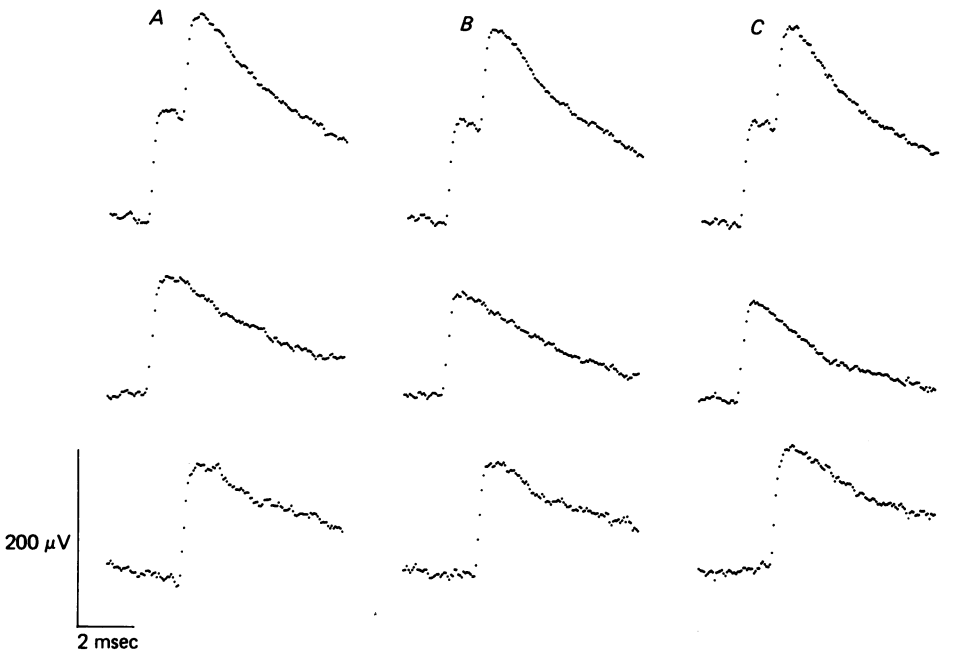

Fig. 5. Interaction between facilitation and post-tetanic potentiation. Columns *A*, *B* and *C* illustrate averaged responses recorded at various intervals after a tetanus. The records shown in column *A* were collected between 5 and 11 sec after the tetanus, *B* between 41 and 65 sec after tetanus and *C* between 90 and 125 sec after tetanus. Records in *C* were indistinguishable from control responses obtained prior to tetanus. In each column the upper record is the response produced by a pair of stimuli, the middle record is the response caused by a single stimulus and the lower record is the difference between these two. It can be seen that immediately after the tetanus (*A*) both the single e.p.s.p. and the second of the pair have similar amplitudes. As the effect of the tetanus wanes (*B*) the second e.p.s.p. of the pair begins to give evidence of facilitation. After the tetanus (*C*), p.t.p. is absent and the second e.p.s.p. of the pair is clearly facilitated. Data from this experiment are plotted in Fig. 6. Calibration bars apply to all records.

of e.p.s.p.s was facilitated by 20% to give a peak amplitude of 195 μV. After the tetanus, both the first and the second e.p.s.p.s evoked by a pair of stimuli were of the same amplitude, again 195 μV, i.e. facilitation no longer occurred. As the p.t.p. decreased after the tetanus facilitation of the second e.p.s.p. returned (see Fig. 6). Our interpretation of this result is that the increased effectiveness of transmission following either conditioning procedure results from a common mechanism.

Analysis of fluctuations

The procedures for statistical analysis of the fluctuations of an e.p.s.p., and the separation of its different components, have been fully described in Jack *et al.* (1981*a*). These same techniques have been used to examine the fluctuations of an e.p.s.p. at various times after a tetanus.

The results of this analysis on one e.p.s.p. which showed a maximum p.t.p. of 45% are shown in Fig. 7. The control e.p.s.p. (Fig. 7*C*) consisted of failures, and components at 95 μV and 205 μV. Over the period of 5–45 sec from the end of the

tetanus the pattern of fluctuations altered to that shown in Fig. 7*A*. Failures in the response disappeared, the probability of the component at 95 μV decreased and the probability of the larger component increased. As the effect of the tetanus diminished (in the period 33–78 sec after the tetanus) the fluctuation pattern (Fig. 7*B*) became intermediate to the control pattern and the pattern shown in Fig. 7*A*. The calculated

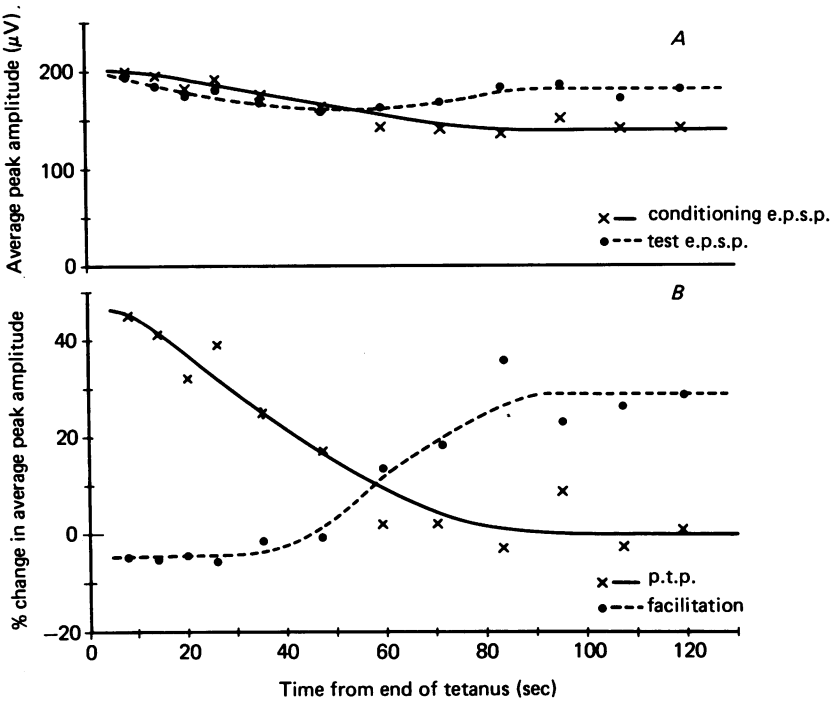

Fig. 6. The crosses in *A* show the peak amplitude of the e.p.s.p. illustrated in Fig. 5 at different times after a tetanus. This result is the same as that shown in Fig. 2*A*. The circles in *A* indicate the peak amplitude of the second of two e.p.s.p.s in response to a paired stimulus with 1 msec separation, at different times after a tetanus. This peak amplitude was obtained by subtracting the averaged response to a single stimulus, as shown in Fig. 5. The averages were obtained from all evoked responses in the interval between adjacent points in the responses to ten successive tetani. *B* shows the percentage change in both the single e.p.s.p. and the test e.p.s.p., based on the control amplitude of the single (conditioning) e.p.s.p. The crosses show p.t.p. and the circles indicate facilitation.

magnitude of the second component is least reliable in the control e.p.s.p., because there it has the smallest probability. A small bias in the sample of peak voltages used in calculating Fig. 7*C* could account for the apparent shift in the magnitude of this component.

The calculations for Fig 7*A* and *B* were made on data collected over a period in which the average amplitude of the e.p.s.p. was decreasing, especially for Fig. 7*A*. It was necessary to extend the calculation over these periods to obtain a sufficiently large sample size (800) even though the responses to ten periods of tetanization have been combined to obtain this result. Because the e.p.s.p. decreased in amplitude over the 5–45 sec period used in Fig. 7*A*, the component probabilities will be averaged.

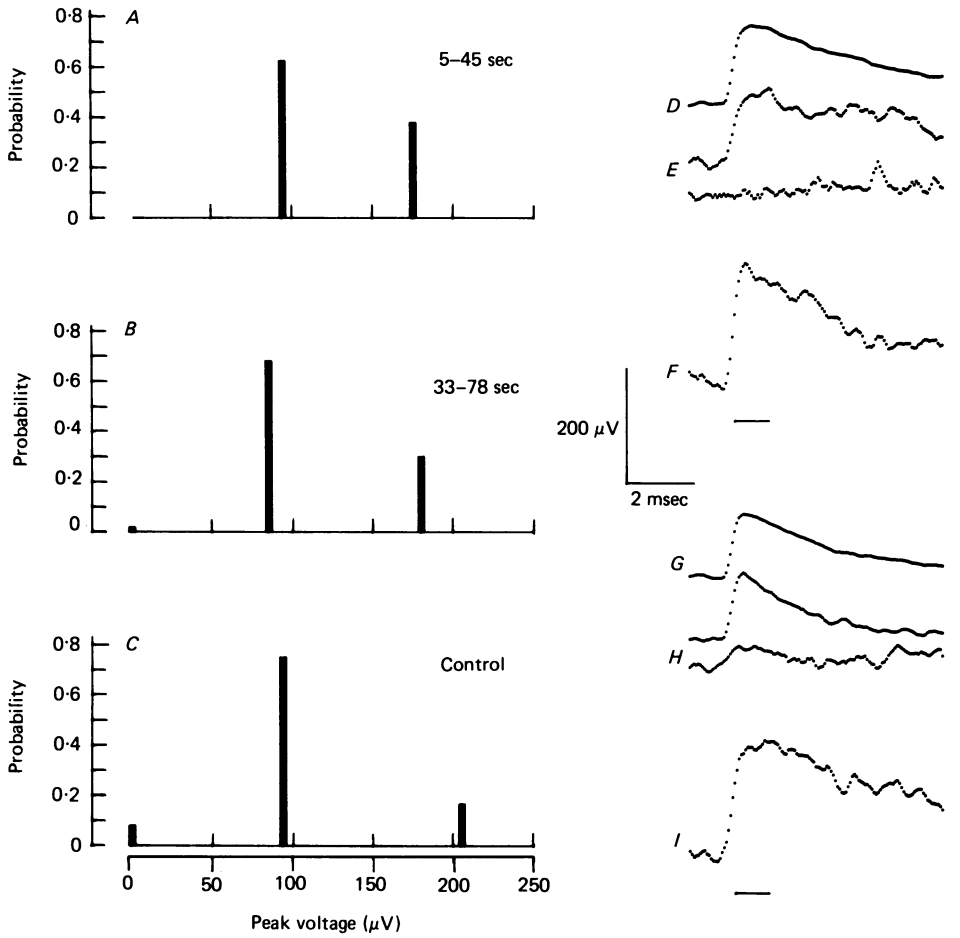

Fig. 7. *A* and *B* are the calculated patterns of fluctuation of an e.p.s.p. in the periods 5–45 sec, and 33–78 sec respectively (measured from the end of the tetanus). *C* is the calculated pattern of fluctuations in the control e.p.s.p. (before the tetanus). 800 responses were used in each peak voltage histogram of the evoked e.p.s.p. The peak voltage was calculated over a 1 msec interval, shown by the bar below *F* and *I*. *D* is the average time course of all evoked responses in the period 5–45 sec. *E* is the average time course of the smaller component in *A*, and (below it) the standard deviation time course (about the mean) of this component. Evoked responses with peak voltages in the range -125 to $-5\ \mu V$ (forty-eight) were used to obtain these averages. *F* is the average time course of the larger component in *A*; calculated from 158 evoked responses with peak voltages in the range 195–415 μV. *G* is the average time course of all evoked responses in the control e.p.s.p. It has two components and *H* is the average time course of the smaller component. Below it is the standard deviation time course (about the mean) of this component. Both averages were calculated from evoked responses (300) with peak voltages in the range $-205\ \mu V$ to 75 μV. *I* is the average time course of the larger component, calculated from 118 evoked responses with peak voltages in the range 195–295 μV.

Thus in the period 5–10 sec after the tetanus, the probabilities of these components would have been 0·27 (95 μV) and 0·73 (175 μV) to allow for 45% p.t.p. To ensure that no change occurred in the magnitude of each component during the period of analysis, and that the two components do not represent the average amplitudes of components with varying amplitudes, it is necessary to calculate the mean and standard deviation time courses for these components (Jack *et al.* 1981*a*). Fig. 7*E* shows the time course of the mean and standard deviation of the smaller component in Fig. 7*A*, while 7*F* is the average time course of the larger component. (The standard deviation time course for the larger component could not be calculated as there was no peak voltage range which did not contain contributions from both components.) There is no detectable variability about the mean of the smaller component. This establishes that this component is in fact a single component rather than an amalgamation of a continuum of components. Furthermore, the absence of variability indicates that this component does not alter its peak amplitude throughout the period of analysis.

A similar result was obtained for the mean and standard deviation time courses of the components in Fig. 7*B*. The time courses of the two components in the control response are shown in Fig. 7*H* and *I*. Responses with peak voltages between -205 μV and 75 μV were used to obtain the mean and standard deviation of the smaller component. It can be seen from Fig. 7*C* that some of these responses would have been failures. The standard deviation (corrected for noise variability) indicates that more than one component contributes responses in this range. Its peak value of 33 μV is consistent with 37 μV predicted from the result shown in Fig. 7*C* for the voltage range -205 μV to 75 μV. In this range the probability of a response being a failure is 0·19 and the probability of a response being the smaller component is 0·81.

Our interpretation of the results illustrated in Fig. 7 is that the smaller component of the e.p.s.p. is the same in each period of analysis, as is the larger component. The increase in amplitude of the e.p.s.p. after the tetanus is due to an increase in the probability of occurrence of the larger component, a decrease in the probability of the smaller component, and the disappearance of failures as possible responses. The gradual recovery of the averaged amplitude of the e.p.s.p. to its control amplitude occurs by a gradual alteration of these probabilities and a reappearance of failures in the evoked responses. There is no evidence for an alteration in the magnitude of each component.

The average time courses of the two components shown in Fig. 7*E* and *F* appears to be different from the time courses of the corresponding components in Fig. 7*H* and *I*. However, the amount of correction for noise bias (Jack *et al.* 1981*a*) which is required to extract these e.p.s.p. time courses is so great that little confidence can be placed in these apparent differences.

The analysis of fluctuations in peak voltage was applied to two other e.p.s.p.s where a sufficient number of sets of responses to successive tetani allowed reliable statistical analysis. The results of these two e.p.s.p.s are summarized in Table 1. One e.p.s.p. showed no variability in peak amplitude before the tetanus. It did not potentiate, nor did its peak amplitude fluctuate after the tetanus. A second e.p.s.p. consisted of failures and one component under control conditions. After the tetanus the failures disappeared from the responses, the probability of the larger component (90 μV)

increased and a new component (190 μV) appeared. The increment between these two components is similar in magnitude to the first components. These changes are consistent with those described in Fig. 7.

At the beginning of this investigation we used the voltage–time integral of the e.p.s.p. (evoked charge) in the analysis of fluctuations, as was done by Edwards, Redman & Walmsley (1976*a*, *b*). It was shown by Jack *et al.* (1981*a*) that peak voltage obtained by integrating the e.p.s.p. only over the period enclosing its peak voltage gives better resolution of fluctuations than does charge. Only the charge associated with individual responses was retained for thirteen different e.p.s.p.s analysed at an earlier stage of this investigation. The analysis of fluctuations using charge gave results consistent with those described above, but they have not been included as they are less reliable.

TABLE 1. Analysis of fluctuations in peak voltage of two e.p.s.p.s

		Control		After tetanus (5–45 sec)	
E.p.s.p.	Max. % p.t.p.	Peak voltage (V)	Prob.	Peak voltage (V)	Prob.
1	0	150	1	150	1
2	54	0	0·22		
		90	0·78	90	0·82
				190	0·18

When two e.p.s.p.s were evoked with an interval of 1 msec separating the two stimuli the analysis of fluctuations in the peak amplitude of the second e.p.s.p. was not reliable. If the noise records are used as base line for individual responses of the test e.p.s.p., the calculated noise-free fluctuation pattern for the test e.p.s.p. is compounded by the fluctuations in the conditioning e.p.s.p. at the time when the peak of the test e.p.s.p. occurs. If it could be shown that the fluctuations in peak voltage of the conditioning e.p.s.p. were statistically independent of the fluctuations in the peak voltage of the test e.p.s.p., then it might be possible to separate this compound fluctuation pattern, and obtain the fluctuation pattern of the test e.p.s.p. alone. But it is not even possible to calculate the correlation between the noise-free peak voltages of the conditioning and test e.p.s.p.s, as this calculation requires the standard deviation of the fluctuations of the test e.p.s.p. Also the noise which adds to these two peak responses is strongly correlated. We would not expect the two peak voltages to fluctuate independently.

Another approach was to select those conditioning e.p.s.p.s which had peak voltages which could be reliably associated with a particular component, and then to assume that the average of that component's time course could be used to calculate a base line for the second e.p.s.p. By this means a set of conditional probabilities could be calculated. The difficulties with this approach were that responses associated with a particular component could not be selected reliably for all components of an e.p.s.p., and for those that could be selected usually a very small sample size was obtained. For these reasons we are unable to report any details on fluctuations of the test e.p.s.p.

DISCUSSION

The synaptic potential evoked by an impulse in some single group Ia afferents can be increased by a prior tetanus or by a single conditioning stimulus. It is important to note that other group Ia e.p.s.p.s are not increased by these conditioning stimuli. The ability of an e.p.s.p. to facilitate was correlated with its ability to show p.t.p. Futher evidence of the inter-relationship between the synaptic mechanisms for generating p.t.p. and facilitation came from an experiment in which the ability of an e.p.s.p. to facilitate was altered by a prior tetanus. If the first of two evoked e.p.s.p.s was smaller than the second before a tetanus, it became the same size as the second e.p.s.p. after the tetanus. That is, whenever p.t.p. occurred, any pre-tetanus facilitation was removed. These results contrast with the results of a similar experiment at the neuromuscular junction (Landau *et al.* 1973) and suggest that at Ia synapses both p.t.p. and facilitation share a common mechanism. This could be an increased probability of transmission at the same boutons.

Where p.t.p. occurred, the e.p.s.p. consisted of several components. These components maintained the same amplitude throughout the post-tetanus period. The amplitude increase in the potentiated e.p.s.p. resulted from an increased probability of occurrence of components with larger peak amplitudes and a decreased probability of occurrence of components with smaller peak amplitudes.

This mechanism is consistent with our hypothesis that at a single bouton transmission occurs in an all-or-nothing manner caused by receptor saturation when transmitter is released. The different components of an e.p.s.p. are generated when transmission occurs at different numbers of boutons (Jack *et al.* 1981*a*, *b*). It may be that a decreased probability of failure to release transmitter following a conditioning stimulus is accompanied by an increased probability of multi-quantal release, such as occurs at peripheral synapses (Martin, 1977). However, receptor saturation would prevent such an increase being detected post-synaptically.

For the e.p.s.p. which did not facilitate nor show any p.t.p. (*1, Table 1) the simplest explanation is that there were no failures at the bouton(s) involved in transmission either before or after the conditioning stimuli, and that at least one quantum of transmitter was released per impulse both before and after the conditioning stimulation. This quantum is sufficient to saturate the available receptors. The simplest explanation for e.p.s.p. *2 (Table 1) and for the result in Fig. 7 is that two boutons were involved in generating the potentiated e.p.s.p. The conditioning stimulus decreased the probability of failure at one or both boutons. Also, the occlusion regularly observed between p.t.p. and facilitation indicates that any decrease in the probability of failure to release transmitter by a tetanus is not further decreased by a subsequent conditioning stimulus.

It has been suggested that failure to release transmitter at a bouton was due to a failure of the impulse to propagate into that bouton (Edwards *et al.* 1976*b*; Redman, 1979). If this was correct, p.t.p. would result from an increased likelihood of impulse invasion following the tetanus (Lüscher, Ruenzel & Henneman, 1979). The absence of detectable latency fluctuations in the components of an e.p.s.p. (Jack *et al.* 1981*a*) suggests that this proposal is an unlikely explanation.

In an earlier investigation on facilitation and p.t.p. of group Ia e.p.s.p.s evoked by impulses in single afferents, Kuno (1964) applied classical quantal analysis to the

fluctuations of the e.p.s.p. before and after conditioning stimuli. Assuming that the fluctuations followed Poisson statistics, this analysis showed that after a tetanus the probability of failures decreased but the unit e.p.s.p. size remained constant. A similar result was found for the facilitated e.p.s.p. in a paired stimulus. Although the results presented here, and by Jack *et al.* (1981*a*, *b*), cannot be interpreted in terms of the classical quantal release hypothesis there are similarities to Kuno's results. If the unit e.p.s.p. of quantal analysis becomes the incremental e.p.s.p. between components in this analysis, and if the probability of failure is not used to obtain the average quantal content (m), then the explanations given by Kuno for the increase in magnitude of a conditioned e.p.s.p. are essentially the same as those given in this paper.

Although a corresponding analysis of fluctuations was not possible for the test e.p.s.p. in a conditioning-test pair, the common basis for facilitation and p.t.p. suggests that the increase in magnitude of the test e.p.s.p. may also involve an increased probability of transmission at boutons which did not always transmit before the conditioning stimulus.

These results support the suggestion that transmission at a single bouton consists of either a constant amplitude e.p.s.p. or a failure. To be more convincing, it will be necessary to identify the boutons involved in generating the potentiated e.p.s.p. Further evidence for the mechanisms of transmission at a single bouton has been obtained from an investigation into the effects of 4-aminopyridine on the fluctuations of e.p.s.p.s, given in the following paper (Jack *et al.* 1981*b*).

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