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EARLY FACILITATION AT CORTICOMOTONEURONAL SYNAPSES

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SUMMARY

1. Corticomotoneuronal EPSPs have been generated in lumbar motoneurones of the monkey by single and paired corticospinal volleys. The facilitation of the second of a pair of EPSPs with respect to the size of the first has been measured.

2. The relationship between the degree of facilitation of the second response and the interval between the two volleys has been studied. Average facilitation of minimal EPSPs was found to be maximal about 2 msec after the arrival of the corticospinal volley and to decay roughly exponentially thereafter with a time constant of about 10 msec.

3. The degree of facilitation varied from one minimal corticomotoneuronal EPSP to another but this facilitation was not statistically correlated with the time course of the individual EPSPs.

4. Significant facilitation (0·4) was still present 10 msec after a corticospinal volley so that this phenomenon could play a part in the initiation of motoneuronal discharge by corticospinal activity at natural frequencies of the order of 100 impulses/sec.

INTRODUCTION

In 1962, Landgren, Phillips & Porter described the growth of excitatory post-synaptic potentials (EPSPs) which occurred in spinal motoneurones of the baboon when the motor cortex was stimulated with repetitive shocks at 200 c/s. The increased response to successive shocks was not accounted for by recruitment of pyramidal neurones at the site of cortical stimulation because the amplitude of the compound action potential in the pyramidal tract remained constant for each stimulus in the train. Thus it was concluded that the increasing size of the EPSPs produced by successive volleys resulted from an increased transmitting potency at the corticomotoneuronal synapses. Facilitation of this sort has been reported

subsequently for the cortical excitation of reticular neurones (Willis & Magni, 1964) and of cells in the red nucleus (Tsukahara & Kosaka, 1968).

Some of the synapses of group I afferent fibres in the spinal cord have also been reported to demonstrate facilitation with high frequency stimulation (Eccles, Hubbard & Oscarsson, 1961). However depression of synaptic responses produced by high frequency stimulation of group I afferents is more usually observed in spinal motoneurones of cats (Lloyd, 1957; Lloyd & Wilson, 1957; Curtis & Eccles, 1960). Moreover, Phillips & Porter (1964) demonstrated no facilitation of EPSPs produced by group I fibre stimulation in the same individual spinal motoneurones of the baboon for which marked facilitation of corticomotoneuronal EPSPs was evident.

A definitive study of facilitation requires that the responses produced by repetitive discharge in single fibres be analysed to assess the influence of changes in sensitivity of the post-synaptic membrane or in the output of transmitter from the presynaptic terminals. Kuno (1964) performed such an analysis on the 'unit' EPSPs produced in spinal motoneurones by activity in single group I afferent fibres. In contrast to the findings of Curtis & Eccles (1960) on large composite EPSPs, he demonstrated that paired stimuli applied to the afferent fibre usually produced some facilitation of the second EPSP when the interval between the stimuli was short (4–10 msec) and he concluded that this early facilitation was due to an increased probability of occurrence of the individual components of the EPSP. Even at these short intervals the average facilitation was small (about 20 %).

The use of electrical stimulation of the cerebral cortex in the experiments on corticomotoneuronal EPSPs made it impossible to limit the study to repetitive activity in single corticomotoneuronal fibres. Nevertheless, many of the minimal monosynaptic EPSPs produced in lumbar motoneurones of the monkey by single cortical shocks were similar in size to spontaneously occurring unit EPSPs and could be produced in an all-or-nothing manner (Porter & Hore, 1969). These minimal responses to synchronous pyramidal tract volleys seemed suitable for investigation of the early facilitation of corticomotoneuronal EPSPs. Computer averaging of the responses was required in order to make reliable measurements of the small responses in the presence of physiological and physical noise.

METHODS

Six cynomolgus monkeys (*Macacus fascicularis*) were used in these experiments. The animals were anaesthetized with pentobarbitone sodium (Sagatal, May & Baker Ltd.) in a dose of 30 mg/kg administered intraperitoneally, and were maintained in a lightly anaesthetized state with intermittent intravenous doses of 3 mg/kg as required. A tracheal cannula was inserted, and venous and arterial

catheters were fixed in the right femoral vessels for administration of drugs and for continuous recording of arterial blood pressure.

The right cerebral hemisphere was exposed through a small craniotomy overlying the 'leg' motor area. This region of cortex was explored with a focal stimulating electrode through which brief bursts of surface anodal shocks (0·2 msec duration) at 400/sec were applied in order to locate the motor point from which flexion of the contralateral hind limb digits was obtained with the weakest stimuli. The vascular landmarks and the stereotaxic co-ordinates of this lowest threshold motor point were recorded and all subsequent cortical stimulation was delivered at this same locus.

A lumbar laminectomy was performed and dissection of nerves in the left hind limb was carried out to denervate the limb muscles and to prepare the nerve to flexor digitorum longus muscle for electrical stimulation. This nerve was frequently separated into a number of filaments and these filaments were all stimulated either singly or together.

The spinal cord was explored with capillary micro-electrodes filled with 3 M-KCl while electrical stimulation of the nerve to flexor digitorum longus (FDL) was being delivered above threshold for the motor fibres in the nerve and at a rate of 2 or 5/sec. It was sometimes very difficult to locate the motor nucleus of this muscle and a prolonged search for the field potential generated by antidromic stimulation of the motor nerve was necessary. Once the pool of motoneurones was located, attempts were made to obtain stable intracellular recordings from FDL motoneurones. At this stage an open pneumothorax was produced on both sides of the animal's chest and artificial ventilation at high rate (60/sec) and small volume was instituted in an attempt to reduce the movements of the spinal cord.

Motoneurones were identified by the antidromic spikes produced in them following stimulation of the FDL nerve. Each motoneurone so located was then examined to detect its responses to single and paired stimuli applied at the rate of 1/sec to the motor point on the cerebral cortex. Simultaneously with the recording of the transmembrane potential changes produced in the motoneurone, a pair of electrodes on the dorsum of the spinal cord at the level of insertion of the micro-electrode detected the volley of impulses conducted in corticospinal fibres to this level. Only those intracellular responses which were unequivocally due to D waves (Patton & Amassian, 1954) in the corticospinal volley without any later I waves were subjected to further study. In addition to photography of these responses displayed on a Tektronix 565 oscilloscope, recordings on magnetic tape were made of the corticospinal volley, the prevailing membrane potential of the cell and the EPSPs evoked by single or paired electrical stimuli applied to the motor point on the cerebral cortex. These responses were subsequently averaged using a special purpose computer (Biomac 1000, Data Laboratories Ltd.). The average amplitude of the EPSP produced by a single corticospinal volley was compared with the average amplitude of the EPSP produced by the second of a pair of corticospinal volleys separated in time by an interval which could be varied from 1 to 30 msec.

Throughout the experiment the animal's body temperature and the temperature of the pools of mineral oil covering the cerebral cortex, the spinal cord and the leg nerves were kept between 36 and 38 °C by means of heating units controlled by thermosensitive probes. The animal's mean blood pressure was maintained above 80 mm Hg by intravenous infusion of Dextran as required and was usually kept at about 100 mm Hg.

RESULTS

Observations have been made on thirty cells innervating the flexor digitorum longus muscle. All these observations were obtained in cells with stable membrane potentials of 60 mV or more and all the corticomotoneuronal EPSPs were produced by pyramidal tract volleys consisting of D waves without the complication of effects from later volleys. The relationship of the amplitude of a typical minimal corticomotoneuronal EPSP to the amplitude of spontaneously occurring EPSPs is indicated in Fig. 1*B* and *C* where some spontaneous EPSPs have occurred during

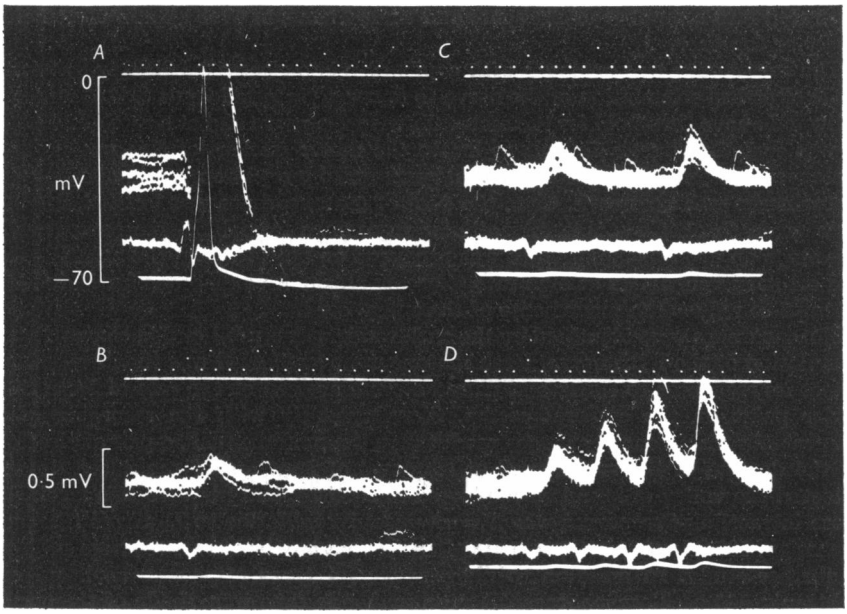

Fig. 1. Superimposed records of the responses of an FDL motoneurone. In each frame the top trace indicates time in msec and also serves as a voltage reference for the bottom trace which records at low gain the potential at the tip of the intracellular micro-electrode. The second trace is a high amplification record of the transmembrane potential and the third trace is a record of the potential difference between two points on the dorsum of the cord at the point of insertion of the micro-electrode. Frame *A*: the antidromic spike produced by a stimulus applied to the FDL nerve at the time of the first time mark is shown in the bottom trace. Frame *B*: the EPSP produced by a single shock to the cerebral cortex is shown in the second trace while the corticospinal volley produced by this shock is seen on the third trace. Frame *C*: the EPSP responses produced by paired corticospinal volleys separated by 10 msec, showing some facilitation of the second response. Frame *D*: facilitation of the EPSPs produced by four corticospinal volleys at a frequency of about 300/sec. Scales: 0 and −70 mV for bottom trace, 0·5 mV for second trace.

the photography of the superimposed corticomotoneuronal EPSPs produced by single and by paired corticospinal volleys (recorded in the third trace of each frame). Frame *A* of Fig. 1 illustrates the antidromic spike produced in the motoneurone by electrical stimulation of the FDL nerve (lowest trace). In the subsequent frames are displayed, from above downwards, a time scale (msec) and zero voltage reference, a highly amplified record of the potential changes produced across the cell membrane in response to cortical shocks, a record of the corticospinal volley registered on the surface of the spinal cord at the level of the micro-electrode penetration and a low gain DC record of the potential at the electrode tip. All the frames are superimposed recordings of twenty observations. Frame D gives a clear indication of the degree of facilitation produced by a train of four corticospinal volleys at about 300/sec, but it also indicates that some changes in the amplitude and time course of the D waves often occurred in such responses. Accordingly the paired shock technique illustrated in Fig. 1*C* was considered to be more useful in assessing facilitation and both the corticospinal volleys and the EPSPs were averaged for paired shocks at different intervals.

The facilitation produced by a corticospinal volley was measured by the increase in amplitude of a test EPSP produced by a preceding volley. The method is illustrated in Fig. 2. Each trace in the Figure is the average of sixty-four responses to cortical stimulation. Trace *C* is the average corticospinal tract response to paired cortical stimuli, S_1 and S_2, separated by an interval t. Trace *B* is the average EPSP in the test cell produced by the first volley alone and trace *A* is the average response of the cell to the paired volleys. Facilitation was calculated by measuring the difference in amplitude of the pair of EPSPs ($v_1 - v_0$) and expressing this as a decimal fraction (f) of the control amplitude, v_0.

It was necessary to consider only the amplitude of the two peaks because the wave form of the second EPSP sometimes differed from that of the first. As has already been reported (Landgren *et al.* 1962), corticospinal volleys are able to produce inhibitory actions on spinal motoneurones and frequently the later components of the synaptic response to repetitive cortical shocks were distorted by inhibitory events. This phenomenon was seen in some of the observations using paired cortical stimuli and Fig. 2 provides an example of an inhibitory influence on the decaying phase of the second EPSP.

For each of the corticomotoneuronal EPSPs the relationship between facilitation and the interval between the corticospinal volleys was studied. An example is shown in Fig. 3. The upper trace (*A*) of the Figure is the average EPSP produced by the single corticospinal volley illustrated in the averaged record *B*. The facilitation of this EPSP observed in the

responses to a second identical corticospinal volley arriving at different intervals after the volley seen in *B* is plotted on the lower graph. It is seen that at short intervals (2–5 msec) the facilitation is greater than at longer intervals (6–15 msec).

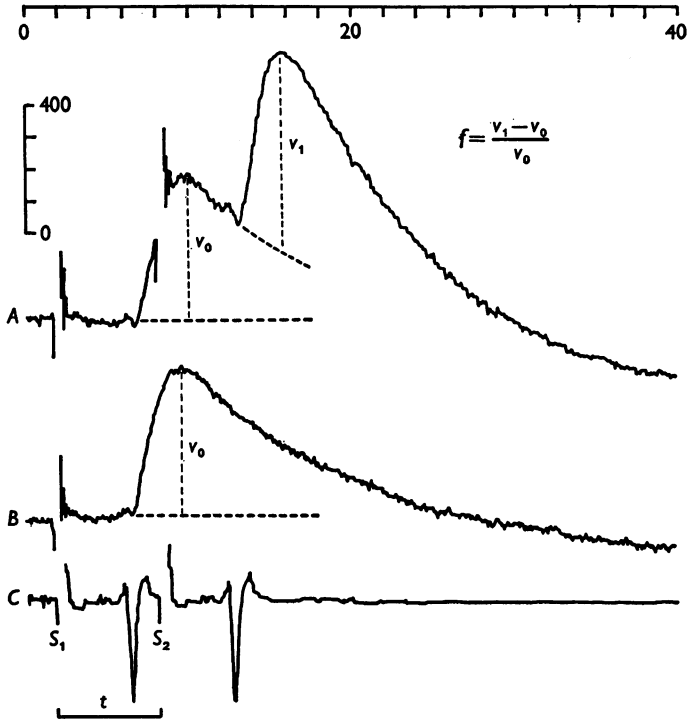

Fig. 2. Averaged EPSPs produced by single and paired cortical shocks. The Figure is redrawn from Fig. 6 of Porter & Hore (1969) to indicate the method of measuring facilitation (f) at an interval (t) between two cortical stimuli (S_1 and S_2). *A* indicates the average response of the cell to sixty-four applications of the paired stimuli at a rate of 1/sec. *B* indicates the average response of the cell to sixty-four applications of S_1 alone and *C* is the average corticospinal volley recorded simultaneously with the registration of *A*.

Facilitation:

$$f = \frac{v_1 - v_0}{v_0}.$$

Because of the necessity to average a large number of separate responses at any interval, only a few intervals could be examined in any one cell. Control observations of the responses to single cortical shocks were made between each set of observations for paired shocks and it was necessary to have stable intracellular recording for about an hour in order to make the series of observations in Fig. 3. In many cells fewer intervals could be

tested before the cell was 'lost' or the membrane potential fell below 60 mV. Nevertheless, as has been reported by Porter & Hore (1969), in all the cells examined, facilitation of minimal corticomotoneuronal EPSPs was observed and this facilitation was greater at short intervals (less than 10 msec) than at longer intervals.

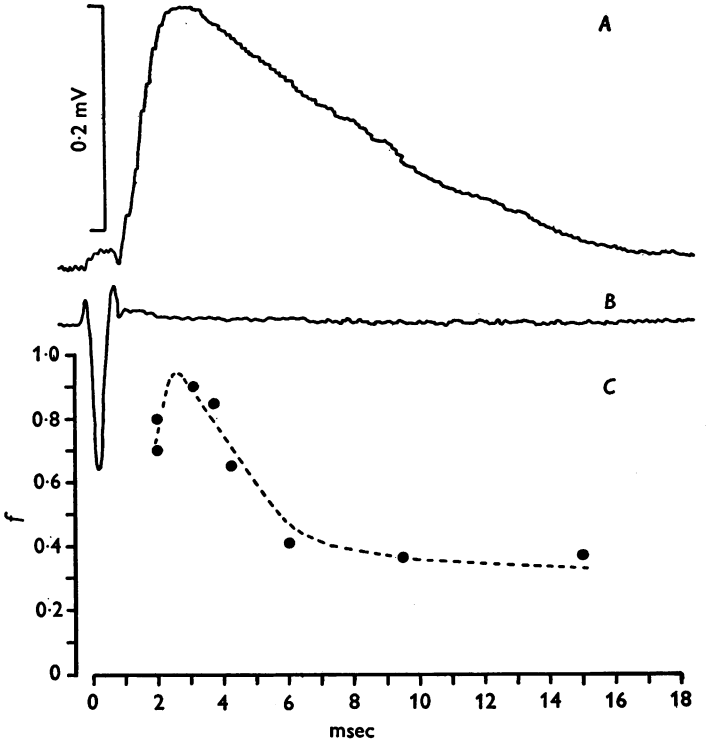

Fig. 3. *A:* the average EPSP produced in an FDL motoneurone by the corticospinal volley simultaneously recorded in *B*. *C:* on the same time scale is plotted the average facilitation (*f*) of this EPSP revealed by a second identical volley reaching the spinal cord at various intervals after the arrival of the first volley shown in *B*. The facilitation is greatest 2–4 msec after the arrival of the first volley and thereafter declines.

The degree of facilitation varied from one corticomotoneuronal EPSP to another, but this could have been a consequence of different presynaptic fibres involved or of different properties of the individual cells in which the responses were recorded because only one minimal EPSP was investigated in each cell. In Fig. 4 are illustrated the facilitation curves for seven corticomotoneuronal EPSPs recorded in different FDL motoneurones in a single experiment. In each case a number of different intervals between the paired corticospinal volleys were tested. In those five curves which

showed a peak, the degree of the facilitation varied (from 0·6 to 1·3) but the time at which the maximal facilitation was reached was usually less than 5 msec and in three cases was probably about 2–3 msec after the conditioning corticospinal volley. Similar observations have been made for the cells in all the other experiments.

When all the observations on the relationship between facilitation and interval were assembled together either for a single experiment or for all six experiments, very wide scatter of the points resulted. The scatter was

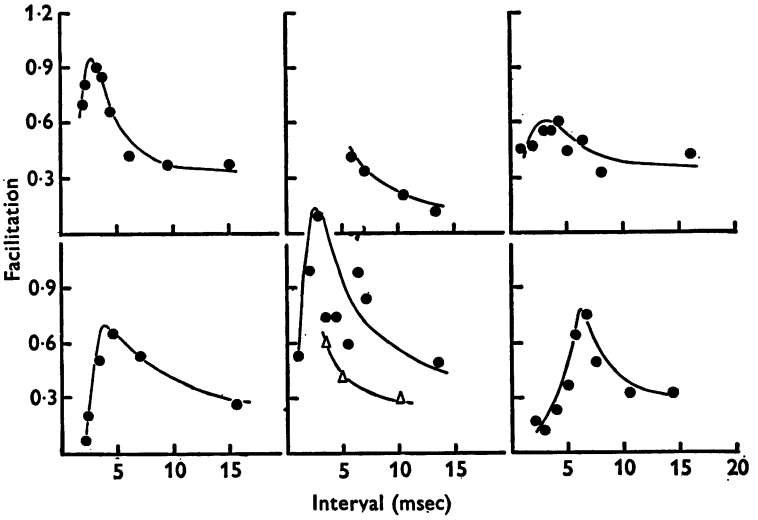

Fig. 4. The time course of facilitation of corticomotoneuronal EPSPs in seven cells recorded in a single experiment (in the lower middle graph the responses of two cells are plotted separately).

contributed to by the differences referred to above. Yet the over-all results of individual experiments accorded well with one another. Hence the linear regression line which described all the observations made in the experiment from which the examples in Fig. 4 were drawn was calculated and the observations were fitted by the relationship $f = 0{\cdot}74 - 0{\cdot}03\,t$. Exactly the same relationship was found for the pooled observations from all the experiments. Hence the findings were consistent from one experiment to another.

The curves plotted in Fig. 4 reveal that there is not a linear relationship between facilitation and the interval between the presynaptic volleys. It was consistently observed that at very brief intervals (0·5 and 1 msec) the facilitation was less than at intervals of 2–5 msec. A possible explanation may have been the obvious reduction in amplitude of the second corticospinal volley which occurred with paired stimuli at less than

2 msec interval, some of the fibres responsible for production of the second response being refractory when the second shock was applied to the cortex. But it is noteworthy that, even with such a reduction in amplitude of the volley, significant facilitation was often produced even at intervals of 1 msec and less.

While realizing that there were individual differences in the facilitation of corticomotoneuronal EPSPs for different cells, an attempt has been made to assess the average time course of the facilitation in the pooled

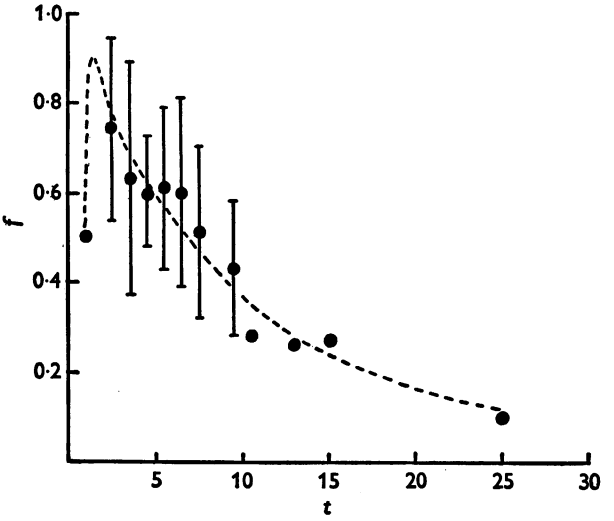

Fig. 5. The average time course of facilitation of corticomotoneuronal EPSPs in thirty FDL motoneurones recorded in six experiments.

results by lumping the observations about twelve separate time intervals and averaging the facilitation produced in each of the cells about these intervals. The result of this averaging is indicated in Fig. 5. For those intervals where five or more observations were averaged both the mean and the standard deviation are plotted. The interrupted curve has been fitted by eye after assuming a peak value at an interval of about 2 msec. When the average values were plotted on a semi-logarithmic scale they could be fitted by a line indicating an exponential decay of facilitation with a time constant of 10·5 msec.

The EPSPs examined in this work varied in wave form suggesting that they were generated on different parts of the soma-dendritic membrane of cells with different time constants. The range of different wave forms of the EPSPs is indicated in Fig. 6 which plots the rise time and half width of each of the corticomotoneuronal EPSPs about the line derived by Rall (1967) for the relationship between these two shape indices for a model

cat motoneurone with a time constant of 5 msec and sites of transmitter action at different distances from the intrasomatic recording electrode. Because of this variety of EPSP wave forms it was important to consider whether or not some of the variation in degree or time course of the facilitation was related to the shape indices of the EPSP and hence to possible post-synaptic factors.

Some of the results seemed to indicate a positive correlation between the maximal facilitation observed for an EPSP and its time course. Thus

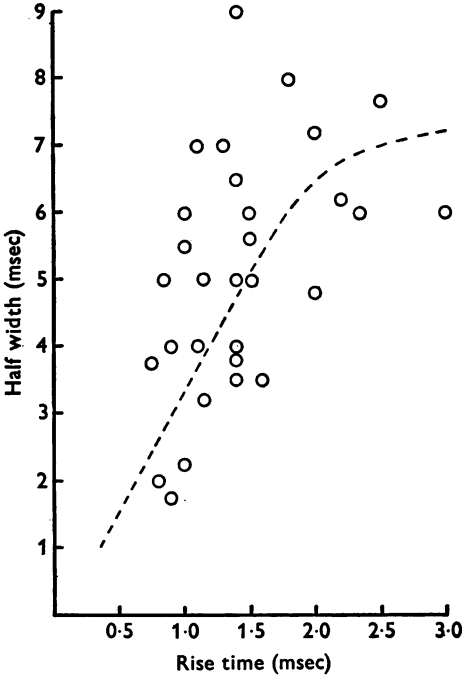

Fig. 6. The relationship between rise time and half width for each of the minimal corticomotoneuronal EPSPs.

the maximal facilitation recorded for some of the slowly rising and slowly decaying EPSPs was greater than that for some of the rapidly rising and rapidly decaying EPSPs. A similar tendency is indicated in the responses illustrated in Fig. 4 of Landgren *et al.* (1962). However, when the relationship was tested statistically for those sets of observations in which a clear maximal facilitation was observed this positive correlation was present but not significant. Moreover, there was no statistically significant correlation between the interval at which maximal facilitation was reached and the shape indices of the EPSPs even though the facilitation of some of the more slowly rising and decaying responses reached its peak later than that of some of the more rapidly rising synaptic potentials.

DISCUSSION

If a constant time course of transmitter action is assumed, it may be reasoned that the corticomotoneuronal synapses in the lumbar spinal cord of monkeys are situated on peripheral regions of the dendritic processes (Porter & Hore, 1969). At these sites, pronounced facilitation of EPSPs is produced by repetitive activity in corticospinal fibres. Phillips & Porter (1964) considered that this pronounced facilitation might be of significance in the initiation of motoneuronal discharge by pyramidal cells in the motor cortex because it had been observed (Phillips, 1956; Hern, Phillips & Porter, 1962) that stimulation of the motor cortex with shocks adequate to produce movement resulted in bursts of high frequency discharge in pyramidal tract units. Frequencies up to 500 impulses/sec were commonly produced. These would be particularly effective in producing facilitation.

Evarts (1968) has recorded the behaviour of single cortical cells whose discharge was associated with the beginning of limb movements in monkeys. His experiments indicated that the peak frequencies of firing of these cells were generally lower than the frequencies which had been used to demonstrate marked facilitation. Only one out of thirty-one pyramidal tract neurones showed a frequency higher than 100/sec and the majority produced bursts of 80–100 impulses/sec in relation to the development of flexor or extensor muscle contractions. It was therefore of some interest to measure the time course of facilitation and to discover whether this might have a significant role in initiation of motoneuronal discharge at the frequencies of pyramidal tract activity which occurred naturally.

It has not been possible to examine facilitation in the responses produced by activity in single corticomotoneuronal fibres. Nevertheless, a serious attempt has been made to examine minimal responses and to exclude influences which could have resulted from recruitment of additional pyramidal cells or of interneuronal discharge. The results have indicated that, in spite of individual differences in the wave form of the EPSPs, in the degree of facilitation and in the timing of this facilitation, an average behaviour could be defined. This average response indicates that maximal facilitation is produced by corticomotoneuronal discharges separated by brief intervals (2–5 msec) but that significant facilitation (0·4) is still present at longer intervals such as those which would result from the natural discharge of a cortical cell at 100 impulses/sec. Thus it is possible that early facilitation may play a part in the initiation of motoneuronal discharge by cortical activity even at the frequencies of pyramidal cell discharge recorded by Evarts (1968).

The facilitation measured for these synapses with the motoneurone is much more marked than that seen for the group IA excitatory synapses.

Indeed Curtis & Eccles (1960) recorded only a 'relative' facilitation (with respect to behaviour at intervals of 100 msec) of such synapses by high frequency stimulation. Kuno (1964) on the other hand, found facilitation of unit EPSPs in all but one of his experiments when the stimulus intervals were between 4 and 10 msec. The difference between Kuno's results and those reported here for corticomotoneuronal synapses would seem to be one of the degree of facilitation produced. The average facilitation at brief intervals in Kuno's experiments was 0·2 compared with an average of 0·74 at similar intervals in the present study.

In situations such as the amphibian neuromuscular junction where the process of facilitation has been subjected to extensive investigation, a presynaptic mechanism is involved (del Castillo & Katz, 1954; Katz & Miledi, 1968). Kuno has also invoked a presynaptic change in probability of transmitter release for the early facilitation at group IA synapses. The present experiments can contribute little to an understanding of the mechanism involved in corticomotoneuronal facilitation. But the lack of correlation between the degree or timing of the facilitation and the wave form of the corticomotoneuronal EPSPs is indirect evidence against the existence of a post-synaptic component of this facilitation.

The time course of corticomotoneuronal facilitation has been measured and this has some of the characters of early facilitation at the frog neuromuscular junction (Mallart & Martin, 1967). Defining the temporal characteristics of the phenomenon may provide a starting point for consideration of the process of mobilization of transmitter by the presynaptic impulse. Relatively few observations on the time course of early facilitation at group IA synapses are available but these (Curtis & Eccles, 1960; Kuno, 1964) indicate a similarity to the description given here for corticomotoneuronal synapses. That such pronounced facilitation occurs in spite of progressive depolarization of the cell by the successive EPSPs argues for even greater individual conductance changes with successive presynaptic impulses than would be predicted from the curve of Fig. 5. (See also Landgren *et al.* 1962 for marked examples with bigger corticomotoneuronal EPSPs.)

Following accepted usage of the term facilitation to describe the phenomenon which occurs at the neuromuscular junction, it has been applied to the changes in the effects produced by repetitive activity at corticomotoneuronal synapses. Until a mechanism is demonstrated, this term is to be preferred to the previously used alternatives of potentiation or increased transmitting potency, even though the observations available to date focus attention on a presynaptic site for the occurrence of the phenomenon.

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