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FREQUENCY-DEPENDENT *N*-METHYL-D-ASPARTATE RECEPTOR-MEDIATED SYNAPTIC TRANSMISSION IN RAT HIPPOCAMPUS

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SUMMARY

1. The effects of the *N*-methyl-D-aspartate (NMDA) antagonist, D-2-amino-5-phosphonovalerate (APV) were examined on synaptic responses evoked by high-frequency stimulation of the Schaffer collateral–commissural pathway, in the presence of Mg^{2+} (1 or 2 mM) and functional synaptic inhibition.

2. The synaptic response evoked by 100 Hz stimulation comprised fast excitatory postsynaptic potentials (EPSPs) evoked by each shock and a slow depolarization. APV reduced the size of the depolarization without depressing the fast EPSPs.

3. The mean (± 1 S.E.) amplitude of the APV-sensitive component ($3{\cdot}0 \pm 0{\cdot}3$ mV), evoked by 100 Hz stimulation at membrane potentials near rest, was invariably smaller than the first fast EPSP ($9{\cdot}8 \pm 0{\cdot}7$ mV). Both of these synaptic components had similar thresholds and increased in amplitude as the stimulus intensity was raised. There was a positive correlation between the amplitude of the two components ($r = 0{\cdot}57$, $P < 0{\cdot}01$).

4. The amplitude of the APV-sensitive component was positively correlated ($r = 0{\cdot}97$, $P < 0{\cdot}05$) with the frequency of stimulation during the trains (between 10 and 100 Hz). The threshold frequency for evoking an APV-sensitive component was approximately 10 Hz.

5. In contrast to the fast EPSPs the amplitude of the APV-sensitive component increased with depolarization, and decreased with hyperpolarization, of a neurone from its resting membrane potential. The component was no longer present in some cells which had been hyperpolarized sufficiently.

6. It is suggested that during high-frequency stimulation a neurone may become depolarized for a sufficient time to reduce the Mg^{2+} block of NMDA channels. This enables the NMDA receptor system to contribute transiently to the synaptic response, despite the inhibitory synaptic mechanisms which prevent its activation during single-shock stimulation. The characteristics of the NMDA receptor-mediated synaptic response may explain properties relating to the induction of long-term potentiation (LTP).

INTRODUCTION

Schaffer collateral–commissural fibres innervate the region of the brain which, on the basis of binding studies, appears to have the highest concentration of *N*-methyl-

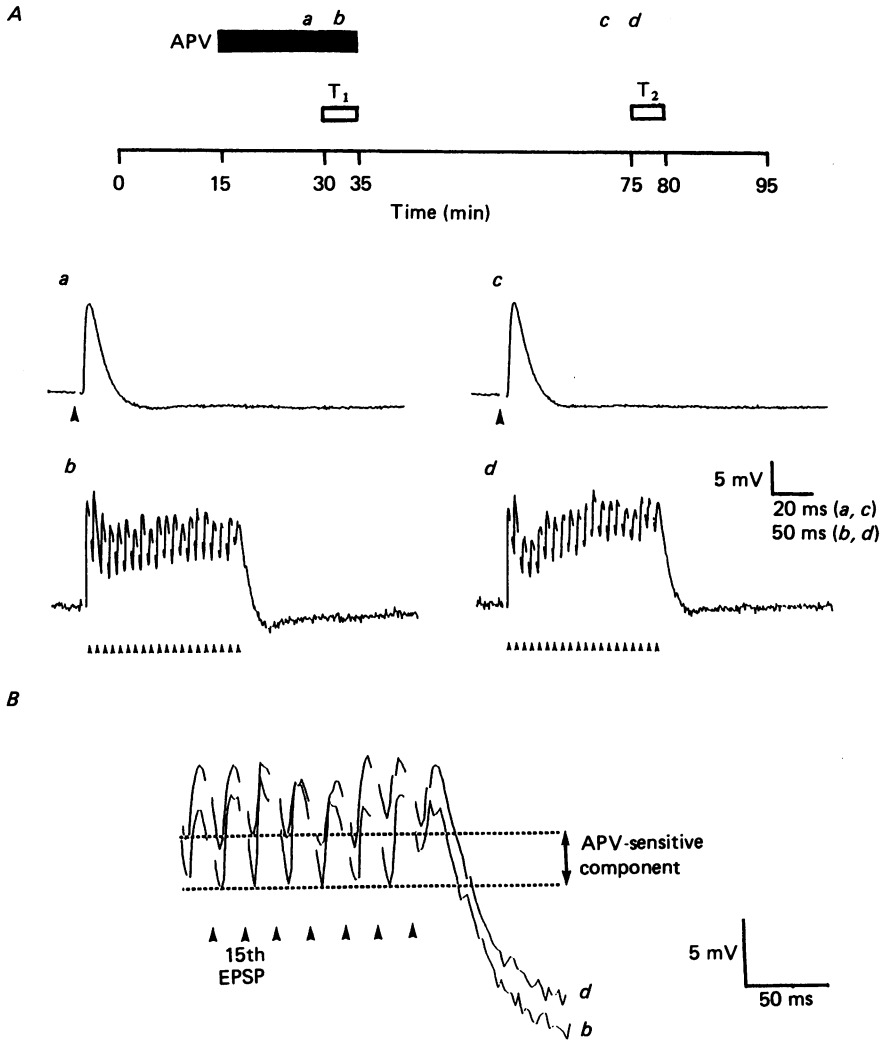

Fig. 1. *A*, experimental protocol and effects of APV on synaptic potentials at resting membrane potential. The records *a* and *c* are averages of ten successive responses obtained immediately prior to the periods of high-frequency stimulation in 50 μM-APV (T_1) and following wash-out (T_2), respectively. The records *b* and *d* are single responses obtained during the respective high-frequency trains. The effect of APV on the third and fourth EPSPs was not a consistent finding. *B*, part of the records *b* and *d* are shown superimposed to illustrate the APV-sensitive component. The component was measured routinely at the base of the 15th EPSP evoked during the train. In this and subsequent records stimulus artifacts have been blanked for purposes of clarity and the times of stimulation are indicated by arrow-heads. Action potentials when shown are truncated.

D-aspartate (NMDA) receptors (Monaghan, Yao, Olverman, Watkins & Cotman, 1984). As discussed in the previous paper (Collingridge, Herron & Lester, 1988) NMDA receptors only contribute to the synaptic response induced by low-frequency (0·033 Hz) stimulation of this pathway under certain conditions: when Mg^{2+} is omitted from the perfusate, synaptic inhibition is depressed by a convulsant drug, or

the cell is strongly depolarized by current injection. None of these conditions is likely to occur under physiological conditions. Recently, however, it has been reported that NMDA receptors mediate a component of the synaptic response evoked by high-frequency (100 Hz) stimulation of this pathway in the presence of Mg^{2+} (1–2 mM) and intact synaptic inhibition at resting membrane potentials (Herron, Lester, Coan & Collingridge, 1986). The purpose of the present study has been to determine the characteristics of this frequency-dependent synaptic component.

These properties are discussed in relation to the initiation of long-term potentiation (LTP), a form of activity-dependent synaptic plasticity (Bliss & Lømo, 1973; Bliss & Gardner-Medwin, 1973) which, in this pathway, requires NMDA receptor activation (Collingridge, Kehl & McLennan, 1983; Harris, Ganong & Cotman, 1984; Wigström & Gustafsson, 1984; Slater, Stelzer & Galvan, 1985).

Some of these results have appeared in a preliminary form (Collingridge, Herron & Lester, 1987).

METHODS

Experiments were performed on rat hippocampal slices in the presence of 1 or 2 mM-Mg^{2+} as described in the previous paper (Collingridge *et al.* 1988). Intracellular recordings were obtained from CA1 neurones using microelectrodes containing 3 M-potassium acetate or 2 M-potassium methylsulphate (40–80 MΩ). Unless otherwise stated, cells were maintained at the potential corresponding to rest at the start of the experiment (−63 to −74 mV). Typically this required less than ±0·1 nA over the experimental period.

Neurones usually required a period of approximately 15 min for the membrane potential and input resistance to stabilize after impalement. The following standard protocol was then adopted (Fig. 1). The Schaffer collateral–commissural pathway was stimulated at 0·033 Hz to monitor the low-frequency synaptic response. Continuous recordings were obtained for 15 min before, 20 min during and 45–60 min following administration of 20 or 50 μM-D-2-amino-5-phosphonovalerate (APV). Two identical periods of high-frequency stimulation were delivered, the first in the presence (T_1) and the second following wash-out (T_2) of APV. Each period comprised ten to twelve high-frequency trains which were presented at 30 s intervals. A train comprised twenty shocks and, unless otherwise stated, these were delivered at 100 Hz. The membrane potential, prior to each high-frequency train, and the stimulus intensity were kept the same as those used to monitor the low-frequency response (i.e. a membrane potential close to rest and an intensity which evoked a subthreshold EPSP of approximately 10 mV). Only one parameter (stimulus intensity, stimulus frequency or membrane potential) was altered per cell.

RESULTS

Effects of APV on synaptic transmission

Low-frequency stimulation of the Schaffer collateral–commissural pathway evoked a characteristic fast EPSP and biphasic IPSP. These synaptic potentials (Fig. 1*A*), and passive membrane properties, were not appreciably affected by APV, as reported in the previous paper (Collingridge *et al.* 1988). During high-frequency stimulation fast EPSPs were associated with a slow depolarization. In confirmation of a previous report (Herron *et al.* 1986), the slow depolarization was depressed selectively by APV in each of the twenty-eight cells analysed in the present investigation (Fig. 1*A* and *B*). D-2-Amino-7-phosphonoheptanoate (APH), the higher homologue of APV, had a similar effect in the one cell examined.

Conditioning effects of high-frequency stimulation

To be able to determine the properties of the component sensitive to NMDA antagonists it was a requirement that the size of the low-frequency response remained constant throughout the experiment (and that the stimulus intensity, and

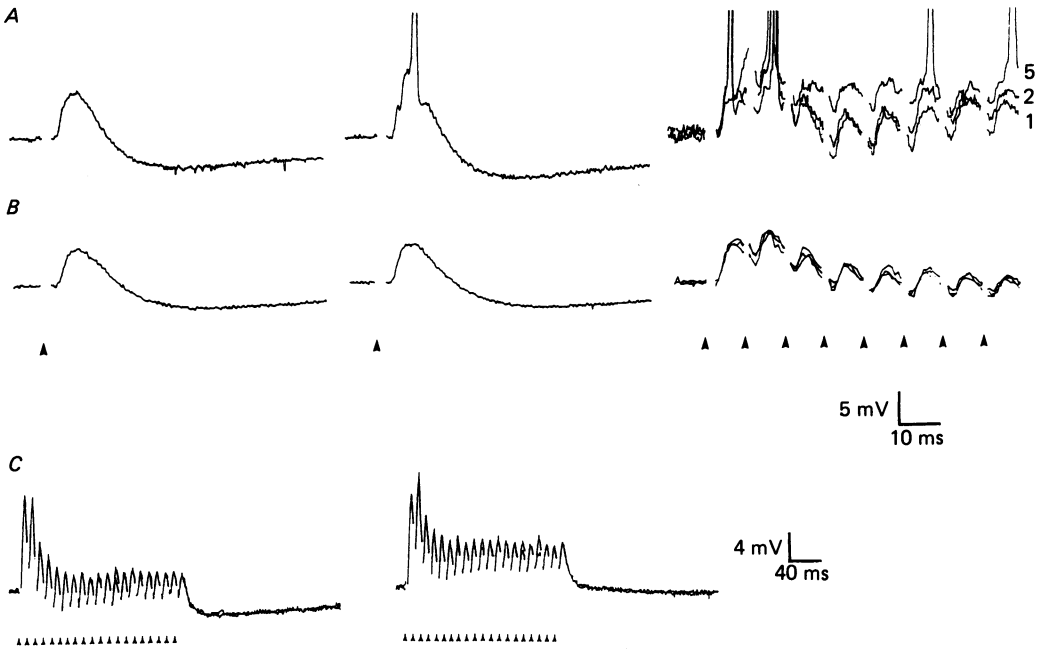

Fig. 2. Conditioning effects of high-frequency trains. In *A*, high-frequency trains were delivered within 30 min of impaling the cell and resulted in both LTP and conditioning during the trains (seen as a progressively increasing synaptic response). In *B*, recordings were obtained from another cell in 50 μM-APV and no LTP or inter-train conditioning was observed. In both cells records show (from left to right) averages of five records immediately prior to high-frequency stimulation, 10–15 min following high-frequency stimulation and a superimposition of the initial 80 ms of the first, second and fifth trains in the period of high-frequency stimulation. In *C* is shown superimposed records from another cell of the first two trains in the periods of high-frequency stimulation in the presence (left) and following wash-out (right) of 50 μM-APH.

hence the amount of neurotransmitter released, was not altered). The parameters used for the high-frequency trains often induced LTP, if delivered within 1 h of impaling the neurone (Fig. 2*A*). When LTP was induced there was a conditioning of the high-frequency response, such that it increased in amplitude with successive trains (Fig. 2*A*). To prevent the induction of LTP and the associated conditioning the first set of high-frequency trains were delivered in the presence of APV (Fig. 2*B*). Following wash-out of APV (or APH), high-frequency stimulation did not usually induce LTP or conditioning (possibly as a consequence of the long duration of intracellular recording). Thus, a direct comparison of the responses during the two periods of high-frequency stimulation was often possible (Fig. 2*C*).

Since the second set of high-frequency trains was delivered 45 min following the

first, it was considered possible that the alteration in the high-frequency response was a time-dependent phenomenon rather than an effect of APV. To examine this possibility recordings were obtained from two cells after the LTP process had been saturated by repeated periods of high-frequency stimulation (Bliss & Lømo, 1973).

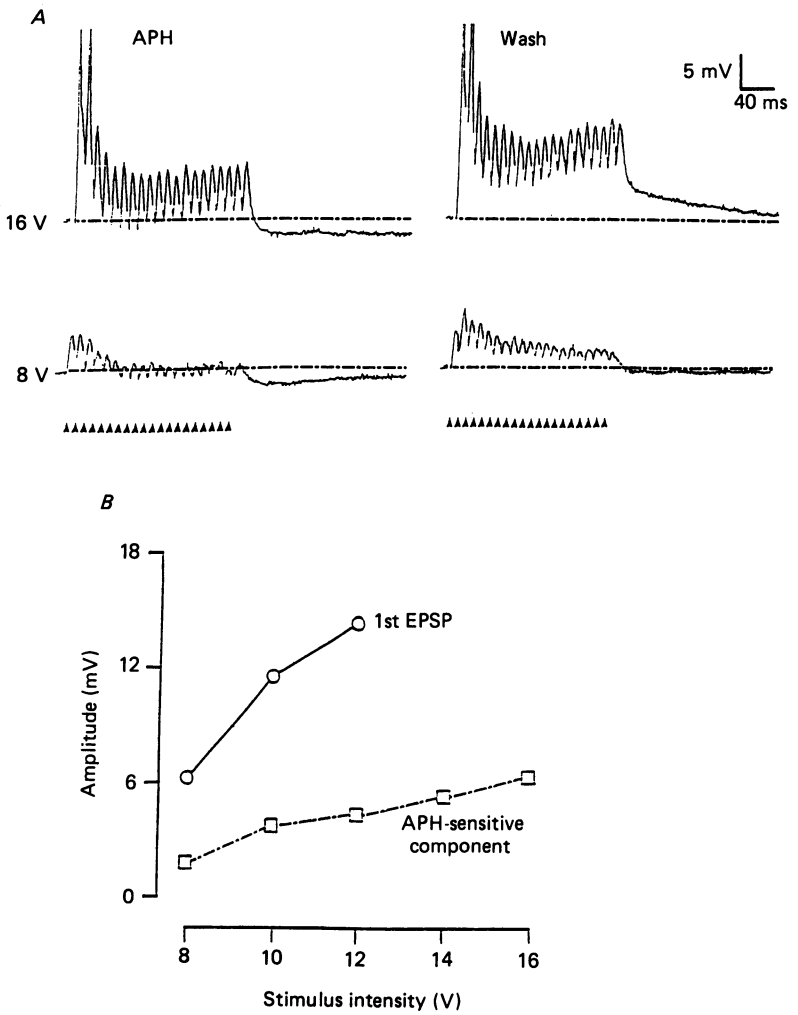

Fig. 3. The effect of stimulus intensity on high-frequency (100 Hz) synaptic transmission. Recordings were obtained in the presence and following wash-out of 50 μM-APH over a range of stimulus intensities. The responses at 8 and 16 V are illustrated in *A*. The graph in *B* plots the amplitudes of the first EPSP in the train (measured in APH) and the APH-sensitive component. At the two highest intensities the first EPSP elicited an action potential.

High-frequency trains were delivered firstly under control conditions and secondly in the presence of APV. Under these conditions APV had a similar effect to that observed using the standard protocol. Thus, the reduction in the slow depolarization was not a time-dependent effect but correlated with the presence of APV.

The amplitude of the fast EPSPs declined during the high-frequency train

presumably due to a depletion of Ca^{2+} in presynaptic terminals and the shunting influence of IPSPs. The decline in amplitude was similar in the presence and absence of APV (Fig. 2*C*). The amplitude of the fast EPSPs evoked at an equivalent time during the train, was either unaffected (Fig. 2*C*) or slightly increased by APV (Fig. 3). The latter effect may be explained, in part, by an increased driving force due to the reduction of the slow depolarizing potential.

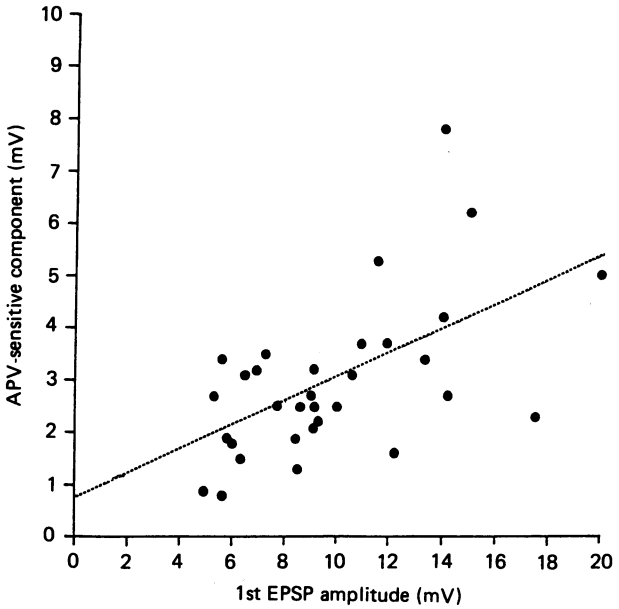

Fig. 4. Relationship between the amplitudes of the first EPSP in the train, measured in APV (or APH), and the APV- (or APH-) sensitive component. Thirty-two measurements were obtained from twenty-five cells, as described in Fig. 3. The line was fitted by a least-squares method.

Time course of the APV-sensitive component

The time course of the APV-sensitive component was markedly different from that of the fast EPSPs. Although its latency to onset was variable from cell to cell it was always longer than the first fast EPSP in the train. Usually it was evident by the time of the eighth fast EPSP. This corresponds to a latency to onset of between 10 and 70 ms.

The APV-sensitive component was of longer duration and had slower rise and decay times, compared to the fast EPSPs. The depolarization usually reached a plateau by the time of the 15th fast EPSP in the train (at which time measurements were obtained, Fig. 1*B*). Usually the response had not fully decayed by the end of the records (which outlasted the period of high-frequency stimulation by 50–250 ms).

Dependence on stimulus intensity

The effect of a range of stimulus intensities was examined in five cells. The size of the APV- (or APH-) sensitive component increased with stimulus intensity in four of these cells (Fig. 3). At the lowest stimulus intensity that accurate measurements

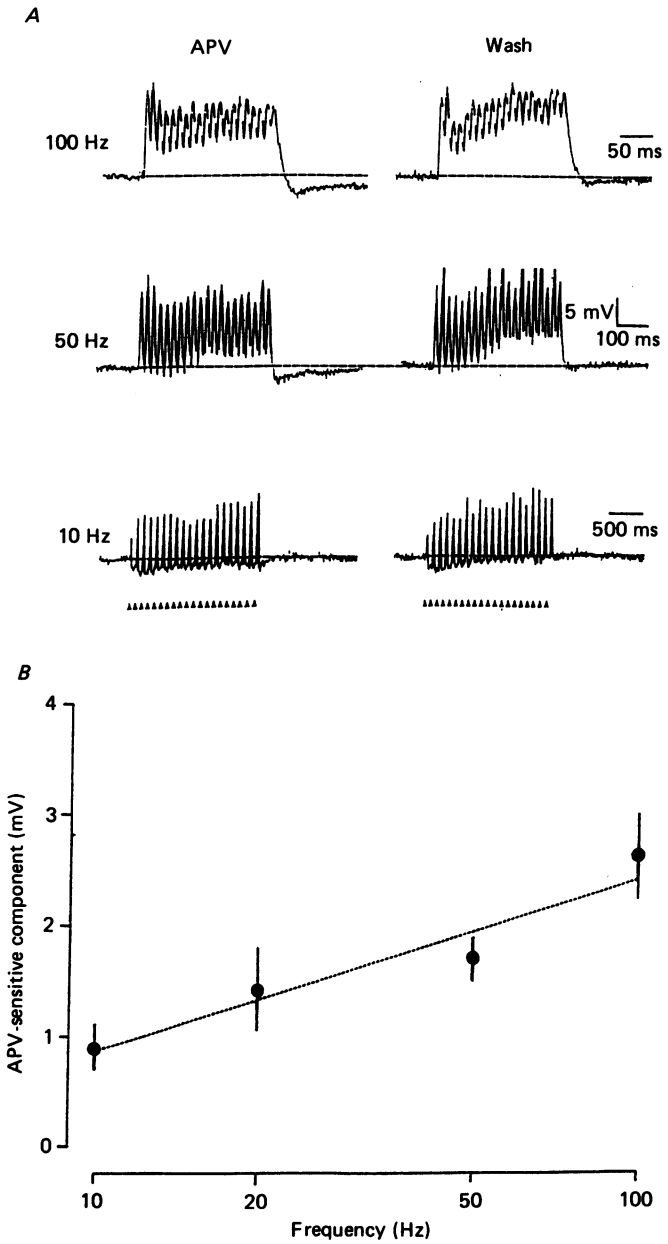

Fig. 5. Frequency-dependent activation of the APV-sensitive component. *A*, single records from a cell in 50 μM-APV and following wash-out of APV at three rates of stimulation. The fast EPSPs are attenuated in the records at 10 Hz due to the sampling rate used. In *B*, the size of the APV-sensitive component is plotted against the frequency of stimulation during the trains. Each point is the mean ($\pm$1 S.E.) amplitude of the component in four cells. The line was fitted by a least-squares method.

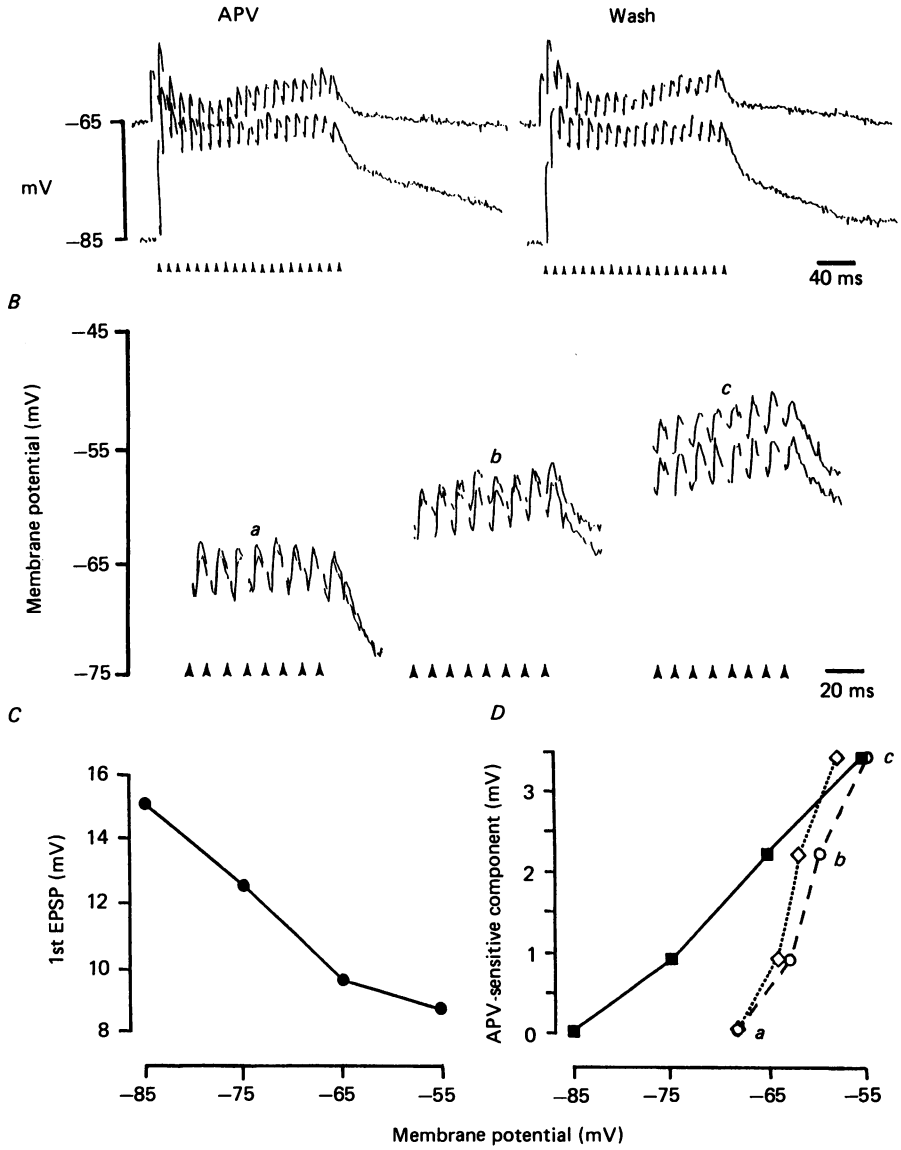

Fig. 6. Voltage dependence of the synaptic components during high-frequency (100 Hz) stimulation. Recordings were obtained at four membrane potentials which prior to stimulation were −55, −65, −75 and −85 mV. *A*, single records at the resting potential (−65 mV) and at −85 mV in the presence and following wash-out of 20 μM-APV. In *B*, the last part of the trains recorded in APV and following wash-out are superimposed for the pre-stimulus membrane potentials of −85 (*a*), −65 (*b*) and −55 mV (*c*). The graph in *C* plots the peak amplitude of the first fast EPSP (measured in APV) against pre-stimulus membrane potential. In *D*, the amplitude of the APV-sensitive component is plotted against the pre-stimulus membrane potential (■) and the membrane potential at the base of the 15th fast EPSP in the presence (◇) and following wash-out of APV (○). The horizontal distance between ■ and ○ is the size of the depolarization, at the time of the 15th fast EPSP, from the pre-stimulus membrane potential. The distance between ◇ and ○ is the component of the depolarization that is sensitive to APV.

could be made the APV- (or APH-) sensitive component was always present. It continued to increase in size as the stimulus intensity was increased beyond that necessary to induce action potential firing.

The amplitude of the APV- (or APH-) sensitive component ($3{\cdot}0 \pm 0{\cdot}3$ mV) was invariably smaller than the peak amplitude of the first fast EPSP ($9{\cdot}8 \pm 0{\cdot}7$ mV; $n = 32$) in the high-frequency train. There was a positive correlation ($r = 0{\cdot}57$, $P < 0{\cdot}01$) between the amplitudes of the two components (Fig. 4).

Frequency dependence

The effects of varying the frequency of stimulation were studied in four cells. In each cell, twenty shocks were delivered at frequencies of 10, 20, 50 and 100 Hz. The APV-sensitive component was just detectable at 10 Hz and increased in amplitude as the frequency was increased (Fig. 5*A*). There was a positive correlation ($r = 0{\cdot}97$, $P < 0{\cdot}05$) between the size of the APV-sensitive component and the frequency of stimulation (Fig. 5*B*).

Membrane potential dependence

The synaptic components were compared at three or more membrane potentials over the range -100 to -50 mV in seven cells. In all cases, the fast EPSPs decreased in amplitude with membrane depolarization in an identical manner to the EPSPs evoked during low-frequency stimulation. In contrast the APV-sensitive component increased in amplitude with depolarization in six of these cells (Fig. 6). In four cells, the APV-sensitive component was not detected at the most hyperpolarized membrane potentials. In the example illustrated in Fig. 6, it can be seen that at -85 mV the synaptic response comprises a large depolarization (Fig. 6*A*) but is not sufficient to activate the APV-sensitive component (Fig. 6*B* and *D*). On the other hand, at rest (-65 mV) the synaptic potential depolarizes the cell only slightly more (Fig. 6*A*) but activates this component (Fig. 6*B* and *D*). This illustrates the steepness of the voltage-dependent activation of the APV-sensitive component and shows that it can be activated by high-frequency stimulation at resting membrane potentials.

DISCUSSION

The present study has described the properties of a slow depolarizing potential that can be recorded as a component of the synaptic response during high-frequency stimulation of the Schaffer collateral–commissural pathway. It is considered that it is mediated by NMDA receptors since it is blocked by selective NMDA antagonists (Watkins & Evans, 1981) and displays an anomalous dependence on membrane potential expected for an NMDA receptor-mediated response recorded in the presence of Mg^{2+} (Nowak, Bregestovski, Ascher, Herbet & Prochiantz, 1984; Mayer & Westbrook, 1985; Dingledine, Hynes & King, 1986). Despite its slow characteristics it is likely to be a monosynaptic potential since NMDA receptors have been shown to mediate a monosynaptic response in this pathway, in response to single-shock stimulation, under conditions where the Mg^{2+} block of NMDA channels has been removed (Collingridge *et al.* 1988). Furthermore, in the present study, the NMDA receptor component and the fast EPSPs appeared to have similar thresholds and

increased in size in a linearly related manner. This is consistent with the possibility that both synaptic components are mediated by neurotransmitter released from the same population of afferent fibres (Collingridge *et al.* 1988).

The high-frequency stimulation of the Schaffer collateral–commissural pathway used to evoke the slow synaptic component can induce LTP. Since both the component and LTP are selectively blocked by APV it seems probable that they are causally related, depending on the synaptic activation of NMDA receptors. In support of this is the finding that both the ability to induce LTP (Dunwiddie & Lynch, 1978) and the amplitude of the NMDA receptor component are decreased as the frequency is reduced from 100 Hz. The threshold frequency for both synaptic mechanisms is approximately 10 Hz.

Although a requirement for the generation of LTP in this pathway, synaptic activation of NMDA receptors does not by necessity lead to LTP. This is illustrated by the continued existence of the NMDA receptor component after the LTP process had been saturated. Similar conclusions have been made previously on the basis of extracellular recordings (Wigström & Gustafsson, 1984).

The voltage-dependent nature of the synaptic activation of the NMDA receptor system recorded in the present study may explain several observations concerning the induction of LTP. As neurones were hyperpolarized from rest the NMDA receptor component decreased in amplitude and in some cells was blocked. This could account for the finding that when the depolarization due to high-frequency stimulation is limited by current injection, LTP is not observed (Kelso, Ganong & Brown, 1986; Malinow & Miller, 1986). Conversely, the observation that as cells were depolarized from rest the NMDA receptor component increased in size could explain the associative induction of LTP seen when high-frequency stimulation subthreshold for inducing LTP is paired with depolarizing current steps (Kelso *et al.* 1986; Sastry, Goh & Auyeung, 1986) or stimulation of other afferent fibres (McNaughton, Douglas & Goddard, 1978; Levy & Steward, 1979).

In addition, this observation may explain why the induction of LTP is facilitated by GABA antagonists (Wigström & Gustafsson, 1985) and, in the dentate gyrus, is suppressed by co-activation of a separate inhibitory pathway (Douglas, Goddard & Riives, 1982), since synaptic inhibition would tend to maintain the membrane in a region where the NMDA receptor system is not activated.

It has been suggested that NMDA receptors do not contribute to the synaptic potentials evoked by single-shock stimulation of the Schaffer collateral–commissural pathway because synaptic inhibition prevents neurones becoming sufficiently depolarized to remove the Mg^{2+} block of NMDA channels (Herron, Williamson & Collingridge, 1985; Dingledine *et al.* 1986). It is likely that an NMDA receptor component was observed in the present study since high-frequency stimulation provided the necessary depolarization to overcome the Mg^{2+} block. Temporal summation of fast (non-NMDA receptor-mediated) EPSPs occurred at 100 Hz but was not observed at lower frequencies (e.g. 10 Hz) where an NMDA receptor component could still be recorded. Thus although summation of fast EPSPs could at higher frequencies contribute to, it is not a requirement for, activation of the NMDA receptor system. During high-frequency stimulation of this pathway there is a reduction in the GABA-mediated inhibitory synaptic conductance, a depolarizing

shift in the chloride reversal potential (E_{Cl}), and an elevation of extracellular K^+ (Ben-Ari, Krnjević & Reinhardt, 1979; Benninger, Kadis & Prince, 1980; McCarren & Alger, 1985). These factors could allow the cell to become depolarized sufficiently to reduce the Mg^{2+} block of NMDA channels. Since the NMDA receptor-mediated component evoked by a single volley in depolarized cells can last for up to approximately 200 ms (Collingridge *et al.* 1988), this component would summate at frequencies above 5 Hz. In view of the voltage dependence of the underlying conductance the NMDA receptor component would summate in a non-linear manner, increasing with successive stimuli as the cell is further depolarized.

In summary, the synaptic activation of the NMDA receptor system in the Schaffer collateral–commissural pathway can account for many of the known properties concerning the induction of LTP. The requirement for high-frequency stimulation to activate this system, at resting membrane potentials in the presence of Mg^{2+} and synaptic inhibition, suggests that, in this region, the NMDA receptor system may be specifically involved in neurotransmission only when appropriate temporal summation occurs.

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