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PROPERTIES OF EXCITATORY POSTSYNAPTIC CURRENTS RECORDED *IN VITRO* FROM RAT HIPPOCAMPAL INTERNEURONES

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SUMMARY

1. We studied excitatory synaptic currents activated by stimulation of Schaffer collateral–commissural fibres and recorded from interneurones in the CA1 region of hippocampal slices using whole-cell techniques.

2. Interneurones were identified by their location outside the cell layer and their morphology as seen with differential interference contrast (DIC) microscopy and by filling with Lucifer Yellow (LY).

3. The excitatory postsynaptic current (EPSC) had a fast, voltage-insensitive component and a slow component which had a region of negative slope resistance between −70 and −40 mV. The slow voltage-dependent component was abolished by the *N*-methyl-D-aspartate (NMDA) receptor antagonist (DL-2-amino-5-phosphonovalerate (APV) 50 μM) which had little effect on the fast component. Conversely, the fast component was abolished by the non-NMDA receptor antagonist 6-cyano-7-nitoquinoxaline-2,3-dione (CNQX; 10 μM), which had no effect on the slow component.

4. The rise time of the fast component ranged from 1 to 3 ms and the decay time constant ranged from 3 to 15 ms. The rise time of the slow component ranged from 5 to 11 ms and the decay time constant ranged from 50 to 100 ms.

5. It is concluded that although the morphology of the excitatory synapses onto interneurones differs considerably from those onto pyramidal cells, their electrophysiological and pharmacological properties are very similar.

INTRODUCTION

It is generally accepted that glutamate is the major excitatory neurotransmitter in the hippocampus. In the CA1 field of the rat hippocampus the Schaffer collateral–commissural system of afferents provides the main excitatory input to the neurones in this region. Apart from the pyramidal neurones several types of interneurones have also been described in the CA1 region of the hippocampus (Ramón Y Cajal, 1911; Lorenté de Nó, 1934). While the synapses made by Schaffer collateral–commissural afferents are primarily on the dendritic spines of pyramidal

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cells, the synapses from these same afferents onto interneurones are made directly onto the shaft of aspiny dendrites (Seress & Ribak, 1985). Since the same fibre system makes synapses onto the two types of neurones, it is likely that the transmitter released at the synapses onto interneurones is also glutamate (Dale, 1935). These interneurones exhibit immunoreactivity to glutamic acid decarboxylase (GAD), indicating that they are γ-aminobutyric acid(GABA)ergic neurones (Somogyi, Hodgson, Smith, Nunzi, Gorio & Wu, 1984) and many have also been shown to be immunoreactive to a number of small peptides (Somogyi *et al.* 1984; Kunkel & Schwartzkroin, 1988).

Intracellular recordings from CA1 interneurones have shown that the intrinsic electrical properties of these cells are quite different from those of the pyramidal neurones (Schwartzkroin & Mathers, 1979; Lacaille & Schwartzkroin, 1988*a* & *b*). It has also been demonstrated physiologically that these interneurones receive both feedforward and feedback excitatory input via the Schaffer collateral–commissural system (Schwartzkroin & Mathers, 1979; Knowles & Schwartzkroin, 1981; Lacaille, Muller, Kunkel & Schwartzkrowin, 1987; Lacaille & Schwartzkroin, 1988*a* & *b*). At the synapse between these afferents and the pyramidal neurones it has been demonstrated that the transmitter activates both NMDA and non-NMDA receptors on the postsynaptic cell (Collingridge, Herron & Lester, 1988*a*; Andreasen, Lambert & Jensen, 1989; Hestrin, Nicoll, Perkel & Sah, 1990). Whether the properties of the excitatory synapses onto interneurones are similar to those onto pyramidal cells is unknown. In this paper we characterize, using whole-cell recording, the physiology and pharmacology of the excitatory input onto interneurones in the CA1 region of the rat hippocampus.

METHODS

Methods for preparation of slices, whole-cell recording and data analysis were generally the same as described elsewhere (Edwards, Konnerth, Sakmann & Takahashi, 1989; Hestrin *et al.* 1990). Rats were anaesthetized with halothane and decapitated with a guillotine. In most experiments described here thicker slices were used (200–250 μm) and typically deeper cells (within 50 μm of the surface) were exposed. Exposing neuronal somata was facilitated by using 3- to 4-week-old animals and placing the slices for 1 h in Ringer solution that had previously been heated to 37 °C. By the age of 3 to 4 weeks the morphology of the interneurones and pyramidal cells are approaching that of the adult (Minkwitz, 1976*a*, *b*). In some experiments older animals were used (5–8 weeks) and showed no difference. With thicker slices, visualization of the cells was facilitated by the use of a TV camera (Cohu, 6500), with black level adjustment. The slice was continuously perfused with Ringer which consisted of (mM): NaCl, 126; KCl, 2·5; $MgSO_4$, 1·3; $CaCl_2$, 2·5; NaH_2PO_4, 1; $NaHCO_3$, 20; glucose, 11; bubbled with 95% O_2, 5% CO_2. Glycine (1 μM) was routinely added to the Ringer to ensure a constant saturating concentration of glycine for the NMDA receptor. GABA-mediated chloride currents were blocked by including 100 μM-picrotoxin in the superfusing solution.

Whole-cell pipettes were filled with an intracellular solution of the following composition (in mM): CsF, 130; KCl, 10; EGTA, 10; HEPES, 10; pH 7·2. When Lucifer Yellow (LY) was used to stain neurones it was dissolved in the above solution to give a final concentration of 0·1–0·2%. Excitation with blue–purple epifluorescence resulted in deterioration of the recording and was therefore applied at the end of the recording.

The Schaffer collateral–commissural afferents were stimulated with stainless-steel electrodes (Frederick Haer) placed within 100 μm of the soma of the recorded cell. A patch clamp amplifier (List Electronics, EPC-7) was used to record excitatory postsynaptic currents, which were filtered at 2 kHz (8-pole Bessel filter, Frequency Devices) and recorded on-line using an PDP 11/23

computer (DEC). Data was analysed off-line on a microVax II. All traces are averages of two to five records unless otherwise stated. Measurements are given as mean ± S.D.

Most of the neurones in this study were in stratum oriens, however we did record from several cells in s. radiatum. No differences in excitatory synaptic input was found between these two types of neurones. The drugs APV, CNQX and picrotoxin were all obtained from Cambridge Research Biochemical. All experiments were performed at room temperature 22–24 °C.

RESULTS

Morphological observations

Whole-cell recordings were obtained from twenty-seven interneurones. These cells were identified as interneurones by their location well outside the pyramidal cell layer, the non pyramidal shape of their somata and the lack of a main apical dendrite. The electrophysiological properties of interneurones, such as narrow action potentials and lack of accommodation (Schwartzkroin & Mathers, 1979) could not be used to define interneurones, since the Cs^+ in the intracellular solution obscured these properties. We were able to visualize the soma and primary dendrite of pyramidal neurones (Fig. 1*Aa*) and interneurones (*Ba*) without staining, taking advantage of the relatively good contrast obtained using DIC optics. In addition, most experiments were carried out with LY in the recording solution. The morphology of an interneurone as revealed by LY epifluorescense (Fig. 2*Bb*) was markedly different from that of the pyramidal cell (*Ba*). Interneurones were generally more symmetrical and clearly lacked a main apical dendrite. The dendrites usually extended into both s. radiatum and s. oriens.

Properties of EPSC

Stimulation of the afferent fibres led to an excitatory postsynaptic current (EPSC) in all interneurones. At a holding potential of −80 mV, the EPSC had a fast rise time (1–3 ms) and decayed with a single exponential time constant. Membrane depolarization revealed a second slowly decaying component (Fig. 2*A*). At membrane potentials more positive than about 0 mV, the current was outward and was dominated by the slowly decaying component. The current–voltage (*I–V*) relation of the fast component, measured at the peak of the EPSC, was linear with a reversal potential of about 0 mV (Fig. 2*B*, ●). The *I–V* relation of the slow component, measured at 25 ms after the peak had a negative slope region between −70 and −40 mV (Fig. 2*B*, ●). These properties of the EPSC are similar to those reported for glutamatergic synapses in other preparations where the two components have been shown to result from activation of non-NMDA and NMDA receptors (Dale & Roberts, 1985; Andreasen *et al.* 1989; Collingridge *et al.* 1988*a*; Forsythe & Westbrook, 1988; Hestrin *et al.* 1990).

The effect of the selective NMDA receptor blocker DL-APV (50 μM) is illustrated in Fig. 3. At a holding potential of −80 mV application of APV had no effect on the EPSC. At more depolarized potentials, APV selectively blocked the late component of the EPSC (Fig. 3*A*). As shown in Fig. 3*B* APV had little effect on the *I–V* relation measured at the peak of the EPSC (triangles), however, the slow component measured at 25 ms after the peak was blocked over the whole voltage range (circles). This effect of APV was reversible and was seen in five other cells.

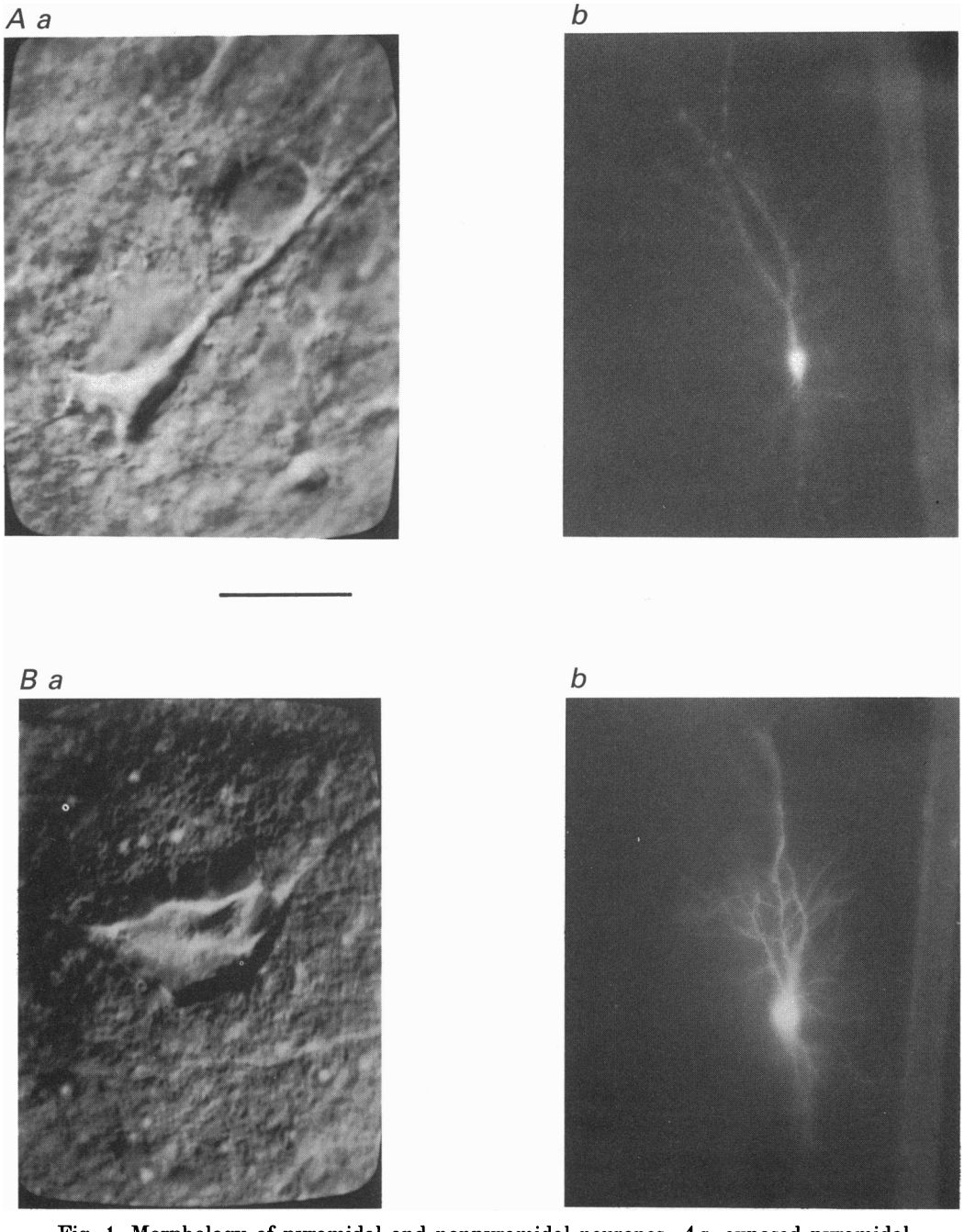

Fig. 1. Morphology of pyramidal and nonpyramidal neurones. *Aa*, exposed pyramidal neurone in s. pyramidale, photographed directly from the TV screen. *Ab*, a LY filled pyramidal neurone, low magnification. *Ba*, exposed nonpyramidal neurone in s. oriens. *Bb*, a LY filled nonpyramidal neurone, low magnification. The scale bar represents 20 μm (*Aa*, *Ba*). Note the out of focus image of the net seen to the right in *Ab* and *Bb*.

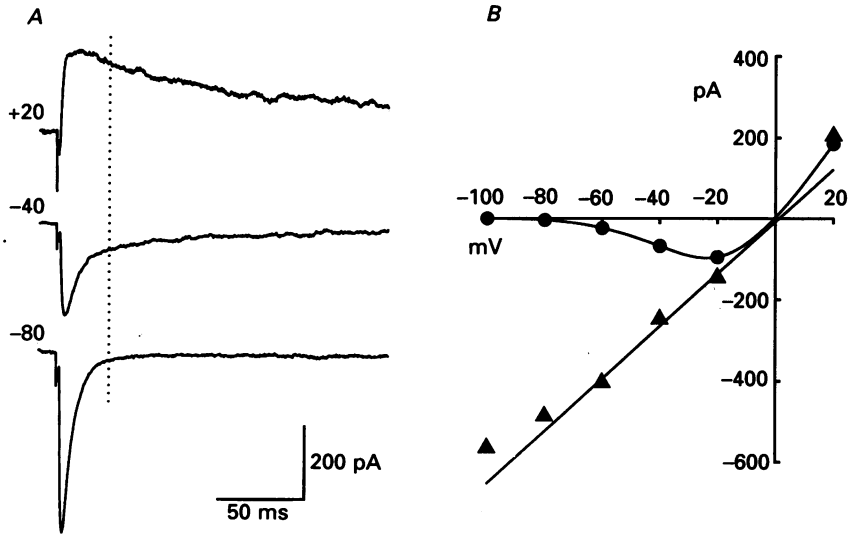

Fig. 2. The voltage-dependent properties of the EPSC. *A*, the EPSC was recorded at the indicated membrane potentials. *B*, the currents measured at the peak of the EPSC (▲) and at 25 ms after the peak (●) (dotted line in *A*) are plotted in relation to the membrane potential.

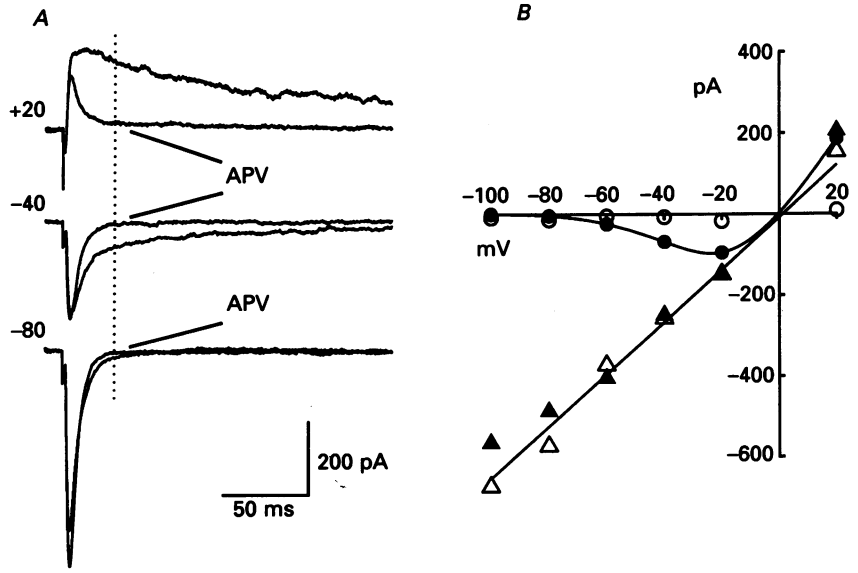

Fig. 3. The effect of APV. *A*, the EPSC was recorded before and during the application of 50 μM-DL-APV at the indicated membrane potentials. *B*, peak current–voltage relations are shown before (▲) and during (△) the applications of APV. The current–voltage relation measured 25 ms after the peak of the EPSC (dotted line in *A*) before (●) and (○) during the application of APV are also shown. Same cell as in Fig. 1.

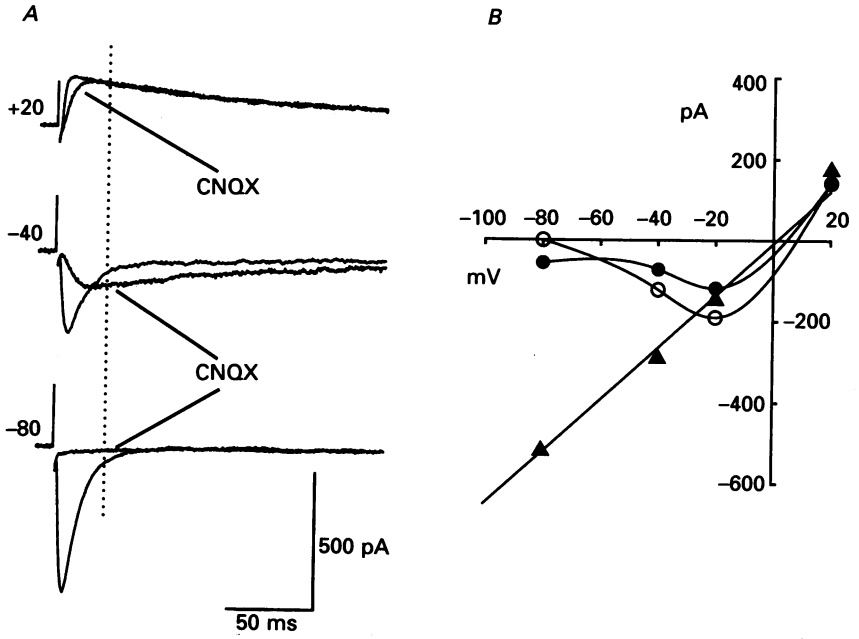

Fig. 4. The effect of CNQX. *A*, the EPSC was recorded before and during the application of 10 μM-CNQX at the indicated membrane potentials. *B*, peak current–voltage relation in control solution (▲) and current–voltage relation measured 25 ms after the peak EPSC (dotted line in *A*) before (●) and during (○) the application of CNQX.

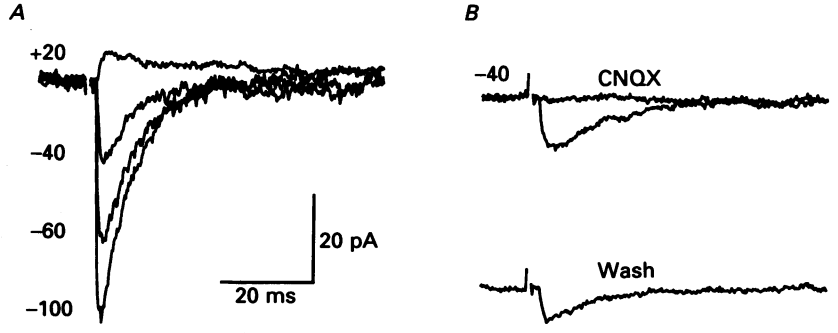

Fig. 5. In some cells the EPSC lacks an NMDA component. *A*, the EPSC recorded in a cell at the indicated membrane potentials. Note the absence of a slow component as the cell is depolarized. *B*, the EPSC recorded in the same cell in control solution, during the application of 10 μM-CNQX and after washing out CNQX.

The NMDA component of the EPSC was isolated by blocking the non-NMDA component with the selective blocker CNQX (10 μM). Application of CNQX, abolished the EPSC at hyperpolarized potentials but only blocked the early part of the EPSC at more depolarized potentials (Fig. 4). The remaining synaptic current in the presence of CNQX was abolished by addition of APV, indicating that it is entirely mediated by NMDA receptors. As seen at other synapses (Forsythe &

Westbrook, 1988; Collingridge *et al.* 1988*a*, *b*; Andreasen *et al.* 1989; Hestrin *et al.* 1990), the rise time of the NMDA receptor-mediated EPSC was markedly slower than the rise time of the non-NMDA component. In four cells voltage clamped at −40 mV the 10–90% rise time of the EPSC changed from 3·4 ± 1·1 to 8·0 ± 2·5 ms after addition of CNQX. The voltage sensitivity of the NMDA activated conductance has been shown to result from a voltage-dependent block of the NMDA channel by extracellular Mg^{2+} (Mayer, Westbrook & Guthrie, 1984; Nowak, Bregestovski, Ascher, Herbet & Prochiantz, 1984). Thus, as expected from this observation, the NMDA component of the EPSC could be seen over a much wider voltage range when Mg^{2+} was removed from the extracellular solution ($n = 3$, not illustrated).

In the majority of the interneurones the EPSC was found to have both NMDA and non-NMDA components. However, two cells were found which apparently had only a non-NMDA component to the EPSC. The EPSC, from one such cell recorded over a range of membrane potentials is shown in Fig. 5*A*. In contrast to the EPSC recorded in most interneurones (e.g. Fig. 2), the time course of the EPSC in this interneurone was voltage independent, lacking the slow component even at depolarized membrane potentials. Application of CNQX completely abolished the EPSC at all membrane potentials (Fig. 5*B*). No obvious difference in the morphology of these neurones from the others was noted.

Comparison of pyramidal cells and interneurones

The non-NMDA component of the EPSC (measured at −90 mV) had a rise time of 1–3 ms. The decay time course was well fitted with a single exponential function. The range of exponential time constants was 3–15 ms. In a previous study of the kinetics of the non-NMDA component measured in pyramidal neurones (Hestrin *et al.* 1990) we found that the EPSC rise time likely reflects filtering by the dendritic cable. However, our data suggested that the decay time constant of synaptic inputs located close to the soma is likely to reflect the time course of the synaptic conductance. For synapses located far from the soma we found a positive correlation between the rise times and the decay time constants, while for close synapses the time constant of decay was independent of the rise time. The relation of the rise time to the decay time constant of the non-NMDA component is plotted for twenty-seven interneurones in Fig. 6*A* (●). The general shape of the scatter plot is similar to that obtained previously for sixty-one pyramidal neurones (○, Fig. 6*A*). The time constant of decay measured from interneurones with a rise time less than 2·5 ms was 5·1 ± 1·8 ms ($n = 21$). These data suggest that the time course of the non-NMDA component of interneurones is similar to that recorded from pyramidal neurones under identical conditions. Kinetic data for both components of the EPSC in interneurones and pyramidal neurones are compared in Table 1. As can be seen the properties of the EPSC in the two cell types are very similar.

Since the majority of the interneurones as well as the pyramidal neurones we studied had both NMDA and non-NMDA components to the EPSC we compared the relative contribution of these two components in the two types of cell. At a holding potential of −40 mV we measured the ratio of the amplitude of the non-NMDA component (measured at the peak of the EPSC) to the amplitude of the NMDA component (measured at 25 ms after the peak). A comparison of the ratios is shown

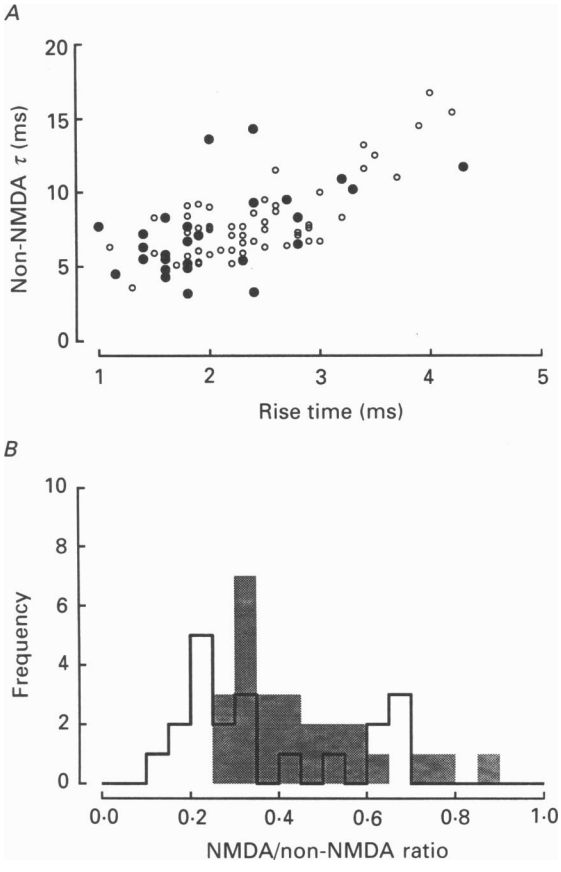

Fig. 6. The kinetics of the non-NMDA component. The rise times are plotted against the decay time constants of the non-NMDA component for twenty-seven interneurones (●). Identical data previously measured (Hestrin *et al.* 1990) from sixty-one pyramidal cell synapses is also plotted for comparison (○). *B*, ratio of the size of the NMDA component measured 25 ms after the peak at a holding potential of −40 mV to the size of the non-NMDA component measured at the peak of the EPSC at −40 mV. Data are shown for twenty interneurones (open histogram) and for a population of twenty-six pyramidal neurones (shaded histogram).

TABLE 1. Comparison of components of EPSC

	τ non-NMDA* (ms)	τ NMDA† (ms)
Pyramid	6·7 ± 1·3 (n = 35)	93·0 ± 38 (n = 4)
Interneuron	5·1 ± 2·8 (n = 21)	72·9 ± 33 (n = 7)

* Rise time less than 2·5 ms.
† Measured at −40 mV with CNQX.

in Fig. 5*B*. In interneurones the ratio, which was quite variable, was $0{\cdot}32 \pm 0{\cdot}15$ ($n = 20$) and in pyramidal cells it was $0{\cdot}45 \pm 0{\cdot}16$ ($n = 26$). This difference is significant at the 0·05 level (two tailed Student t test).

DISCUSSION

In this study we have examined the properties of excitatory synapses made by Schaffer collateral–commissural fibres onto interneurones in the CA1 region of the rat hippocampus. Interneurones were identified as such by their location outside the cell layer, their non-pyramidal somata and lack of a main apical dendrite as observed with DIC optics and their morphology as seen with LY epifluorescence. We have found that the EPSC at this synapse is mediated by both NMDA and non-NMDA receptors. However, the relative contribution of the two components is quite variable and the contribution of the NMDA component on average was somewhat smaller in interneurones than in hippocampal pyramidal cells. In a small fraction of cells, the EPSC apparently lacked the NMDA component suggesting that there may be some heterogeneity in the properties of interneurones. An heterogeneity has also been found for the intrinsic properties of interneurones (Lacaille & Schwartzkroin, 1988*a*; Lacaille *et al.* 1987).

The finding that EPSCs on interneurones have an NMDA component is in agreement with recent results in which stimulation of Schaffer collateral–commissural fibres in the CA1 region in the presence of CNQX evoked APV sensitive IPSPs in pyramidal cells (Davies & Collingridge, 1989), indicating that excitatory afferents activate NMDA receptors on GABAergic interneurones. In addition local application of NMDA can evoke IPSPs in dorsolateral septal neurones (Gallagher & Hasuo, 1989) indicating that in this structure GABAergic interneurones possess NMDA receptors.

The non-NMDA receptor-mediated component of the EPSC had a rise time of about 2 ms and decayed exponentially with a decay time constant of 3–15 ms. The I–V relation of this component was linear and had a reversal potential of 0 mV. The NMDA receptor mediated component of the EPSC had a much slower rise time of about 8 ms and decayed with time constants of 50–100 ms. The I–V relation was nonlinear with a region of negative slope between -70 and -40 mV. These properties of the two components of the EPSC are in agreement with the properties of non-NMDA and NMDA synaptic potentials found in CA1 pyramidal cells (Collingridge *et al.* 1988*a*; Andreasen *et al.* 1989; Hestrin *et al.* 1990) and in other pyramidal neurones (Dale & Roberts, 1985; Thompson, 1986; Forsythe & Westbrook, 1988; Jones & Baughman, 1988).

Interneurones in the CA1 region of the hippocampus have been shown to be GAD positive suggesting that they are GABAergic (Somogyi *et al.* 1984). As is true for GABAergic interneurones elsewhere in the cortex these cells lack spines (Seress & Ribak, 1985) and the excitatory synapses are formed directly onto the dendritic shaft. In contrast, the pyramidal cells, which receive the same excitatory input as the interneurones are spiny cells which have the majority of their excitatory input onto dendritic spines (Seress & Ribak, 1985). Our finding that the time course of the EPSC onto these two very different types of cells is very similar suggests that the

electrotonic parameters of the spines probably do not play an important role in shaping the EPSC recorded at the soma. This is in agreement with conclusions reached from modelling dendritic spines (Koch & Poggio, 1983) but leaves open the possibility that in the unclamped neurone the spine neck resistance could affect the postsynaptic response indirectly, e.g. allowing for activation of voltage-dependent conductances in the spine head (Perkel & Perkel, 1985; Miller, Rall & Rinzel, 1985; Segev & Rall, 1988).

The excitatory synapse onto CA1 pyramidal neurones has the property of a use-dependent plasticity referred to as long term potentiation (LTP). It has been demonstrated that the trigger for LTP is the influx of calcium through NMDA channels (for review see Malenka, Kauer, Perkel & Nicoll, 1989). Various roles have been proposed for spines in relation to LTP. These include changes in spine morphology (Rall, 1970) and restriction of diffusion of chemicals (e.g. Ca^{2+}) from activated synapses and to inactive synapses (Levy & Steward, 1983; Wigström & Gustafsson, 1985; Gamble & Koch, 1987; Nicoll, Kauer & Malenka, 1988; Wickens, 1988). Given the finding that the excitatory synapse onto the interneurones contacts the dendritic shaft and also has an NMDA component to the EPSC raises the interesting but still unresolved issue (Buzsáki & Eidelberg, 1982; Haas & Rose, 1982; Abraham, Gustafsson & Wigström, 1987; Taube & Schwartzkoin, 1987) of whether these synapses exhibit LTP and if so whether the potentiation is limited to the tetanized synapses.

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