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The expression of N-methyl-D-aspartate-receptor-mediated component during epileptiform synaptic activity in the hippocampus

[2]T.J. Ashwood & [1]H.V. Wheal

Department of Neurophysiology, University of Southampton, Bassett Crescent East, Southampton S09 3TU

1 The possible involvement of N-methyl-D-aspartate (NMDA)-receptors in epileptiform synaptic activity in the kainic acid (KA) lesioned hippocampus was investigated. In this chronic model of epilepsy there is a loss of both the early and the late components of synaptic inhibition as well as changes in the membrane properties of the surviving CA1 pyramidal cells.

2 The action of the specific NMDA-receptor antagonist D-2-amino-5-phosphonovalerate (D-APV) was tested on evoked bursts of action potentials recorded intracellularly from cells of lesioned hippocampi. The effects of D-APV on control synaptic responses from the contralateral, unlesioned hippocampi were also recorded.

3 In the presence of Mg^{2+} (1 mM), D-APV (20 μM) had a profound effect on the evoked epileptiform activity. Both the number of action potentials in the burst, as well as the area under the excitatory postsynaptic potential (e.p.s.p.) was considerably reduced. Furthermore this D-APV-sensitive component of the epileptiform burst had a very early onset, coincident with the first action potential in the burst.

4 D-APV (20 μM) was ineffective in blocking the e.p.s.p. evoked by Schaffer collateral afferents onto CA1 cells in slices of hippocampus contralateral to the KA lesion.

5 D-APV had no effect on the passive membrane properties of either population of cells. Hyperpolarizing potentials such as the inhibitory postsynaptic potentials (i.p.s.ps) or the afterhyperpolarization following a current-induced burst of action potentials were also unaffected.

6 It appears that an NMDA-receptor component is expressed during synaptically evoked epileptiform activity in this chronic model of epilepsy.

Introduction

There is a growing body of evidence which suggests that N-methyl-D-aspartate (NMDA)-receptors may contribute to the functioning of excitatory synapses in the mammalian central nervous system (see Dingledine, 1986). NMDA-receptor-mediated excitatory synaptic potentials have been recorded in the spinal cord and cerebral cortex (Davies & Watkins, 1982; Thomson *et al.*, 1985; Thomson, 1986). In the hippocampus binding studies suggest that there is a high density of NMDA-receptors in the termination sites of the Schaffer collateral and commissural afferents in the stratum oriens and stratum radiatum of the CA1 area (Monagham *et al.*, 1983). However, the control monosynaptic excitatory postsynaptic potential (e.p.s.p.) evoked by the stimulation of these afferents is insensitive to NMDA antagonists (Koerner & Cotman, 1982; Collingridge *et al.*, 1983). An NMDA-receptor component is normally only expressed during the induction of long-term potentiation (Collingridge *et al.*, 1983; Harris *et al.*, 1984; Wigstrom & Gustaffson, 1984) or in the presence of low extracellular Mg^{2+} (Herron *et al.*, 1985) which removes a voltage-dependent Mg^{2+} block of the channels linked to the NMDA-receptors (Nowak *et al.*, 1984; Mayer *et al.*, 1984).

NMDA-receptors also appear to participate in epileptiform activity. Various NMDA antagonists have been found to be effective in blocking seizures in several *in vivo* animal models of epilepsy (Croucher *et al.*, 1982; Meldrum *et al.*, 1983). One of the most potent and specific antagonists, D-2-amino-5-phos-

[1] Author for correspondence.
[2] Present address: Astra Clinical Research Unit, Edinburgh.

phonovalerate (D-APV) (Watkins & Evans, 1981) has also been shown to reduce epileptiform activity in the *in vitro* hippocampus produced by certain convulsants (Herron *et al.*, 1985; Dingledine *et al.*, 1986).

A chronic animal model of epilepsy has been developed in the rat using unilateral intracerebroventricular injections of kainic acid (Lancaster & Wheal, 1982). This produces a unilateral lesion of the CA3/CA4 area of the hippocampus but the ipsilateral CA1 pyramidal cells survive. Stimulation of the commissural afferents to these cells evokes a long duration e.p.s.p. which triggers an epileptiform burst of action potentials. This is associated with a loss of both the early bicuculline-sensitive chloride-mediated inhibitory postsynaptic potential (i.p.s.p.) and the late bicuculline-insensitive potassium-mediated i.p.s.p. (Wheal *et al.*, 1984; Newberry & Nicoll, 1984; Alger, 1984; Ashwood *et al.*, 1986).

Extracellular studies have shown that the epileptiform activity is markedly attenuated by D-APV (Ashwood & Wheal, 1986). In order to investigate the mechanism of this anticonvulsant effect intracellular recordings were made from the kainic acid lesioned hippocampus *in vitro*. Of particular interest was the possibility that an NMDA-receptor-mediated potential was expressed in the presence of a normal extracellular concentration of Mg^{2+} (1 mM). A preliminary account of this study has been published (Ashwood & Wheal, 1987).

Methods

Kainic acid lesion

Male Wistar rats (180 g) were anaesthetized with sodium pentobarbitone (60 mg kg^{-1} i.p.), placed in a Kopf stereotaxic frame and prepared for an intraventricular injection. Kainic acid (0.5 μg in 0.5 μl phosphate buffer, pH 7.4) was slowly injected into the left lateral ventricle. The injection syringe was left in position for a further 10 min before the scalp was sutured. Following a recovery period of 7 days these animals have a discrete unilateral lesion of the CA3/CA4 area of the hippocampus. The surviving pyramidal cells in the CA1 area show epileptiform activity (Wheal *et al.*, 1984). Further details of this method have been published (Lancaster & Wheal, 1982).

Preparation of slices

Seven days after the treatment with kainic acid the rats were lightly anaesthetized with halothane (Fluothane, ICI) and decapitated. The brain was removed and the hippocampi dissected out in cold artificial cerebrospinal fluid (ACSF). Transverse slices (400 μm) of the hippocampus ipsilateral and contralateral to the lesion were cut on a McIlwain tissue chopper. The slices were then either placed in an oxygenated and humidified holding chamber at room temperature (20°C) or maintained partially immersed in an experimental bath at 32–34°C. The bath was perfused at a rate of 2 ml min^{-1} with ACSF that contained (mM): NaCl 118, KCl 3.3, KH_2PO_4 1.2, $CaCl_2$ 2.5, $NaHCO_3$ 26, D-glucose 10, pH 7.4 when gassed with 95% O_2/5% CO_2. The solution also contained 1 mM Mg^{2+} in the form of $MgSO_4$.

Recording and stimulating techniques

Intracellular recordings were made from cells with the characteristics of CA1 pyramidal neurones in lesioned and unlesioned (contralateral) hippocampal slices (Ashwood *et al.*, 1986). Electrodes were filled with 3 M potassium acetate and had resistances of 60–90 MΩ. Recordings were made using an Axoclamp II in bridge mode. The data were stored on a Racal FM taperecorder and analysed on an Analogic D6000 waveform analyser or a BBC microcomputer. Where possible the signal was averaged on line.

The stimulating electrodes used in this study were bipolar and made from twisted Trimel insulated Ni/Cr wire. Orthodromic activation of cells in the CA1 area was obtained by positioning this electrode in the stratum radiatum on the border of the CA3 and CA1 areas. The duration of the monophasic stimulus pulse was 0.08 ms, with an interval of 15 s between stimuli.

D-2-amino-5-phosphonovalerate application protocol

The D-APV was made up to a concentration of 20 μM in normal ACSF. Once a cell had been penetrated a period of about 10 min was allowed for the cell to settle down. The control data on membrane properties and synaptic function were then collected (full test protocol 20 min). The solution containing D-APV in ACSF was then perfused and at 2 min intervals the input resistance, resting-potential and excitatory synaptic response were tested (short protocol). Ten minutes after the onset of perfusion of the D-APV the full test protocol (20 min) was repeated. Following the completion of this protocol the preparation was washed for a period of 40 min with normal ACSF before finally repeating the full test protocol for a third time. During the first 40 min of the washout, the short protocol was repeated every 10 min.

Results

D-APV was applied to fourteen pyramidal cells recorded from fourteen slices of lesioned hippocampus. For comparison recordings were also made from 7 cells in

the contralateral (control) hippocampus. Table 1 shows data from those cells impaled for sufficient time to wash out the APV. The mean resting potentials of these two groups of cells were not only nearly identical to each other, but also to previous results from this laboratory (Wheal *et al.*, 1984; Ashwood *et al.*, 1986). Unlike these previous studies, the input resistance of the cells from the unlesioned hippocampus measured in this study were higher than those from slices ipsilateral to the lesion. Despite this difference, D-APV (20 μM) had no effect on the resting membrane properties of either cell group (Table 1).

Effect of D-2-amino-5-phosphonovalerate on orthodromic bursting activity

Stimulation of the stratum radiatum of lesioned hippocampal slices at an intensity 1 V supra-threshold produced either a single spike or sometimes a burst of two or three action potentials. At higher stimulus intensities, i.e. 2 × threshold, between 2 and 10 action potentials were evoked (Figure 1). Bursts of action potentials were triggered from e.p.s.ps of relatively long duration (Table 1). At 2 × threshold intensity the duration was in the range of 18–206 ms. In contrast only a single action potential was evoked at 2 × threshold stimulation in the slices contralateral to the lesion (Figure 1). The underlying e.p.s.p. was very short (7–22 ms) with a mean of 11.3 ± 2.0 ms (± s.e.mean), as shown in Table 1.

When the lesioned slices were perfused with 20 μM D-APV both the number of action potentials and the amplitude and duration of the e.p.s.p. underlying the epileptiform burst were profoundly reduced in 14/14 cells tested (Figures 1 and 2). The number of action potentials that were blocked depended on the size of the burst. A burst of two or three action potentials evoked by 2 × threshold stimulation was reduced to a single spike. Larger bursts were reduced by 50% or more (Figure 1). The first action potential in the burst was never blocked by D-APV. The mean e.p.s.p. duration that was evoked by 2 × threshold stimulation was reduced from 50 ± 8.7 ms ($n = 7$) to 29.4 ± 2.0 ms (Table 1). After washing the preparation with normal ACSF the mean value of the response recovered to 47.5 ± 6.6 ms. This effect of the D-APV could also be seen on the response evoked by lower stimulus intensities (1 V suprathreshold) (Table 1). The D-APV (20 μM) had little or no effect on the excitatory response of cells in the contralateral unlesioned hippocampus (Figure 1; Table 1). Only 3/7 cells showed a slight reversible reduction in the duration of the e.p.s.p. at 2 × threshold stimulation. This was seen as a very small change in the shape of the after-positivity following the action potential (Figure 2).

Table 1 Effect of D-2-amino-5-phosphonovalerate (D-APV) (20 μM) on CA1 cells in the hippocampus ipsilateral and contralateral to a kainic acid lesion of CA3

Ipsilateral	*Control*	*D-APV*	*Wash*	
Resting potential (mV)	−62 ± 1.0	−62 ± 1.0	−63 ± 1.0	($n = 10$)
Input resistance (MΩ)	34 ± 2.5	35 ± 3.0	36 ± 2.7	($n = 8$)
E.p.s.p. duration (ms)				
1 V suprathreshold	38 ± 6.6	25 ± 4.0	29 ± 7.0	($n = 7$)
2 × threshold	50.0 ± 8.6	29.4 ± 2.0	47.5 ± 6.6	($n = 7$)
AHP peak amplitude (mV)	4.2 ± 1.0	3.6 ± 1.0	4.1 ± 1.1	($n = 7$)
I.p.s.p. amplitude* (mV)	3.3 ± 0.5	2.8 ± 0.6	1.9 ± 0.4	($n = 8$)
Contralateral				
Resting potential (mV)	−61 ± 1.5	−61 ± 1.6	−60 ± 1.3	($n = 7$)
Input resistance (MΩ)	45 ± 7.1	47 ± 8.1	47 ± 7.2	($n = 6$)
E.p.s.p. duration (ms)				
1 V suprathreshold	9.4 ± 1.4	8.4 ± 0.9	9.4 ± 1.5	($n = 7$)
2 × threshold	11.3 ± 2.0	10.0 ± 1.0	13.5 ± 2.5	($n = 7$)
AHP peak amplitude (mV)	5.4 ± 1.1	4.7 ± 1.0	4.0 ± 1.1	($n = 7$)
Early i.p.s.p. peak amp. (mV)	7.1 ± 1.1	7.0 ± 1.0	5.3 ± 1.0	($n = 7$)
Late i.p.s.p. peak amp. (mV)	7.6 ± 0.9	6.2 ± 1.0	4.4 ± 0.6	($n = 7$)

*No early i.p.s.p. only a late residual response.
Values are expressed as the mean ± s.e.mean. AHP = afterhyperpolarization.

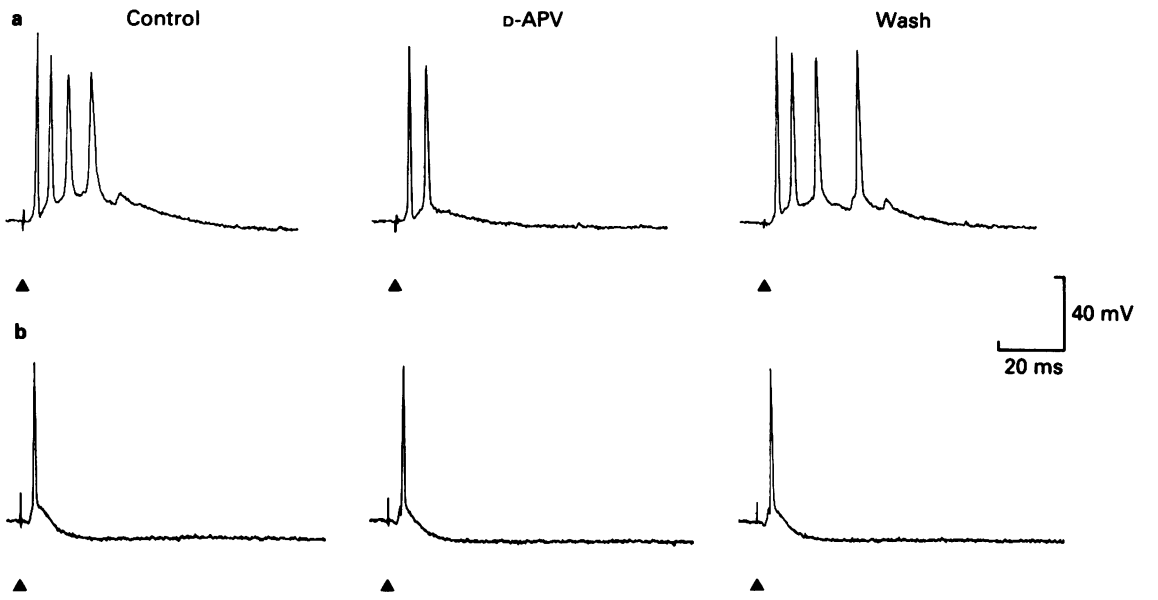

Figure 1 The effect of D-2-amino-5-phosphonovalerate (D-APV; 20 μM) on orthodromic activity evoked in CA1 cells (a) ipsilateral and (b) contralateral to the kainic acid lesion. In (a) 2 × threshold stimulation (▲) of cells in ipsilateral slices evoked an epileptiform burst of action potentials. In the presence of D-APV the burst was profoundly reduced. This effect was reversible following 40 min perfusion with normal ACSF. (b) D-APV had very little if any effect on the normal e.p.s.p. and action potential recorded in a contralateral cell in response to 2 × threshold stimulation.

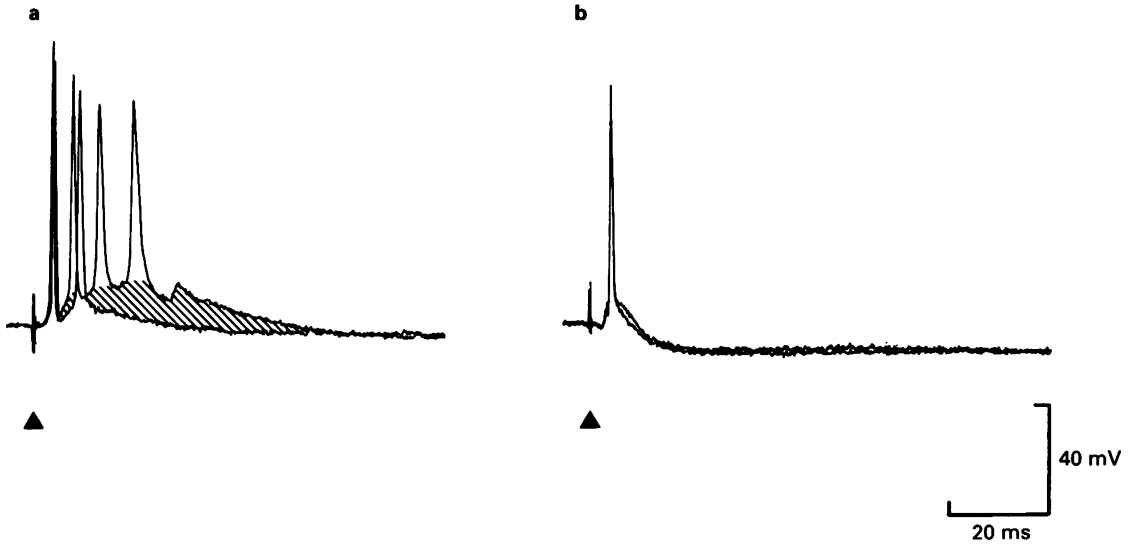

Figure 2 Recordings reformatted from Figure 1 to highlight the D-2-amino-5-phosphonovalerate (D-APV)-sensitive NMDA-receptor component of the evoked epileptiform burst (shaded area) in the slice ipsilateral (a) to the lesion. These are orthodromically activated (▲, 2 × threshold) responses before and during the application of 20 μM D-APV. (b) The control e.p.s.p. recorded in the contralateral hippocampus was relatively insensitive to D-APV. Only a very small change in the e.p.s.p. following the action potential was observed.

Effect of D-2-amino-5-phosphonovalerate on synaptic inhibition

In order to investigate the effects of D-APV on synaptic inhibition the intensity of the orthodromic stimulus was set at just suprathreshold for generating an action potential. The normal early and late i.p.s.ps were observed in hippocampal cells contralateral to the lesion and can be clearly seen in Figure 3. Only 2/14 cells from the lesioned hippocampi expressed an early i.p.s.p. whilst all the others only showed a residual late i.p.s.p., as shown in Figure 3. The mean peak amplitude of this late i.p.s.p. was only half that of cells in the contralateral hippocampus (Table 1). D-APV had no consistent effect on the peak amplitudes of the orthodromic i.p.s.ps in either type of preparation (Figure 3; Table 1). The mean peak amplitude of the late i.p.s.p. was slightly reduced in the presence of the drug but this was not reversible and reflected a gradual decline in the response size over the 2 h recording period (Table 1).

Effect of D-2-amino-5-phosphonovalerate on the afterhyperpolarization

An afterhyperpolarization (AHP) of long latency (approx. 230 ms) and duration (> 1 s) was evoked in cells from contralateral slices following injection of a depolarizing current pulse sufficient to trigger five action potentials (Figure 4). This response is thought to be mediated by a calcium-activated potassium conductance (Alger & Nicoll, 1980; Hotson & Prince, 1980; Lancaster & Wheal, 1984). In cells from lesioned slices this response was reduced or absent but a short latency AHP remained (Figure 4). There was no consistent effect of D-APV on either the late AHP recorded from ipsilateral or contralateral cells (Figure 4; Table 1) or on the current necessary to generate the burst of action potentials.

Discussion

D-APV was ineffective in blocking the e.p.s.p. evoked by Schaffer collateral afferents on to CA1 cells in slices of the hippocampus contralateral to the kainic acid lesion. This is in agreement with previous observations on the e.p.s.p. evoked in normal slices by stimulation of Schaffer collateral and commissural afferents (Koerner & Cotman, 1982; Collingridge *et al.*, 1983). A component of the e.p.s.p. sensitive to D-APV was only expressed in cells from lesioned slices where the

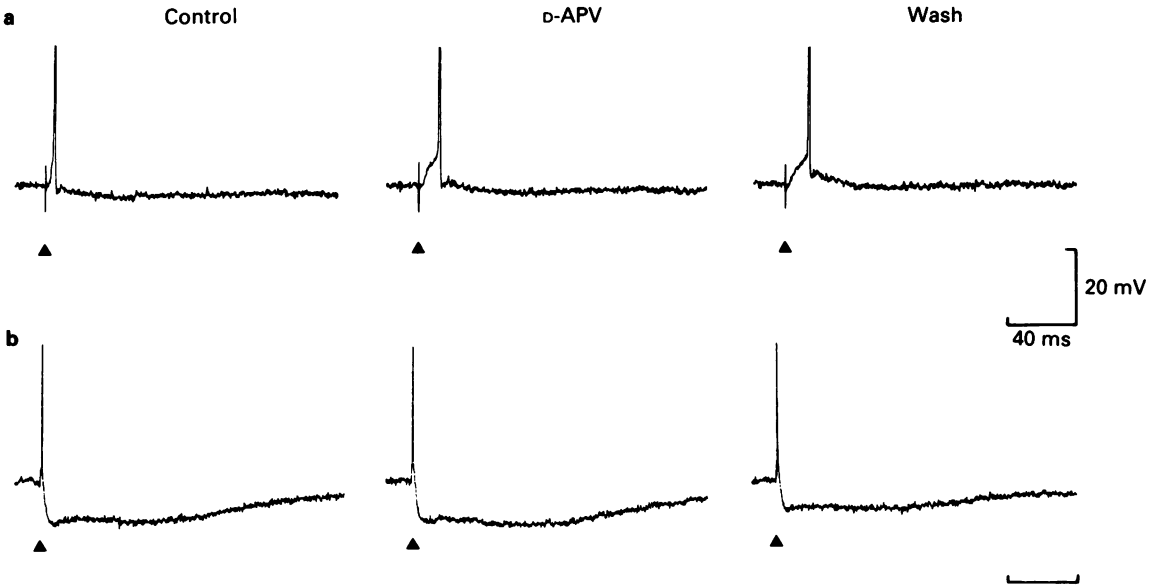

Figure 3 Orthodromically activated i.p.s.ps in cells (a) ipsilateral and (b) contralateral to the lesion in response to just suprathreshold (+ 1V) stimulation of the surviving commissural and Schaffer collateral afferents respectively. (b) A two component hyperpolarization consisting of an early and a late i.p.s.p occurred following the orthodromically evoked action potential. D-2-amino-5-phosphonovalerate (D-APV; 20 μM) had no effect on the amplitudes of these i.p.s.ps (resting membrane potential = − 58 mV). (a) Very little of either the early or the late i.p.s.p. was present following suprathreshold orthodromic activation in the lesioned hippocampus (resting membrane potential = − 60 mV). D-APV had no effect on the slight residual hyperpolarization. The amplitudes of the action potentials were attenuated by the digital sampling frequency.

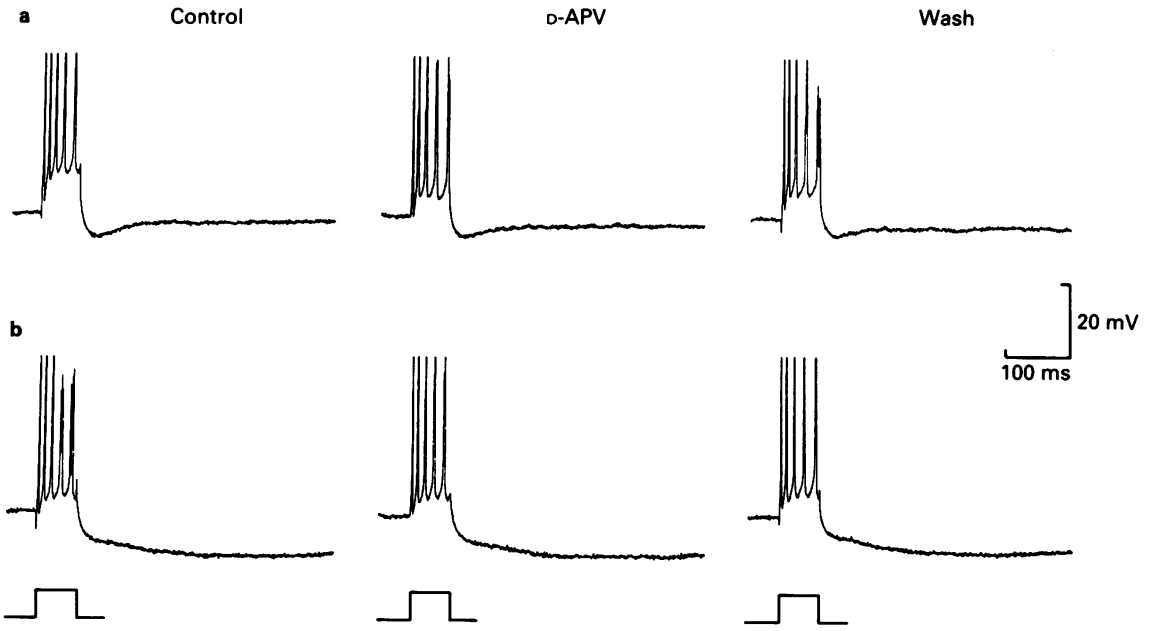

Figure 4 Recordings of the afterhyperpolarizations (AHPs) following bursts of 5 action potentials evoked by injecting depolarizing current pulses (60 ms). (b) Shows the lack of effect of D-2-amino-5-phosphonovalerate (D-APV) on the long latency and duration AHP that followed a burst of action potentials in a cell contralateral to the lesion. The timing of the current pulse, but not its amplitude is indicated. In contrast (a) shows the slow AHP was absent in a cell ipsilateral to the lesion, leaving a short latency and duration AHP. This response was also not affected by the perfusion of D-APV (20 μM). The action potential amplitudes were attenuated by sweep averaging ($n = 4$) and the digital sampling frequency.

NMDA antagonist not only reduced the area of the depolarization but also the number of action potentials in the epileptiform burst. This did not appear to be due to any non-specific effects of D-APV because the cell membrane potential and input resistance were unaltered by the drug. It was also not a result of any effects of D-APV on the spike generating mechanism as the current required to trigger a burst of five action potentials was unaltered. Furthermore, D-APV had no effect on i.p.s.p. or the AHP which makes it unlikely that the epileptiform burst of action potentials was attenuated by potentiation of these responses. It therefore seems reasonable to suggest that D-APV is blocking a component of the e.p.s.p. that is due to stimulation of NMDA receptors by an excitatory transmitter. This component is represented by the shaded area in Figure 2. It can clearly be seen that the NMDA-receptor-mediated component to the epileptiform e.p.s.p. is expressed very early, coincident with the first evoked action potential. Thus this response could well be associated with the genesis of the burst rather than just its maintenance. This contrasts with the relatively late occurrence of an NMDA receptor component in epileptiform bursting described by Dingledine *et al.* (1986). An early onset but slow synaptic response involving NMDA-receptors has also recently been observed in mouse spinal cord cultures (Mayer *et al.*, 1986) and hippocampal cultures (Forsythe, personal communication).

It has been suggested that a single excitatory transmitter such as glutamate may produce the conventional fast e.p.s.p. in normal CA1 pyramidal cells and also activate NMDA receptors (Herron *et al.*, 1985). This latter would not contribute to the generation of the e.p.s.p. because the ion channels were under voltage-dependent block by magnesium ions (Nowak *et al.*, 1984; Mayer *et al.*, 1984; Herron *et al.*, 1985). If this is true then what factors could contribute to the expression of an NMDA component of the e.p.s.p. in cells from lesioned slices? It is difficult to argue that the suppression of the bicuculline-sensitive early i.p.s.p. allows a normal e.p.s.p. to depolarize the cell sufficiently to remove enough of the magnesium channel block to produce the entire response. In our hands D-APV only had a slight attenuating effect on bicuculline-induced multiple population spike bursts compared to

its effect on similar bursts recorded from lesioned slices (Ashwood & Wheal, 1986). Furthermore intracellular studies by others show that D-APV blocks only the last action potential in the epileptiform burst produced by bicuculline (Herron *et al.*, 1986; Dingledine *et al.*, 1986). In contrast D-APV reduced the number of action potentials from lesioned slices by 50% or more. However, in the latter preparation both the bicuculline-insensitive late i.p.s.p. and the calcium-activated AHP are also reduced. A decrease in or loss of these three hyperpolarizing responses could exert a profound influence on the response of the cell to orthodromic input. This could be particularly significant if these hyperpolarizations were electrotonically close to the excitatory synapses and to stimulated NMDA receptors. This may in fact be the case since the AHP, the late i.p.s.p. and a component of the early i.p.s.p. have been localized to the cell dendrites (Bernardo *et al.*, 1982; Alger & Nicoll, 1982; Newberry & Nicoll, 1984) which is where the excitatory synapses and NMDA binding sites are situated in the hippocampus (Monaghan *et al.*, 1983). A conventional e.p.s.p. might then depolarize the membrane in the region of the NMDA-receptor-coupled ion channels to a sufficient level over the first few ms to produce a rapid removal of the channel block by magnesium ions. This could result in the early onset NMDA-receptor-mediated depolarization observed.

In conclusion, we have presented further evidence that NMDA-receptors contribute to the epileptic activity in a chronic model of temporal lobe epilepsy. However, in the hippocampus they do not appear to be involved in conventional excitatory transmission or in the control of early or late inhibition. This raises the possibility that NMDA-receptor antagonists such as D-APV or CPP (Davies *et al.*, 1986) or NMDA channel blockers such as MK 801 (Foster *et al.*, 1987) may be clinically effective as specific anticonvulsants.

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