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1S,3R-ACPD dose dependently induces a slow onset potentiation in the dentate gyrus in vivo

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Abstract

It has been demonstrated by others in vitro that application of 1*S*,3*R*-aminocyclopentane-2,3-dicarboxylic acid (ACPD) facilitates long-term potentiation and triggers a slow-onset potentiation in the hippocampus. This study examined the effect of ACPD in the dentate gyrus when applied in vivo. Weak tetanisation produced a short-term potentiation of field excitatory post-synaptic potential (EPSP) and population spike. A similar response was seen upon application of ACPD (40 μM in 5 μl vehicle) via the lateral cerebral ventricle 30 min prior to tetanus, whereas ACPD (80 μM/5 μl) facilitated short-term potentiation into long-term potentiation. (*R*,*S*)-α-Methyl-4-carboxyphenyl-glycine (MCPG 200 mM/ 5 μl), completely inhibited this effect. ACPD had no effect on baseline recordings at 40 and 80 μM/5 μl, however 4 mM/5 μl ACPD induced a slow-onset potentiation of field EPSP and population spike which was maintained for over 4 h. MCPG or D-2-amino-5-phosphonopentanoate (AP5 20 mM/5 μl) applied prior to ACPD completely inhibited this effect. These results suggest that previously reported in vitro effects of ACPD in the CA1 region, also occur in the dentate gyrus in vivo. Furthermore, they confirm that activation of mGlu receptors by ACPD in vivo facilitates long-term potentiation, and indicate that in the dentate gyrus, ACPD-induced slow-onset potentiation is NMDA receptor-dependent.

Keywords: Hippocampus; Long-term potentiation; 1*S*,3*R*-ACPD (1*S*,3*R*-aminocyclopentane-2,3-dicarboxylic acid); Slow-onset potentiation; MCPG ((*R*,*S*)-α-methyl-4-carboxyphenyl-glycine); Metabotropic glutamate receptor; Dentate gyrus; (In vivo)

1. Introduction

Metabotropic glutamate (mGlu) receptors comprise a class of receptors which are coupled to intracellular second messenger systems (Gasic and Hollman, 1992; Houamed et al., 1991; Martin et al., 1992; Schoepp et al., 1990; Tanabe et al., 1992). They are a significant functional component of the mechanisms underlying synaptic plasticity, illustrated by the fact that mGlu receptor activation plays an important role in the induction of long-term potentiation (Bashir et al., 1993; Behnisch and Reymann, 1993). 1*S*,3*R*-Aminocyclopentane-2,3-dicarboxylic acid (ACPD) is a selective mGlu receptor agonist which can give rise to excitation and depression of synaptic transmission by activation of different classes of mGlu receptors (Baskys and Malenka, 1991a, b; Bortolotto and Collingridge, 1993, 1995; Cahusac, 1994; Pook et al., 1992; Liu et al., 1993). More specifically, with regard to long-term potentiation, ACPD application coupled with a high-frequency stimulation has been shown to facilitate the induction of long-term potentiation in vitro (McGuinness et al., 1991a, b; Aniksztein et al., 1991; Behnisch and Reymann, 1993). Additionally, it has been shown that transient application of ACPD in vitro will induce a slow-onset long-term potentiation of synaptic transmission in the CA1 region of rat hippocampal slices which is NMDA receptor-independent (Bortolotto and Collingridge, 1992, 1993, 1995).

This study set about to examine the effects of ACPD on excitatory synaptic transmission in vivo. We report that ACPD dose dependently facilitates long-term potentiation and furthermore induces a slow-onset long-term potentiation which is NMDA receptor-de-

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pendent. These phenomena occur in a region which has not been examined to date, to wit, the dentate gyrus.

2. Materials and methods

2.1. Animals

Male Wistar rats (7 weeks old at the time of surgery) were used. The animals were fed lab chow and water ad lib and maintained in a thermoregulated environment (19–23°C) during a 12 h light/dark cycle.

2.2. Surgical preparation

Animals were anaesthetised with sodium pentobarbitone (Nembutal, 40 mg/kg, i.p) and placed in a stereotactic unit. A scalp incision of approximately 1 cm in length was made from a point between the eyes, along the midline towards the back of the skull. The periosteum was then removed from the surface of the skull by scraping, and the surface swabbed with 3% hydrogen peroxide to dry and clean it.

Two stainless steel screws (1.5 mm diameter) to which pin socket connectors were subsequently attached were inserted into the skull via a drill hole, without piercing the dura. One served as a ground screw electrode and was placed 8 mm posterior to bregma and 4 mm right of the midline. The other was used as a reference electrode and was placed 4 mm anterior to bregma and 4 mm right of the midline, over the frontal sinus. Following screw insertion the area around the screw was swabbed with 3% hydrogen peroxide and a drop of cyanoacrylate glue placed at the junction of screw and skull in order to help fix and to seal it. An outer guide cannula was inserted into the lateral cerebral ventricle at 0.8 mm posterior to bregma and 1.6 mm lateral to the midline (coordinates according to Paxinos and Watson, 1986). Dental acrylic (Paladur, Heraeus Kulzer GmbH) was then applied around the screws, cannula and adjacent skull area to anchor the assembly firmly in position. A monopolar recording and a bipolar stimulating electrode, were made from teflon coated stainless steel wire (0.1 mm diameter). The free ends of the electrodes were passed through a rubber pin socket connector which was attached to an oscilloscope and stimulator, respectively.

A drill hole was made (1.5 mm diameter) for the recording electrode which was 2.8 mm posterior to bregma and 1.8 mm lateral to the midline. A second drill hole (1 mm diameter) was then made 6.9 mm posterior to bregma and 4.1 mm lateral to the midline for the stimulating electrodes. The dura was pierced through both holes and the recording and stimulating electrodes lowered into the dentate gyrus granule cells and the medial perforant path, respectively. Once verification of the location of the electrodes was complete the skull was once more swabbed with 3% hydrogen peroxide, superglue applied to the points of electrode insertion and the entire assembly sealed and fixed to the skull with dental cement.

To verify that the electrodes were in fact placed correctly in the dentate gyrus, their location was carefully monitored throughout the process of electrode implantation during surgery. This was done by taking recordings of evoked field potentials via the implanted electrodes. Furthermore, following the conclusion of the study, histological verification of the localisation of the electrodes and cannula was carried out. In brief, animals were given a lethal dose of pentobarbitone (60 mg/ml, i.p.), and the entire brain was removed and fixed in formalin. After a period of 48 h, a block section of the cortex and hippocampal area was prepared. The exact location of the electrodes was then determined using light microscopy of the (100–300 μM) sections.

The animals were allowed between 5–7 days to recover from surgery. During this period they were monitored closely for infection or distress and handled regularly. Throughout each experiment the animals could move freely, being contained in purpose-designed boxes ($40 \times 40 \times 40$ cm), with the implanted electrodes connected by a flexible cable to a stimulation unit and an amplifier. Evoked potentials were displayed and analysed via a PC. Throughout the experiments the electroencephalograph (EEG) of each animal was continuously monitored.

2.3. Measurement of evoked potentials

The field excitatory post-synaptic potential (EPSP) slope function was employed as a measure of excitatory synaptic transmission, and the population spike amplitude was employed as an indication of the level of excitation of the granule cell population in the dentate gyrus. To obtain these measurements, an evoked response was generated in the dentate gyrus granule cell layer by stimulating at low frequency (0.025 Hz) with single biphasic square wave pulses of 0.1 ms duration per half wave, generated by a constant current isolation unit. For each time point measured during the experiments, five records of evoked responses were averaged. The amplitude of population spike was measured from the peak of the first positive deflection of the evoked potential to the peak of the following negative potential. Dentate gyrus field EPSP slope function was measured as the maximal slope through the five steepest points obtained on the first positive deflection of the potential.

By means of input/output curve determination the maximum population spike amplitude was found, and

during experiments all potentials employed as baseline criteria were evoked at a stimulus intensity which produced 40% of this maximum.

2.4. Tetanisation parameters

In the dentate gyrus, long-term potentiation was induced by a 'strong' tetanus of 200 Hz (10 bursts of 15 stimuli, 0.2 ms stimulus duration, 10 s interburst interval) and a stimulus amplitude as was used for recordings. Short-term potentiation was generated by using only three bursts ('weak tetanus') as opposed to ten for long-term potentiation.

2.5. Compounds

ACPD, D-2-amino-5-phosphopentanoate (AP5) and (*R,S*)-α-methyl-4-carboxyphenyl-glycine (MCPG) were obtained from Tocris Cookson, Bristol, UK. For injection, ACPD was dissolved initially in 1 mM NaOH, and then further diluted in 0.9% sodium chloride. MCPG and AP5 were first dissolved in 1 μl sodium hydroxide solution (1 M), and then made up to a 5 μl volume with 0.9% sodium chloride.

2.6. Drug treatment

Throughout the experiments, drug or vehicle injections were administered via a cannula inserted through the outer guide cannula which was placed in the lateral cerebral ventricle, following measurement of the baseline for 30 min from the dentate gyrus of the same hemisphere. The cannula was inserted before the baseline measurements were taken, and left in place for the duration of the experiment so as not to create an artifact in recordings due to its insertion or removal. The drugs were injected in a 5 μl volume over a 6 min period via a Hamilton syringe. In short-term potentiation experiments, a tetanus was applied 30 min following ACPD or vehicle injection, with measurements then taken at $t = 5$, 10, 15 and then 15 min intervals up to 4 h, and then a 24 h measurement was also obtained. For baseline studies, the effect of the compounds was monitored at $t = 5$, 10, 15 and then at 15 min intervals for 4 h. Where MCPG or vehicle pre-injection preceded ACPD or vehicle administration the baseline was monitored for 30 min followed by MCPG or vehicle application, 30 min later ACPD or vehicle was applied, and the protocol followed as described above.

Drug doses were employed that were calculated as those which would theoretically achieve the brain concentration required, assuming the brain volume to be approximately 2 ml. Thus for an estimated brain concentration of ACPD of 0.1, 0.2 and 10 μM, we injected 5 μl of an ACPD solution of 40 μM, 80 μM and 4 mM, respectively. For an estimated brain concentration of 500 μM MCPG and 50 μM AP5, 200 mM and 20 mM in a 5 μl injection volume were used, respectively.

2.7. Data analysis

The baseline field EPSP or population spike data were obtained by averaging the response to stimulating the perforant path, to obtain five sweeps at 40 s intervals, every 5 min over a period of 30 min. Baseline was similarly monitored for a further 30 min following vehicle/drug injection, and then at 5, 10, 15 and every subsequent 15 min intervals for 4 h. In long-term potentiation studies, following tetanus, measurements were taken at 5, 10, 15 and every subsequent 15 min interval with an additional five measurements taken after 24 h had elapsed. The data were then expressed as mean percentages pre-injection baseline reading ± standard error of the mean (S.E.M.).

Statistical significance of the difference between means was estimated using the Student's *t*-test. The probability levels interpreted as statistically significant were $P < 0.001$ (***), $P < 0.01$ (**), $P < 0.05$ (*).

3. Results

3.1. Effect of ACPD on tetanus-induced short-term potentiation

When a weak tetanus was applied via the perforant path synapses to the dentate gyrus granule cells, a short-term potentiation of both population spike ($n = 12$) and field EPSP ($n = 14$) was generated which decayed gradually until approximately 2 h after tetanisation, whereupon the population spike amplitude and field EPSP slope function had returned to baseline values. The same time course for short-term potentiation was found when ACPD vehicle was applied 30 min before tetanus ($n = 11$, population spike; $n = 14$, field EPSP; Fig. 1A,B). ACPD injected into the lateral cerebral ventricle as 40 μM in a 5 μl volume produced a reduction of short-term potentiation of population spike amplitude to 212 ± 15% at $t = 5$ ($n = 11$) which was significant when compared to 250 ± 8% at $t = 5$ in controls ($n = 11$, $P < 0.05$, Fig. 1A). Conversely, an opposite response was noted in field EPSP slope function in that an enhancement of short-term potentiation was seen following application of ACPD ($n = 8$, $P < 0.05$, 170 ± 7% *at* $t = 5$ compared to controls $n = 14$, 145 ± 6% at $t = 5$, Fig. 1B). Both population spike and field EPSP values returned to baseline levels by $t = 120$ approximately.

When 80 μM ACPD in 5 μl was administered 30 min prior to weak tetanisation, no difference in short-

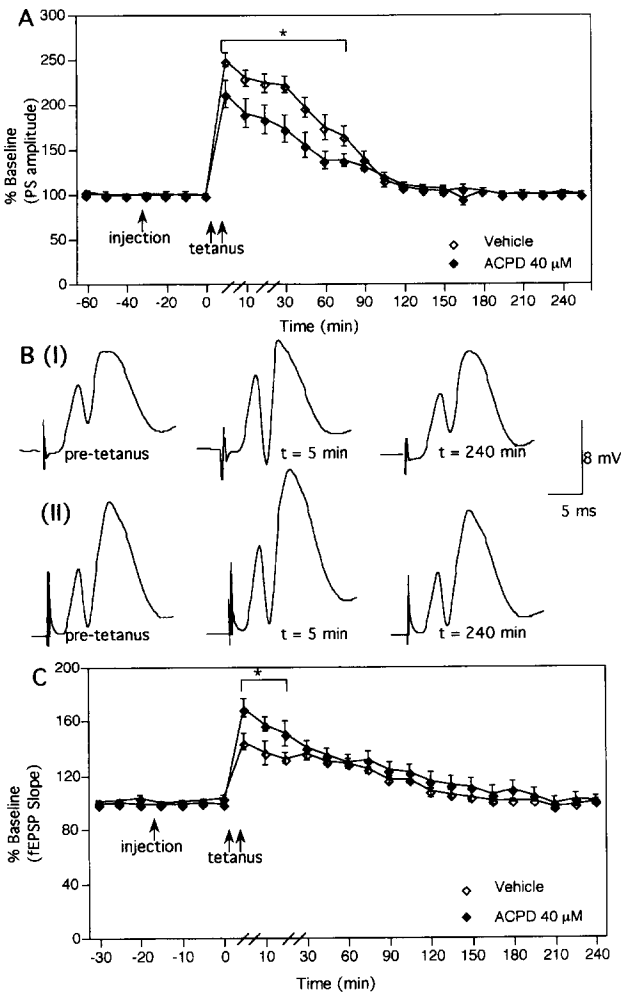

Fig. 1. (A) ACPD (40 μM/5 μl) significantly reduces the amplitude of short-term potentiation with regard to population spike amplitude in the rat dentate gyrus ($n = 11$, $P < 0.05$ from $t = 5$ min compared with vehicle-injected animals, $n = 11$). $^{*}P < 0.05$. (B) Original analog traces showing population spike responses in the dentate gyrus, at three time points: pre-tetanus, $t = 5$ min and $t = 4$ h post-tetanus in (I) a vehicle-injected animal, and (II) an animal injected with ACPD (40 μM/5 μl). (C) ACPD (40 μM/5 μl) significantly enhances the amplitude of short-term potentiation with regard to fEPSP slope function in the rat dentate gyrus ($n = 8$, $P < 0.05$ compared with vehicle-injected animals, $n = 14$). $^{*}P < 0.05$.

term potentiation of population spike ($n = 10$) was noted compared to population spike controls ($n = 11$, Fig. 2A). However, this short-term potentiation was prolonged into a long-term potentiation of population spike which lasted for over 24 h ($P < 0.01$ from $t = 90$ compared to controls). With regard to field EPSP ($n = 10$), a clear enhancement of short-term potentiation was produced by weak tetanus following ACPD application ($P < 0.01$ from $t = 5$, compared to controls $n = 14$). The field EPSP immediately following tetanisation was 134 ± 6% of pre-tetanus baseline in controls and 169 ± 10% in ACPD injected. Additionally, a prolongation of short-term potentiation into long-lasting long-term potentiation was obtained, which persisted over 24 h. The slope function value for field EPSPs in the drug-injected group at 24 h was 152 ± 7% of pre-

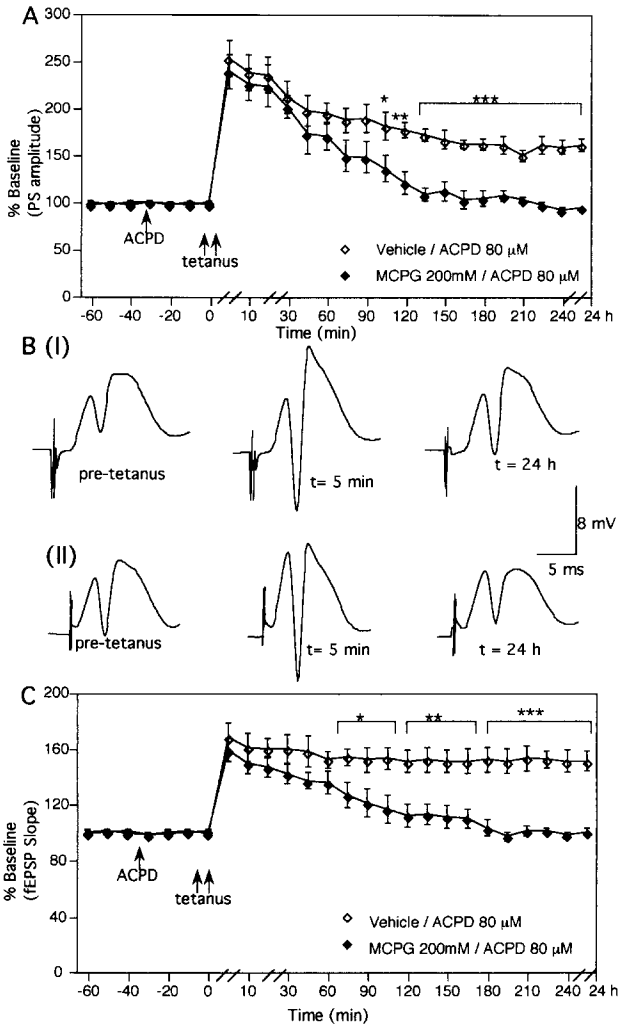

Fig. 2. (A) ACPD significantly prolongs short-term potentiation into a long-lasting long-term potentiation of population spike at a concentration of 80 μM/5 μl ($n = 10$, $P < 0.01$ from $t = 90$ min compared with vehicle-injected animals, $n = 11$, not shown) in the dentate gyrus. MCPG (200 mM/5 μl) applied before the ACPD dose significantly inhibits this effect resulting in short-term potentiation ($n = 8$, $P < 0.05$ from $t = 105$ min). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. (B) Original analog traces showing long-term potentiation responses in CA1. Three time points are shown: pre-tetanus, $t = 5$ min and $t = 24$ h post-tetanus in (I) an ACPD (80 μM/ 5 μl)-injected animal, and (II) an animal injected with MCPG (200 mM/5 μl) before ACPD (80 μM/5 μl). (C) ACPD (80 μM/5 μl) significantly increases the short-term potentiation of fEPSP, and additionally enhances short-term potentiation into a long-lasting long-term potentiation of fEPSP ($n = 10$, $P < 0.01$ from $t = 90$ min compared with vehicle-injected animals, $n = 14$, not shown) in the dentate gyrus. MCPG (200 mM/5 μl) applied before the ACPD dose significantly inhibits both the increase in short-term potentiation and the enhancement to long-term potentiation, resulting in a time course of short-term potentiation which is not significantly different from controls ($n = 8$, $P < 0.05$ from $t = 75$ min). $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

tetanus baseline, whereas the control group returned to baseline values by $t = 120$ min.

Strong tetanus given after vehicle injection normally results in a long-term potentiation of both population spike and field EPSP which lasts over 24 h. MCPG, however, when administered prior to vehicle injection and strong tetanus, is able to block the induction of long-term potentiation leaving only a short-term potentiation of about 2 h. This response is similar in profile to a weak tetanus-induced short-term potentiation (Manahan-Vaughan and Reymann, 1995b). MCPG (200 mM in 5 μl) when applied 30 min prior to 80 μM ACPD and weak tetanus completely inhibited both the enhancement of short-term potentiation and the production of long-term potentiation of both population spike ($n = 8$) and field EPSP ($n = 8$) following weak tetanus ($P < 0.05$ from $t = 105$ compared to population spike controls, $n = 10$, Fig. 2A; $P < 0.05$ from $t = 75$ compared to field EPSP controls, $n = 10$, Fig. 2B). Immediately after tetanus the population spike amplitude was $240 \pm 17\%$ compared to $254 \pm 15\%$ in controls, and the field EPSP was $160 \pm 8\%$ compared to a control value of $169 \pm 10\%$. This short-term potentiation returned to baseline values at $t = 135$ for population spike, and $t = 120$ approximately for field EPSP.

3.2. Effect of ACPD on baseline responses

When ACPD was injected into the lateral cerebral ventricle as 40 μM or 80 μM in a 5 μl volume, and the baseline response monitored for 4 subsequent h, no effect was seen either with regard to population spike (40 μM: $n = 7$; 80 μM: $n = 10$, compared to controls, $n = 11$) or field EPSP (40 μM: $n = 6$; 80 μM: $n = 8$ compared to controls, $n = 13$). However, when ACPD was applied in a concentration of 4 mM in 5 μl a clear enhancement of both population spike ($n = 8$) and field EPSP ($n = 8$) was seen which was statistically significant from $t = 60$ post-injection for population spike compared to controls ($n = 11$, Fig. 3A), and significant from $t = 15$ for field EPSP ($P < 0.05$ compared to controls, $n = 13$, Fig. 3B). At $t = 60$ min post-injection the amplitude of the population spike was $150 \pm 19\%$ in drug-injected animals compared to $98 \pm 2\%$ in controls. For field EPSP the slope function was $110 \pm 9\%$ at $t = 15$ compared to $102 \pm 2\%$ in controls. This effect persisted until measurement ceased at $t = 4$ h post-injection wherupon population spike was $185 \pm 26\%$ in drug-injected animals and $103 \pm 3\%$ in controls. At $t = 4$ h field EPSP was $146 \pm 6\%$ in drug-injected animals and $102 \pm 2\%$ in controls.

When MCPG (200 mM in 5 μl) was administered 30 min prior to 4 mM ACPD, this enhancement was completely inhibited, and a response which was not statistically significant from control baseline values was observed in both population spike ($n = 6$ compared to controls, $n = 8$, Fig. 3A) and field EPSP ($n = 6$ compared to controls, $n = 8$, Fig. 3B). Similarly, when AP5 (20 mM in 5 μl) was applied 30 min before 4 mM ACPD, the enhancement of both population spike amplitude ($n = 8$) and field EPSP slope ($n = 6$) by ACPD was also inhibited, leaving only a slight increase of baseline which was not significant compared to controls (AP5 administered prior to ACPD vehicle, $n = 10$). AP5 itself has no effect on baseline with

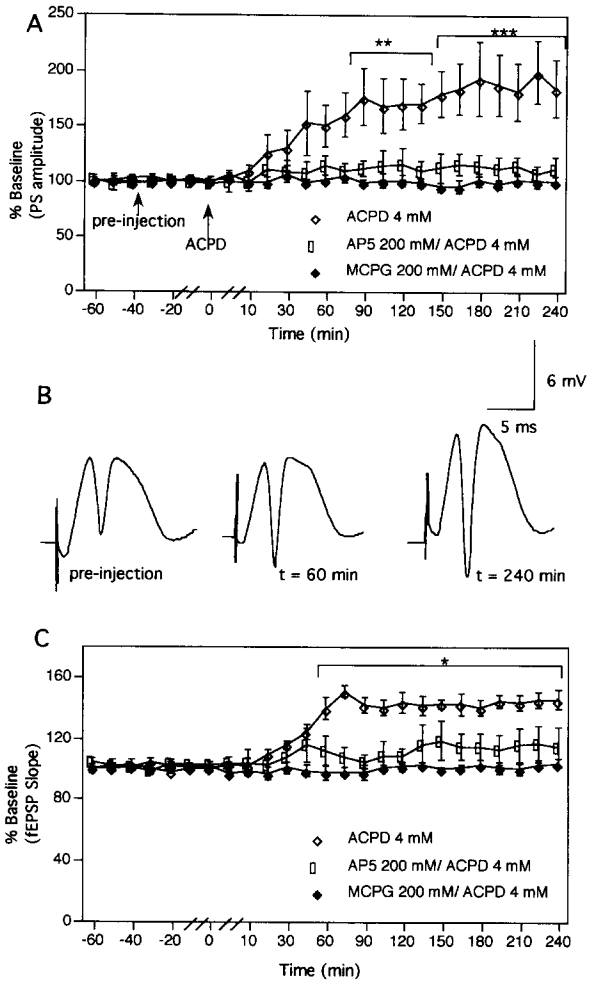

Fig. 3. (A) ACPD (4 mM/5 μl) induces a slow-onset potentiation of population spike in the dentate gyrus ($n = 8$) which is significant compared to vehicle-injected controls ($n = 11$, $P < 0.01$ from 60 min after ACPD injection, not shown). Both MCPG (200 mM/ 5 μl, $n = 6$, $P < 0.01$ from $t = 60$ min) and AP5 (20 mM/5 μl, $n = 8$, $P < 0.05$ from $t = 75$ min) completely block the potentiation induced by ACPD (4 mM/5 μl) of population spike amplitude. (B) Original analog traces showing the field potentials evoked from the dentate gyrus before, 60 min and 4 h following application of ACPD (4 mM/5 μl). (C) ACPD (4 mM/5 μl) induces a slow-onset potentiation of fEPSP slope function in the dentate gyrus ($n = 8$), which is statistically significant compared to vehicle-injected controls ($n = 10$, $P < 0.05$ from $t = 30$, not shown). Both MCPG (200 mM/5 μl, $n = 6$) and AP5 (20 mM/ 5 μl, $n = 6$) completely block the effect of ACPD (4 mM/5 μl) on fEPSP slope function ($P < 0.05$ from $t = 45$ min and $P < 0.05$ from $t = 60$ min post-injection of ACPD respectively).

regard to population spike or field EPSP ($n = 10$) when compared to saline-injected animals ($n = 12$).

4. Discussion

4.1. The effect of ACPD on weak tetanus-induced short-term potentiation

The aim of this study was to examine the effects of ACPD on synaptic transmission in vivo, and to investigate whether previously reported in vitro effects of the compound are also represented in this system. Our results indicate that although similar responses were seen to occur in vivo with regard to reported in vitro data, at the same time differences in the response of the dentate gyrus to ACPD take place when compared to the CA1 region.

ACPD at the lower concentration of 40 μM/5 μl, clearly did not exhibit facilitatory effects on tetanus-induced long-term potentiation. However, evidence of some modulation of short-term potentiation occurred. Whereas a reduction of population spike was seen with regard to short-term potentiation following ACPD, an increase in field EPSP was concurrently evoked. It has been widely reported that ACPD produces a depression of synaptic transmission in CNS regions (Taylor and Cahusac, 1994; Baskys and Malenka, 1991a, b; Lovinger, 1991; Garaschuk et al., 1992; Glaum and Miller, 1993; Harvey et al., 1991). Although no such depression was seen with regard to baseline measurements following application of ACPD, a decrease of the short-term potentiation amplitude of population spike following application of ACPD 40 μM/5 μl and weak tetanus occurred.

At a concentration of 80 μM/5 μl, ACPD produced a clear facilitation of short-term potentiation of both population spike and field EPSP, resulting in a long-lasting long-term potentiation. This is in agreement with previous work in vitro (McGuinness et al., 1991a, b) which reports that ACPD facilitates the induction of both short-term potentiation and long-term potentiation. It has been previously shown in vivo that MCPG in a similar concentration has no independent effects on basal synaptic transmision but will inhibit long-term potentiation resulting in a transient short-term potentiation (Manahan-Vaughan and Reymann, 1995a). This response is consistent with the antagonism of mGlu receptors. In this study, the facilitatory effect of ACPD was also blocked by prior application of MCPG; this supports the assumption that this effect is mediated by mGlu receptors. As no reduction in the short-term potentiation amplitude of population spike was seen when this higher concentration of ACPD was used, this could imply that enhancing the ACPD concentration counteracts the effects seen with 40 μM ACPD. This may occur because 80 μM ACPD is at a high enough concentration to recruit other mGlu receptor subtypes which are insensitive to the drug at the lower concentration of 40 μM. That the field EPSP was enhanced at this concentration as well as at 40 μM ACPD whereas the population spike was not, could imply that the population spike and field EPSP responses are modulated by different subtypes of mGlu receptors.

4.2. The effect of ACPD on basal synaptic transmission

In this study, ACPD produced a gradual, pronounced and long-lasting potentiation of synaptic transmission, as seen in the responses of both population spike and field EPSP. Preliminary studies carried out in the CA1 region in vivo indicate that a similar response is seen in this region (Manahan-Vaughan and Reymann, 1995b). A difference in the response to AP5 application when compared to findings with regard to CA1 in vitro was found however, in that AP5 completely blocked the slow onset potentiation produced by 4 mM ACPD. That AP5 blocked this effect implies that unlike reports for the CA1 region (Bortolotto and Collingridge, 1992, 1993, 1995), this effect is NMDA receptor-dependent, but agrees with findings by others in vitro that this mGlu receptor effect is mediated by NMDA receptors in the dentate gyrus (O'Connor et al., 1994).

In dentate gyrus slow onset potentiation would thus seem to occur via a mechanism involving NMDA receptors, whereas in CA1, this effect may be mediated through mGlu receptor interaction with AMPA receptors, as proposed by Bortolotto and Collingridge (1995). However, it is as yet unclear whether a synergistic activation of mGlu receptors and NMDA receptors is necessary for slow-onset potentiation to occur in dentate gyrus, as is the case in electrically induced long-term potentiation (Behnisch and Reymann, 1993). It is possible that in the CA1 region, a sequence of events involving mGlu receptor-triggered glutamate release takes place following application of ACPD. (In fact it has been shown in vivo by Sacaan and Schoepp (1992) that ACPD application induces transmitter release). This is supported by the finding that slow-onset potentiation in CA1 only takes place when the connectivity of CA1 to CA3 neurons is intact (Bortolotto and Collingridge, 1995). This could indicate that following ACPD application, a presynaptically mediated enhanced release of glutamate takes place in CA1 which leads to co-activation of mGlu receptors and ionotropic glutamate receptors. If this is also the case in dentate gyrus, a presynaptic activation of glutamate release from the perforant path could similarly give rise to coactivation of dentate gyrus mGlu receptors and ionotropic glutamate receptors. Perhaps in CA1 the

co-activation of mGlu receptors with AMPA/kainate receptors is sufficient for slow-onset potentiation to occur, whereas in dentate gyrus a co-activation of NMDA receptors is required.

In conclusion, in this study we have found that low concentrations of ACPD induce a dose-dependent alteration in population spike to field EPSP coupling and a facilitation of short-term potentiation into long-term potentiation. These responses could be derived as a result of the differential localisation of mGlu receptors in the hippocampus, their respective sensitivity to ACPD and/or their corresponding coupling mechanisms. Furthermore, it would appear that two forms of ACPD-induced slow-onset potentiation occur in the hippocampus, comprising an NMDA receptor-independent form in CA1, and an NMDA receptor-dependent form in dentate gyrus. These findings add to the growing body of information which supports the assumption that potentiation of synaptic transmission in the hippocampus occurs in distinct, region-dependent forms.

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