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Presynaptic actions of glutamate receptor agonists in the CA1 region of rat hippocampus in vitro

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Abstract

A grease-gap recording technique which allows the monitoring of presynaptic d. c. potentials without contamination of potentials from postsynaptic elements was used to examine presynaptic actions of glutamate agonists in the CA1 region of rat hippocampus. Presynaptic depolarizations through the activation of 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX)-and 2-amino-5-phosphonovaleric acid (APV)-sensitive receptors could be induced by applied agonists. In addition, the *N*-methyl-D-aspartate (NMDA)-induced depolarization was smaller in the presence of extracellular Mg^{2+} suggesting some similarity to postsynaptic NMDA receptors. The (1*S*,3*R*)-1-aminocyclopentane-*trans*-1,3-dicarboxylic acid (t-ACPD)-induced depolarization was antagonized by L-2-amino-3-phosphonopropionic acid (L-AP3) but was also sensitive to APV + CNQX, creating ambiguity as to the type of receptors involved. These results suggest that the activation of glutamate autoreceptors leads to a presynaptic depolarization.

Keywords: Presynaptic action; Glutamate; (D.C. potential); Grease-gap; Hippocampus; Autoreceptor

1. Introduction

In the hippocampus, binding sites for ionotropic and metabotropic glutamate receptors are present throughout the CA1 subfield (Dewar et al., 1991; Greenamyre et al., 1985b; Monaghan et al., 1985). The contributions of the receptors to postsynaptic neuronal function have been well characterized electrophysiologically and pharmacologically (Collingridge and Lester, 1989). Although, biochemical studies suggest that activation of glutamate autoreceptors leads to changes in transmitter release (Crowder et al., 1987; Martin et al., 1991; Potashner and Gerard, 1983), direct electrophysiological evidence for these receptors is lacking mainly due to the difficulty in recording from presynaptic terminals. In the present study, a grease-gap technique for recording presynaptic d. c. potentials (Morishita and Sastry, 1994) was employed to examine the actions of glutamate agonists on Schaffer collateral terminals in the CA1 region of rat hippocampal slices. A preliminary report of these results was presented at a scientific meeting (Shew et al., 1994).

2. Materials and methods

Transverse hippocampal slices (450 μm) from male Wistar rats (100–150 g) were prepared and maintained as previously described (Morishita and Sastry, 1994). Slices were placed in a recording chamber superfused (2 ml/min) with oxygenated (95% O_2-5% CO_2) control medium comprised of (in mM): NaCl, 120; KCl, 3.1; $NaHCO_3$, 26; NaH_2PO_4, 1.8; $MgCl_2$, 2; $CaCl_2$, 2 and D-glucose, 10. Extracellular d. c. potentials were recorded either from an isolated section of stratum radiatum (Fig. 1B) or alveus (Fig. 1A). In some experiments, d. c. potentials were evoked (at 0.1 Hz) with a bipolar concentric stimulating electrode placed in the stratum radiatum outside the recording pipette; presynaptic d. c. potentials evoked by a tetanic stimulation of the stratum radiatum (5 Hz, 5 s) were also recorded in other experiments.

In experiments where blockade of K^+ channels was desired, slices were exposed to a medium containing

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tetraethylammonium chloride (25 mM), 4-aminopyridine (2 mM) and CsCl (3 mM). In this medium the concentration of NaCl was decreased by 27 mM and KCl was not added. In experiments where slices were exposed to a Mg^{2+}-free medium the Ca^{2+} concentration was increased to 4 mM. Conversely, when a Ca^{2+}-free medium was used the Mg^{2+} concentration was increased to 4 mM.

All drugs were applied by superfusion and no liquid junction potentials were detected. Concentration-response curves for glutamate agonists were constructed where d. c. potential shifts (in mV) were expressed as the means ± S.E.M. Data were also expressed by representing the control agonist responses as 100% and normalizing (means ± S.E.M.) these responses in the presence of antagonists. A one-or two-tailed Student's t-test ($P < 0.05$) was used to statistically analyze the data. In experiments involving electrically evoked d. c. potential responses, control studies were performed in which the recording, reference and stimulating electrodes were submerged in the superfusion medium and the stimulations were delivered in the absence of a hippocampal slice. In these experiments, no response, other than the stimulus artifact, was observed.

Sodium glutamate, *N*-methyl-D-aspartate (NMDA), 2-amino-5-phosphonovaleric acid (APV), γ-aminobutyric acid (GABA), picrotoxinin, 4-aminopyridine, cesium chloride (CsCl) and tetrodotoxin were obtained from Sigma Chemicals. 6-Cyano-7-nitroquinoxaline-2,3-dione (CNQX) and L-2-amino-3-phosphonopropionic acid (L-AP3) were purchased from Tocris Neuramin. Tetraethylammonium chloride was obtained from U.B.C. Chemistry Stores. (1*S*,3*R*)-1-Aminocyclopentane-*trans*-1,3-dicarboxylic acid (t-ACPD), Tocris Neuramin, was a gift from Dr. J.W. Goh.

3. Results

In order to demonstrate that the stratum radiatum grease-gap electrode detected d. c. potentials arising from presynaptic and not from postsynaptic elements, we compared evoked (by stimulating the stratum radiatum at 0.1 Hz) d. c. potentials recorded from the stratum radiatum with those recorded from the alveus. Included in the d. c. potential recorded by the alveus electrode was a large population excitatory postsynaptic potential (EPSP) and a population spike (Fig. 1C). CNQX (20 μM, 15 min, Fig. 1C) completely blocked the population spike and the population EPSP and uncovered the presynaptic volley which was blocked by a subsequent exposure to tetrodotoxin (0.1 μM; Fig. 1C). However, the d. c. potential recorded by the stratum radiatum electrode included only a tetrodotoxin-sensitive presynaptic volley which was not antagonized by CNQX or by exposure to a Ca^{2+}-free medium (Fig. 1D). Moreover, superfusion of the slices with a Mg^{2+}-free medium converted the d. c. potential recorded from the alveus into a multiple wave-like response (Fig. 1C), but left the d. c. potential response from the stratum radiatum unchanged (Fig. 1D). These results together with previous observations which have utilized the same recording technique to distinguish presynaptic from postsynaptic GABA receptor-mediated responses in the same subfield (Morishita and

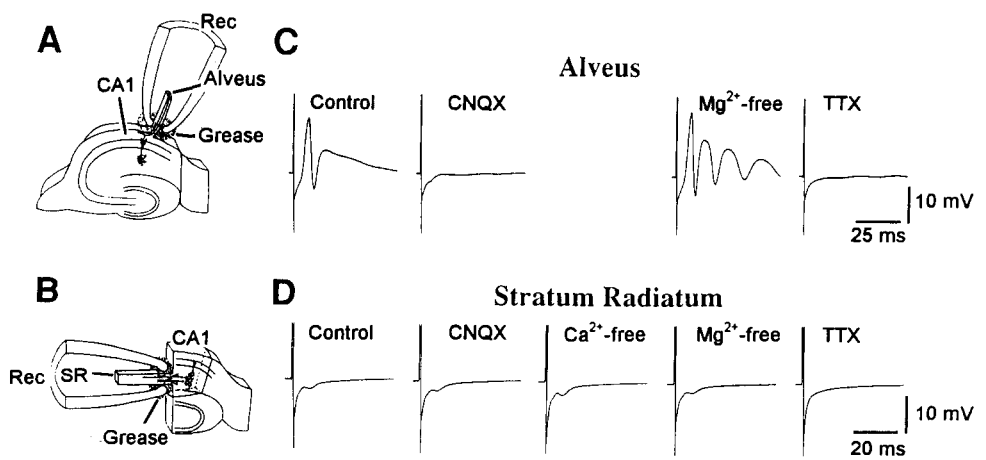

Fig. 1. Grease-gap recordings from the stratum radiatum are presynaptic. (A) and (B) show schematic diagrams of recording electrodes (Rec) and the configurations used to detect post-(alveus) and presynaptic (stratum radiatum, SR) d. c. potentials, respectively. Responses evoked by 0.1 Hz stimulation of the stratum radiatum were recorded from the alveus (C) and from the stratum radiatum (D) in various superfusing media. Note that the field potential recorded from the alveus was suppressed by CNQX (20 μM) while the presynaptic response recorded from the stratum radiatum was not. Furthermore, the alveus, but not the stratum radiatum, recording was transformed to a multiple wave-like response when the slice was superfused with Mg^{2+}-free medium. Tetrodotoxin (TTX, 0.1 μM) eliminated presynaptic volleys recorded from the alveus (revealed in the presence of CNQX) or from the stratum radiatum.

Sastry, 1994) indicate that the grease-gap electrode does not detect electrical responses from postsynaptic elements in the stratum radiatum.

Stable 'baseline' d. c. potential recordings were obtained in control medium, control medium containing tetrodotoxin, Mg^{2+}-free medium containing tetrodotoxin and Ca^{2+}-free medium containing tetrodotoxin. Glutamate (2 mM), NMDA (16 μM), GABA (3 mM) and KCl (9 mM) were superfused for 1 min each. t-ACPD (100 μM) was applied for 2 min. All glutamate agonists as well as GABA and KCl were found to produce depolarizations which recovered within 5 min of wash out. Hence, recovery times of 10 min were used between applications of agonists. Since glutamate agonists can excite hippocampal neurons to discharge action potentials, to minimize indirect actions of glutamate agonists, tetrodotoxin (0.1 μM) was included in the superfusing media when actions of applied agonists were tested.

Glutamate (0.025–10 mM, $n = 14$ slices, Fig. 2A) produced concentration-dependent depolarizations. These responses persisted when slices were superfused with a Ca^{2+}-free medium, as reported previously from this laboratory (Morishita and Sastry, 1994), suggesting that the depolarization was not through an indirect release of transmitters. To examine if glutamate-induced depolarizations were secondary to a release of GABA (GABA has been shown to induce $GABA_A$ receptor-mediated presynaptic depolarizations in the stratum radiatum [Morishita and Sastry, 1994]), the ability of picrotoxinin to suppress the depolarization by glutamate was tested. Picrotoxinin (50 μM, 15 min) suppressed the GABA (3 mM)-induced depolarization (% depression: 46.9 ± 8.0, $n = 6$ slices, Fig. 2B), but enhanced the glutamate-induced depolarization (% enhancement: 33.4 ± 11.7, $n = 6$ slices, Fig. 2B). Presynaptic $GABA_B$ receptor activation leads to a hyperpolarization (Morishita and Sastry, 1994). Therefore, the d. c. potential shift induced by applied glutamate was not due to a release of GABA.

To examine if the presynaptic depolarizing action of glutamate was secondary to a release of K^+, the agent was applied during the superfusion of the slice to the medium containing tetraethylammonium, 4-aminopyridine and Cs^+. On these slices, the presynaptic depolarization induced by glutamate (2 mM, 1 min) was actually greater than when applied in the control medium (Fig. 2C, $n = 5$ slices). Moreover when the slices were superfused with a Ca^{2+}-free medium, the depolarization induced by KCl (6 mM, 1 min 30 s) and not that induced by glutamate (2 mM, 1 min) was blocked in the presence of tetraethylammonium, 4-aminopyridine and Cs^+ ($n = 6$ slices). Taken together these results indicate that the action of the amino acid is not secondary to a release of K^+.

When slices were superfused in the control medium containing tetrodotoxin, CNQX (20 μM, 15 min) significantly decreased the glutamate (2 mM)-induced depolarization (% depression in CNQX: 48.1 ± 10.1, $n = 13$ slices; Fig. 3A). APV (50 μM, 10 min) also decreased the glutamate-induced depolarization (% depression: 27.3 ± 11.3, $n = 7$ slices, Fig. 3B), but the effect was smaller than that of CNQX.

In separate experiments, t-ACPD (25–200 μM) produced concentration-dependent depolarizations. The depolarizations induced by 100 μM t-ACPD were antagonized by 200 μM L-AP3 (% depression: 92.5 ± 7.5, $n = 5$ slices, Fig. 3C) while in the same slices those produced by 2 mM glutamate were mostly unaffected (% depression: 0.7 ± 0.2, $n = 5$ slices, Fig. 3D). t-

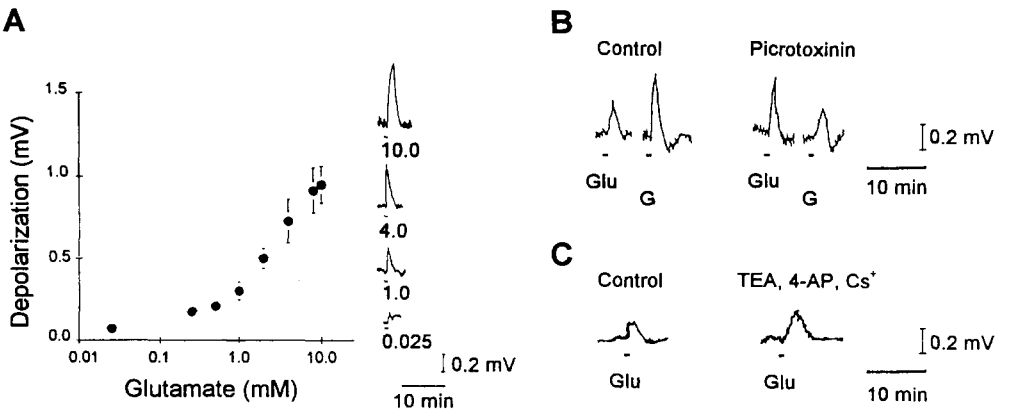

Fig. 2. Glutamate directly depolarizes presynaptic elements. (A) Concentration-response curve for glutamate-induced depolarizations. The individual traces illustrate depolarizations by bath applications (solid bars) of different concentrations (mM) of glutamate. Each point (filled circles) in the graph represents the mean ±S.E.M. ($n = 14$). In (B), from left to right, d. c. potentials induced by glutamate (Glu, 2 mM) and GABA (G, 3 mM), in the absence (control) and in the presence of picrotoxinin, are illustrated. (C) Glutamate (Glu, 2 mM)-induced d. c. potentials in control medium and in medium containing tetraethylammonium (TEA), 4-aminopyridine (4-AP) and Cs^+. The presynaptic depolarizations do not appear to be due to an indirect release of GABA nor due to a release of K^+ from postsynaptic elements.

ACPD-induced depolarizations were also reduced in the presence of CNQX and APV (% depression: 61.7 ± 4.8, $n = 5$ slices, not shown). Interestingly, t-ACPD induced a hyperpolarization in some slices ($n = 4$ slices). However, since this effect diminished with repeated applications, the antagonism by L-AP3 could not be tested.

Superfusion with Mg^{2+}-free medium resulted in a substantial potentiation of the NMDA (16 μM)-induced depolarization (response as a % of control: 499 ± 111, $n = 5$ slices, Fig. 4A). In three of the five slices, the NMDA-induced depolarizations in the presence of Mg^{2+} (2 mM) were negligible, but were significant upon Mg^{2+} removal. In all five slices, removal of Mg^{2+} from the superfusing medium had little effect on the GABA-induced depolarizations (Fig. 4A). Consequently, NMDA concentration-response curves were constructed in the Mg^{2+}-free medium. NMDA (0.5–32 μM) produced concentration-dependent depolarizations (response to 32 μM NMDA: 0.985 ± 0.2 mV, $n = 6$ slices, Fig. 4B). NMDA (16 μM)-induced depolarizations were significantly suppressed by APV (50 μM, 10 min; % depression: 81.2 ± 9.1, $n = 5$ slices, Fig. 4C). In the same slices, APV had little effect on the GABA-induced depolarization (% depression: 7.4 ± 6.2, $n = 5$ slices, not shown).

Although a stimulation of the stratum radiatum at 0.1 Hz did not evoke a measurable presynaptic d. c. potential, a stimulation at 5 Hz for 5 s did in fact induce a presynaptic depolarization ($n = 13$ slices). In separate experiments, CNQX (20 μM, $n = 5$ slices, Fig. 5A) or APV (50 μM, $n = 6$ slices, Fig. 5B) could decrease the 5 Hz stimulation-induced depolarization. It appears that a significant component of the tetanus-induced depolarization is not due to an extracellular build-up of K^+ due to the activation of voltage-gated channels, since superfusion with K^+-channel blockers caused an increase, but not a decrease, in the height and duration of the response ($n = 5$ slices, not shown). The depolarization was increased and prolonged if the slice was exposed to a Mg^{2+}-free medium ($n = 6$ slices,

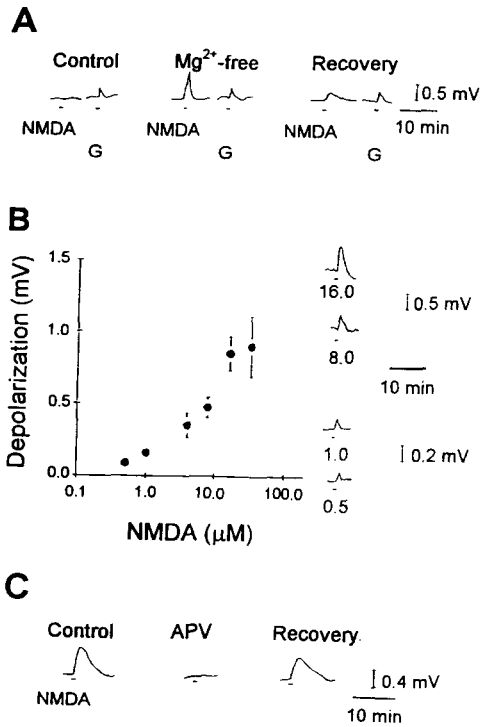

Fig. 4. NMDA autoreceptors in the stratum radiatum. (A) NMDA (16 μM)-and GABA (G, 3 mM)-induced responses in the presence (control) and absence of extracellular Mg^{2+}. (B) Concentration-response curve for NMDA-induced presynaptic depolarizations in Mg^{2+}-free medium ($n = 6$). The individual traces, taken from a single experiment, illustrate depolarizations by bath applications of different concentrations (μM) of NMDA. In (C) the depolarizations to NMDA in the absence, presence and following a 30 min recovery from APV (50 μM) are shown. Solid bars below each trace indicate the duration of application of agonists.

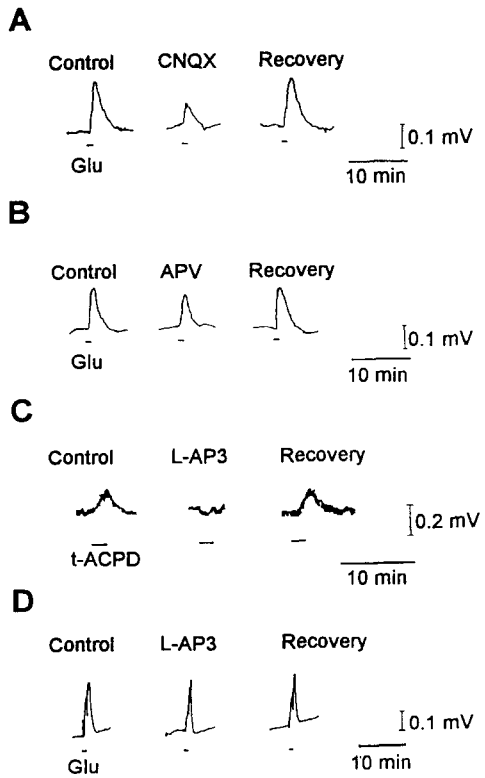

Fig. 3. Characterization of receptors involved in glutamate-induced presynaptic depolarizations. The glutamate (Glu)-induced depolarizations are shown in the presence of CNQX (20 μM, 15 min (A)); APV (50 μM, 15 min (B)) and L-AP3 (200 μM, 15 min (D)). (C) t-ACPD (100 μM)-induced presynaptic depolarizations in the absence, presence and following a 15 min recovery from L-AP3. The duration of applications of the agonists are indicated by the solid bar located below each trace.

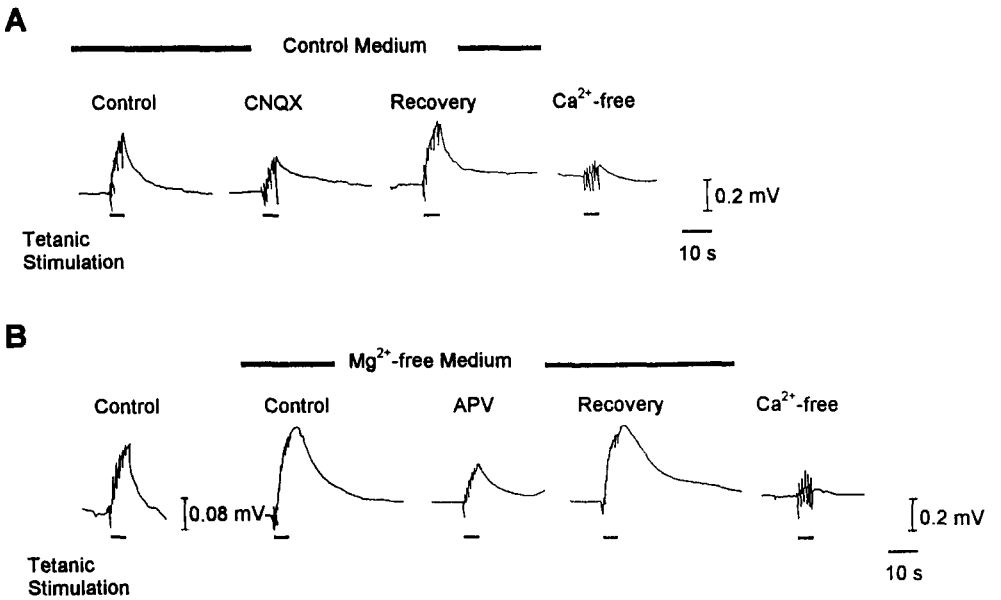

Fig. 5. Presynaptic depolarizations induced by a 5 Hz stimulation of the stratum radiatum in control and Mg^{2+}-free medium. In (A), from left to right, the 5 Hz (5 s)-induced presynaptic depolarization in control medium, the record in the presence of CNQX (20 μM, 15 min), a recovery following 30 min washout of CNQX, and a record taken during the superfusion of the slice in Ca^{2+}-free medium, are illustrated. (B) In the records from left to right, the first two show that the 5 Hz stimulation for 5 s (solid bar) induced a presynaptic depolarization when the slice was superfused in control medium and an enhancement of this depolarization in Mg^{2+}-free medium. In the remaining three records, the 5 Hz-induced presynaptic depolarizations in the presence of APV (50 μM, 15 min), a 15 min recovery from APV and a response in a Ca^{2+}-free medium, are illustrated. In the presence of CNQX + APV, the 5 Hz stimulation-induced depolarization was further reduced but not completely abolished (not shown). In (B), the vertical calibration bar (mV) next to the left record is for the response taken when the slice is exposed to the control medium. The calibration bar next to the last record is for the remaining four records.

Fig. 5B) and was suppressed when exposed to a Ca^{2+}-free medium ($n = 8$ slices).

4. Discussion

It is clear from the control experiments in this study (see Fig. 1) and from a previous report from this laboratory (Morishita and Sastry, 1994), that the stratum radiatum grease-gap electrode detects d. c. potentials generated by presynaptic and not postsynaptic elements.

The observations that glutamate induces a presynaptic depolarization when applied in the normal as well as Ca^{2+}-free medium, and that the action is not secondary to a release of GABA, suggest that glutamate autoreceptors are present in the stratum radiatum. Since the depolarization was intact when the slices were exposed to a medium containing K^+-channel blockers, it is unlikely that the amino acid's action was secondary to a release of K^+ from depolarized postsynaptic elements. Although a release of the ions through the amino acid receptor-gated channels on postsynaptic neurons may still occur, the release of the ions into extracellular fluids due to the activation of the voltage-gated channels would logically be decreased in the presence of K^+-channel blockers. Therefore, if the presynaptic depolarization induced by glutamate is entirely due to a release of K^+ into the extracellular medium, the response should be smaller when the slices are exposed to the K^+-blocker medium. However, glutamate's action was not decreased, suggesting a direct depolarizing action on the recorded presynaptic elements.

The sensitivity of the glutamate-induced depolarization to CNQX and APV indicates that ionotropic glutamate autoreceptors (non-NMDA and NMDA) are present in the stratum radiatum. Since the depolarization induced by NMDA was sensitive to extracellular Mg^{2+}, the presynaptic NMDA receptors appear to be similar to their counterparts on the postsynaptic side (Nowak et al., 1984). The inability of the antagonists to completely block the glutamate-induced presynaptic depolarization suggests that there may be differences in the pre- and postsynaptic receptor sensitivity to the antagonists or that distinctively different receptors are involved.

The depolarization produced by t-ACPD was suppressed by L-AP3 as well as by APV + CNQX, creating ambiguity as to what type of presynaptic glutamate receptors were activated. It is also unclear as to why L-AP3 has little effect on the glutamate response while

significantly suppressing the t-ACPD response. Perhaps, glutamate concentrations used in these experiments were insufficient to activate L-AP3-sensitive metabotropic receptors. Although metabotropic glutamate autoreceptors have been implicated in modulating transmitter release (Baskys and Malenka, 1991; Herrero et al., 1992, 1994), it is difficult to relate the presynaptic effects observed in the present study to such a modulation because of the ambiguities discussed above. A rapidly desensitizing facilitation of glutamate release can occur through the activation of metabotropic autoreceptors (Herrero et al., 1994). It is interesting in the present study that the t-ACPD-induced presynaptic hyperpolarization also declines with repeated applications presumably due to desensitization.

It has been suggested that ionotropic and metabotropic glutamate autoreceptors in the CNS can modulate transmitter release (Barnes et al., 1994; Baskys and Malenka, 1991; Crowder et al., 1987; Ferkany et al., 1983; Gannon and Terrian, 1991; Lovinger, 1991; Martin et al., 1991; Potashner and Gerard, 1983; Herrero et al., 1992, 1994). In the present study, it is unclear as to how a presynaptic depolarization caused by CNQX-sensitive autoreceptors leads to changes in transmitter release. As in the case of presynaptic inhibition (Eccles, 1964), the depolarization may lead to a suppression of evoked release. On the other hand the depolarization itself may facilitate further release if a Ca^{2+} influx occurs. There are conflicting biochemical studies concerning the effects of presynaptic non-NMDA glutamate receptor activation on neurotransmitter release. Some investigators report an enhancement of glutamate and aspartate release by non-NMDA ionotropic glutamate receptor activation (Ferkany et al., 1983; Gannon and Terrian, 1991; Potashner and Gerard, 1983). A recent report further suggests that CNQX-sensitive glutamate receptor activation can cause an enhancement of transmitter release but only when receptor desensitization is decreased (Barnes et al., 1994). However, there is a report suggesting that CNQX-sensitive glutamate receptor activation actually leads to an inhibition of transmitter release (Martin et al., 1991). It is, therefore, unclear as to how the glutamate-induced presynaptic depolarization influences transmitter release. Perhaps, presynaptic d. c. potential recordings coupled with a quantal analysis of transmitter release can resolve this issue.

The relationship between the NMDA-induced presynaptic depolarization and the regulation of neurotransmitter release in the stratum radiatum is also unclear. The activation of presynaptic NMDA receptors has been suggested to increase intracellular $[Ca^{2+}]$ as well as the release of the transmitter in hippocampal slices (Crowder et al., 1987; Martin et al., 1991). If the NMDA-induced d. c. potential shifts are partly mediated by an influx of Ca^{2+} into the presynaptic terminal, transmitter release could logically be facilitated.

It is interesting that high rather than low frequency stimulations of the stratum radiatum induce presynaptic depolarizations that are sensitive to APV and CNQX. If, in fact, the amino acid autoreceptors are activated exclusively during a tetanic stimulation, then, it would be of interest to determine if they are involved in the induction of long-term synaptic potentiation. Moreover, if glutamate autoreceptors are involved in modulating evoked transmitter release, they may play a crucial role in the prevention or facilitation of excitotoxicity due to high frequency synaptic activation (Lovinger and Lambert, 1993; Herrero et al., 1994) and in neurological disorders such as cerebral ischemia (Rothman and Olney, 1986) and Alzheimer's disease (Greenamyre et al., 1985a).

In conclusion, a grease-gap recording technique that allows the monitoring of presynaptic d. c. potentials without contamination from postsynaptic potentials is described. When presynaptic actions of glutamate agonists on the d. c. potentials of Schaffer collaterals in the CA1 region of the hippocampus were tested, depolarizations through the activation of CNQX- and APV-sensitive glutamate receptors could be recorded. The presynaptic actions of metabotropic glutamate receptors are unclear and await further investigation.

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