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Member of the Ampakine Class of Memory Enhancers Prolongs the Single Channel Open Time of Reconstituted AMPA Receptors

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ABSTRACT Ampakines are small benzamide compounds that allosterically produce the positive modulation of AMPA receptors and improve performance on a variety of behavioral tasks. To test if the native synaptic membrane is necessary for the effects of such positive modulators, the mechanism of action of the Ampakine 1-(1,3-benzodioxol-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine (CX509) was investigated in isolated rat brain AMPA receptors reconstituted in lipid bilayers. The drug increased the open time of AMPA-induced single channel current fluctuations with an EC_{50} of 4 μM. The action of CX509 was highly selective since it had no effect on the amplitude or close time of channel events. The open time effect had a maximum enhancement of 70-fold and the modulated currents were blocked by CNQX. It is concluded that the synaptic membrane environment is not necessary for Ampakine effects. In fact, CX509 was about 100 times more potent on the reconstituted AMPA receptors than on receptors in their native membrane. These findings indicate that centrally active Ampakines modulate specific kinetic properties of AMPA currents. They also raise the possibility that AMPA receptors are regulated by factors present in situ, thus explaining the more efficient modulatory effects of CX509 when acting on receptors removed from their synaptic location. **Synapse 40:154–158, 2001.**

INTRODUCTION

Members of the Ampakine drug family are known to positively modulate glutamatergic AMPA receptor-gated currents and slow the deactivation rate of the receptors in hippocampal tissue (Arai and Lynch, 1992; Arai et al., 1994). The centrally active drugs also selectively increase excitatory responses measured in polysynaptic circuits (Arai et al., 1995) and in the hippocampus of freely moving rats (Staubli et al., 1994b), thus leading to the prediction that they would have a positive influence on memory encoding processes controlled by hippocampal and cortical networks. Accordingly, Ampakines have been shown to 1) substantially improve retention scores in radial mazes (Staubli et al., 1994b; Granger et al., 1996), 2) reduce the number of trials for stable olfactory discrimination (Larson et al., 1995), 3) produce progressive improvement of performance on short-term delay-type memory tasks (Hampson et al., 1998a,b), 4) facilitate the encoding of a conditioned response (Shors et al., 1994), and 5) improve delayed recall and other types of memory scores in humans (Lynch et al., 1996). Such an impact on memory encoding likely stems from the fact that facilitation of AMPA currents reduces the amount of afferent stimulation required to induce synaptic plasticity (Arai and Lynch, 1992; Staubli et al., 1994a).

The present study was conducted to test if the Ampakine response in glutamatergic neurons requires the native synaptic environment and to determine if the modulatory action includes a direct effect on the single

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channel kinetics of AMPA receptors. For this, reconstituted AMPA receptors isolated from rat brain were used to test the effects of the Ampakine 1-(1,3-benzodioxol-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine (CX509). The reconstitution procedure utilized an artificial lipid bilayer devoid of cytoskeletal, adhesive, and signal transduction components that are intrinsic to the membrane in which the receptors reside in situ. Such cellular components have been implicated in long-term potentiation (Xiao et al., 1991b; Lithi et al., 1994; Vanderklish et al., 1996; Bahr et al., 1997; Hoffman et al., 1998) where the long-lasting increase in synaptic efficacy is thought to be attributed at least in part to changes in the kinetics of AMPA channels (Ambros-Ingerson et al., 1991; Staubli et al., 1992; Ambros-Ingerson and Lynch, 1993). Several studies also indicate that AMPA receptors' home membrane can dictate their functionality (Hall et al., 1992, 1993, 1996b; Hunter and Wenthold, 1992; Hall and Bahr, 1994) and possibly the number of conductance states they can express (Bahr et al., 1992; Vodyanoy et al., 1993). It is very conceivable, then, that elements of the postsynaptic zone provide a link between AMPA receptors and certain modulatory systems. Data reported in this study, however, indicate that Ampakine modulation does not act through such an indirect pathway but rather involves a direct influence on the AMPA channels. While the present report ruled out indirect Ampakine action on membrane components, it did find evidence that the synaptic environment has a strong control over the extent to which the receptors can be modulated by allosteric modulators.

MATERIALS AND METHODS

AMPA receptors from adult rat forebrain were purified with chromatographic techniques and reconstituted in small "tip-dip" bilayers as described by Bahr et al. (1992). Patch-bilayers were formed in asymmetric saline conditions ("outside-out" configuration) using solution compositions reported previously (Bahr et al., 1992; Vodyanoy et al., 1993; Sinnarajah et al., 1999). After receptor incorporation, AMPA, CX509, aniracetam, and 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX) were applied at various times to the same side of the bilayer. Recorded single-channel events were subjected to computer analysis of amplitude and time distributions. Recorded signals were filtered at 1–5 kHz and digitized between 5–25 kHz, after which they were reduced to series of datasets each containing 2,000–125,000 data points. Histograms were analyzed by Marquardt least squares method (pSTAT module of Axon pCLAMP 6.0 software). The minimum detectable dwell time (0.1 msec) was calibrated by detection of brief events. AMPA and CNQX were purchased from Tocris Cookson (Ballwin, MO). CX509 was obtained from Cortex Pharmaceuticals (Irvine, CA).

Abbreviations

AMPA	α-amino-3-hydroxy-5-methylisoxazole-4-propionate
1-BCP	1-(1,3-benzodioxol-5-ylcarbonyl)-piperidine
CX509	1-(1,3-benzodioxol-5-ylcarbonyl)-1,2,3,6-tetrahydropyridine
CNQX	6-cyano-7-nitroquinoxaline-2,3-dione
DNQX	6,7-dinitroquinoxaline-2,3-dione

RESULTS

AMPA receptors reconstituted by the tip-dip method were activated by the addition of AMPA to the pseudo-extracellular solution. The resulting current fluctuations usually had multiple conductance levels with bursts at principal conductance level of about 50 pS (Sinnarajah et al., 1999). Panel A of Figure 1 shows trace of a recording from a patch bilayer containing AMPA receptors exposed to 150 nM AMPA with the voltage clamped at −98.7 mV. Amplitude distribution of channel currents in trace A is shown in C. Analysis of the amplitude histogram based on the longer, 20-sec trace, (data not shown) revealed that the composite current was an integral multiple of single channel currents of low and high conductance of 12.0 ± 1.2 (SD) and 53 ± 1.5 (SD) pS, respectively, as previously shown (Vodyanoy et al., 1993; Sinnarajah et al., 1999). Addition of CX509 resulted in a dramatic increase in the mean open time (Fig. 1A,B,E,F,G). However, CX509 did not activate the receptors in the absence of AMPA. The principal channel conductance and mean reversal potential were not affected ($P < 0.05$) by CX509 (Fig. 1D). Channel currents under the influence of CX509 were blocked by 10 μM CNQX (data not shown); thus, CX509 does not appear to have an effect on the antagonism of the ligand binding site of AMPA receptors.

As shown in Figure 2, the drug's effect on open time was dose-dependent with a surprisingly high degree of potency (EC_{50} = 4 μM). The open time was augmented 15-fold from 5 to 73 msec by ~1 μM CX509 ($P < 0.0001$; unpaired, two-tailed t-test), and sizable increases (60%; $P = 0.02$) were evoked at a concentration of 70 nM. While the maximum increase in open time was 70-fold, CX509 caused no significant change to the closed time of the current fluctuations (Fig. 2). Control currents and those with maximally induced open time (with 12 μM CX509) were both blocked by 50 μM CNQX (data not shown). Another glutamatergic facilitating compound, aniracetam (Ito et al., 1990; Staubli et al., 1990; Ozawa et al., 1991; Tang et al., 1991; Vyklicky et al., 1991; Xiao et al., 1991a), also elicited a dose-dependent increase in the AMPA currents but at a much lower potency than that of CX509 (Table I). The EC_{50} for aniracetam's modulatory action on single-channel kinetics was similar to that found for the drug's effect on AMPA-elicited currents in bilayers containing many receptors (not shown).

It was of interest that CX509 was about 100 times more effective on the reconstituted AMPA receptors than on receptors in their native environment (Table I).

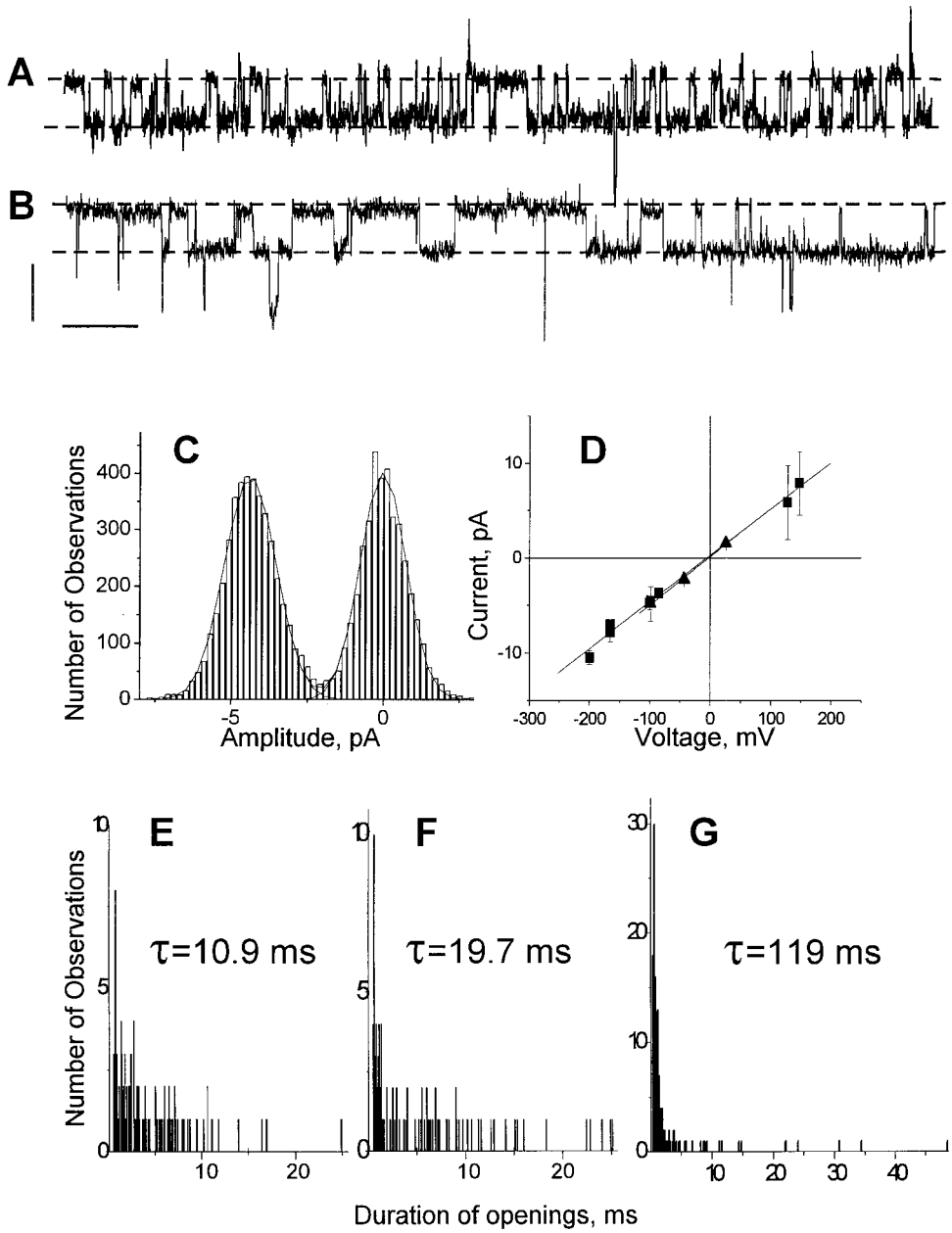

Fig. 1. Effects of CX509 on channel activity elicited by AMPA. Receptors were reconstituted into a lipid bilayer on the end of a patch electrode. Single-channel fluctuations elicited by 150 nM AMPA were recorded at −98.7 mV in the absence (**A**) and presence (**B**) of 25 nM CX509. Openings are downwards. Dashed lines indicate levels 0 and 1. The vertical and horizontal bars are 5 pA and 50 ms, respectively. Amplitude distributions of channel currents in trace **A** is shown in **C** consisting of 6,150 points sampled at intervals of 0.1 ms, segmented with a bin width of 0.25 pA. The distribution was fitted with the sum of two Gaussian components with means of 0 pA (channel-closed current level), −4.5 pA (large channel-open current level). The voltage–current relationships for AMPA elicited single channels and for channels modulated by CX509 are shown in **D,** where current amplitudes were plotted as functions of membrane voltage using linear regression. Squares and a solid line (r^2 = 0.986, slope = 49.0 ± 1.8 pS, V_{rev} = 5.1 ± 4.0 mV) represent the current transition obtained from the amplitude analysis of current records of about 10.2 sec consisting of 51,200 points measured after the addition of AMPA only (150 nM). Triangles and another line (r^2 = 0.981, slope = 51.2 ± 2.6 pS, V_{rev} = 2.5 ± 2.0 mV) represent channel currents after the addition of CX509 (25 nM). Single-channel records in the absence (**E**) and presence of 25 nM (**F**) and 12.5 mM (**G**) of CX509 were analyzed for openings of 50 pS conductance. Openings of lower conductance were also present in the records, but were excluded from analysis. Current traces were segmented with a bin width of 0.2 ms. Histograms of the durations of openings were fitted with two-exponential functions with time constants as follows: **E,** 150 nM AMPA, 0.055 ± 3.53, 10.98 ± 0.47 (SE) ms; **F,** 150 nM AMPA and 25 nM CX509, 0.078 ± 1.35, 19.68 ± 0.83 (SE) ms; **G,** 150 nM AMPA and 12.5 mM CX509, 0.490 ± 0.054, 119.0 ± 3.1 ms. The statistics of fittings are represented by the following values of number of openings, goodness of fit, error and standard deviation of fitting function: **E,** 231, 1.1, 4.3%, 0.65; **F,** 232, 1.1, 4.2%, 0.66; **G,** 283, 2.4, 2.6%, 1.05. The difference in open times after addition of 25 nM CX509 was statistically significant ($P < 0.05$).

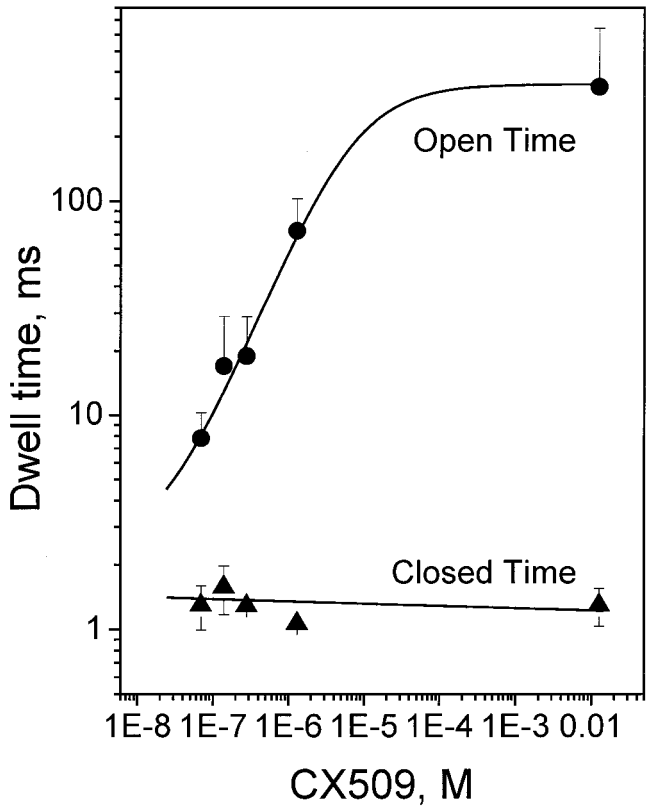

Fig. 2. Dwell times of reconstituted AMPA receptor channels. Channel currents were elicited by the addition of 280 nM AMPA to the *cis*-compartment, followed by CX509 added to the same compartment. Best fits to dwell time histograms usually required two-exponential functions. Typical records were of 2–20 sec of total record time and contained 2,000–100,000 events. Each point represents the summary of 3–4 individual experiments. The curve fitted to open times (t_0) was calculated by the Langmuir absorption equation: $t_0/t_1 = kC/(1 + kC)$, where C was the concentration of CX509, the limited time $t_1 = 350 \pm 140$ msec; (mean ± SD) and the dissociation constant $1/k = 4 \pm 1.6$ μM; mean ± SD. The line fitted to closed times (t_c) was described by equation of linear regression $t_c = 0.97 + AC$, where $A = -0.057 \pm 0.044$ (SE), and C was the CX509 concentration. The dwell times with no CX509 added (AMPA only) were as follows: open time, 4.9 ± 3.6 ms, closed time, 2.2 ± 3.6 ms.

In hippocampal slices, CX509 and its reduced relative 1-(1,3-benzodioxol-5-ylcarbonyl)-piperidine (1-BCP) increased the amplitude and decay time of field EPSPs with an EC_{50} range of 400–600 μM (Arai et al., 1994; Xiao et al., unpublished data). Similarly, aniracetam was 20 times more efficient at facilitating the AMPA currents in the present study than at facilitating EPSPs recorded in field CA1 (Table I). It was of further interest that two AMPA receptor agonists, but not the antagonist DNQX, were also much more potent when acting on the reconstituted receptors than on AMPA receptors residing in a neuronal membrane (Table I).

TABLE I. Relative effector potencies on reconstituted AMPA receptors vs. receptors in their native membrane

	EC_{50} (μM) on AMPA receptors in:		
	Reconstituted membrane	Native membrane	Factor difference
Facilitation Agents			
CX509	4	370[a]	93
1-BCP	—	480–590[b]	—
Aniracetam	100	2000[a]	20
Agonists			
AMPA	0.17[c]	11[d]	65
Kainate	0.58[c]	143[d]	247
Antagonist			
DNQX	0.44[c]	1.0–2.8[e]	2–6

[a]Unpublished data from Xiao et al. measuring changes in amplitude and decay time of field EPSPs in rat hippocampal slices.
[b]Data from Arai et al. (1994) measuring changes in amplitude and decay time of field EPSPs in rat hippocampal slices.
[c]Data from Vodyanoy et al. (1993) measuring changes in conductance of reconstituted, rat forebrain AMPA receptors.
[d]Data from Patneau and Mayer (1990) measuring changes in current of whole-cell recordings from mouse neurons.
[e]Data from Randle et al. (1992) and Goldstein and Litwin (1993) measuring changes in size of field EPSPs in rat hippocampal slices.

DISCUSSION

The properties of the reconstituted receptors in the present report correspond well with those described for AMPA receptors found in binding and physiological studies (Jahr and Stevens, 1987; Tang et al., 1989, 1991; Vodyanoy et al., 1993; Wyllie and Cull-Candy, 1994; Sinnarajah et al., 1999; Smith et al., 2000). The present findings indicate that the Ampakine CX509 specifically increases the open time of AMPA receptor gated currents, and does so 25-fold more potently than aniracetam. CX509's action presumably explains how an Ampakine facilitates AMPA receptor-mediated synaptic responses in vitro and in vivo. CX509 had no effect on the minimum transition conductance, on the closed time, or on the reversal potential of the reconstituted receptors, indicating that AMPA currents are not likely facilitated by changes in channel conductance state.

The results also show that facilitating compounds as well as AMPA receptor agonists are markedly more effective when acting on the steady-state currents of reconstituted receptors than on those of receptors located in neuronal membranes. While functional differences may exist between AMPA receptor types from different brain areas (e.g., forebrain vs. hippocampus), one would still have difficulty explaining the wide potency margin for CX509 and aniracetam, let alone for the agonists. It would not be unreasonable to assume that the biophysical surroundings of reconstituted receptors in a pure lipid bilayer allows easier access to effector binding sites than that of receptors in a synaptic membrane. The lack of a significant potency difference in the case of an AMPA receptor antagonist argues perhaps against such an assumption and favors an alternative idea that the synaptic receptors are influenced, in vivo, by some sort of functional regulation. This interpretation of the data suggests that regulatory factors endogenous to the native environment in which AMPA receptors reside in the brain alter the activation and facilitation properties of the receptors but not the competitive inhibition of active sites. It

should be pointed out that distinct affinity states characteristic of AMPA receptors are interconverted by various agents and that none of the treatments have been reported to affect antagonist binding (Hall et al., 1992, 1996a,b). Thus, as previously proposed (Hall et al., 1992, 1996b), the functional nature of AMPA receptors appears to be regulated by an interaction(s) between the receptors and other components of the synapse. This obviously needs to be considered when studying drugs that facilitate neurotransmission.

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