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Presynaptic inhibition by kainate receptors converges mechanistically with presynaptic inhibition by adenosine and $GABA_B$ receptors

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Abstract

Kainate receptors are widely reported to regulate the release of neurotransmitter in the CNS, but the mechanisms involved remain controversial. Previous studies have found that the kainate receptor agonist ATPA, which selectively activates Glu_{K5}-containing kainate receptors, depresses glutamate release at Schaffer-collateral synapses in the hippocampus. In the present study, we provide pharmacological evidence that this depressant effect is mediated by Glu_{K5}-containing heteromers, but is distinct from a similar depressant effect engaged by the kainate receptor agonist domoate. The depressant effect of ATPA is insensitive to antagonists for $GABA_A$, $GABA_B$, and adenosine receptors, and is also unaffected by lowering the release probability by reducing extracellular calcium. However, the effect of ATPA is partly occluded by prior activation of $GABA_B$ receptors and completely occluded by prior activation of adenosine receptors, suggesting a mechanistic convergence of heteromeric Glu_{K5} kainate receptor signaling with $GABA_B$ receptors and adenosine receptors. The effects of domoate are partially occluded by both adenosine and $GABA_B$ receptor agonists, indicating at least a partial convergence of Glu_{K5}-lacking kainate receptor signaling with these other pathways. The depressant effect of ATPA is not blocked by inhibition of serine/threonine protein kinases. These results suggest that ATPA and domoate inhibit glutamate release through mechanisms that converge with those of classical metabotropic receptor agonists, although they do so through different receptors.
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Keywords: Kainate receptor; Glutamate release; Schaffer-collateral; Synaptic terminals; ATPA; Metabotropic; Neuromodulation

1. Introduction

Kainate receptors (KARs) are ionotropic glutamate receptors composed of a distinct family of subunits (Glu_{K1-2}, Glu_{K5-7}) with strong sequence homology to α-amino-3-hydroxy-5-methyl-4-isoxazole propionate receptors (AMPARs). The functions of KARs in the CNS remain poorly understood. Like AMPARs, KARs can participate in generating excitatory postsynaptic potentials (EPSPs) at some synapses (Castillo et al., 1997; Cossart et al., 1998; Devries and Schwartz, 1999; Frerking et al., 1998; Kidd and Isaac, 1999; Li et al., 1999; Vignes and Collingridge, 1997); however, a more widespread finding has been that KAR activation, either by exogenous agonists or glutamate release, can lead to neuromodulation, either through effects on the presynaptic release of neurotransmitter (Chittajallu et al., 1996; Clarke et al., 1997; Frerking et al., 2001; Kamiya and Ozawa, 2000; Kidd et al., 2002; Lauri et al., 2001; Rodriguez-Moreno et al., 1997; Schmitz et al., 2001; Vignes et al., 1998), or effects on neuronal excitability by modulating the size of the after-hyperpolarization (AHP) following an action potential (Fisahn et al., 2005; Melyan et al., 2004). Several reports implicate the activation of metabotropic cascades in these effects (Cunha et al., 1999, 2000; Fisahn et al., 2005; Frerking et al., 2001; Melyan et al., 2004; Rodriguez-Moreno and Lerma, 1998; Rozas et al., 2003; Ruiz et al., 2005), although some examples of KAR-mediated neuromodulation may involve ionotropic actions of KARs (Kerchner et al., 2001; Schmitz et al., 2001), or indirect effects via KAR-induced release of other neuromodulators (Chergui et al., 2000; Frerking et al., 1999; Schmitz et al., 2000).

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The presynaptic effects of KARs were first described at Schaffer collateral synapses in the hippocampus (Chittajallu et al., 1996), and subsequent studies have determined that glutamate release can be inhibited by several exogenous agonists, including the non-selective agonists kainate and domoate, and the Glu_{K5}-selective agonist ATPA [(*RS*)-2-amino-3-(3-hydroxy-5-*tert*-butylisoxazol-4-yl)propanoic acid] (Chittajallu et al., 1996; Clarke and Collingridge, 2002; Frerking et al., 2001; Vignes et al., 1998). Domoate has been shown to inhibit glutamate release through mechanisms involving a metabotropic effect involving $G_{i/o}$ proteins, and it has been suggested based on analogy to other metabotropic systems that the ultimate effector for this cascade is an inhibition of calcium channels (Frerking et al., 2001). Consistent with this reasoning, kainate has been shown to cause a reduction in calcium influx (Kamiya and Ozawa, 1998). In neonate animals, ATPA has been shown to require G protein function as well (Lauri et al., 2006). However, the mechanisms by which ATPA and domoate reduce glutamate release remain largely obscure. The effect of ATPA is likely to be distinct from that of kainate, as the effect of ATPA is blocked by decahydroisoquinolines, which act as Glu_{K5}-selective antagonists, while the effect of kainate is resistant to these compounds (Clarke and Collingridge, 2002).

In the present study, we examine the mechanisms underlying the depressant effect of ATPA on glutamate release at Schaffer-collateral synapses. We find that domoate and ATPA inhibit release through distinct KARs, with domoate acting via Glu_{K5}-lacking KARs and ATPA acting via Glu_{K5}-containing heteromeric KARs. We provide evidence suggesting that the effect of ATPA is not mediated by the indirect release of a secondary neuromodulator, and find that the effects of ATPA are occluded in part by $GABA_B$ receptor activation and entirely by adenosine receptor activation. The effects of domoate are also occluded by both $GABA_B$ receptor activation and adenosine receptor activation, although for domoate the occlusion is partial in both cases. The ATPA-mediated presynaptic inhibition does not require serine/threonine protein kinases. These results suggest that ATPA inhibits glutamate release via mechanisms that converge at least in part with classical metabotropic receptor agonists, and that a similar mechanistic convergence occurs with the presynaptic inhibition engaged by domoate.

2. Materials and methods

Hippocampal slices 300–500 μm thick were prepared from 2–3-week-old Sprague–Dawley rats as described (Frerking et al., 2001). After >1 h to allow the slices to recover, slices were transferred to a recording chamber perfused at 2 ml/min with an artificial cerebrospinal fluid (aCSF) solution consisting of (in mM): 119 NaCl, 26.2 $NaHCO_3$, 11 glucose, 2.5 KCl, 2.5 $CaCl_2$, 1.3 $MgSO_4$, 1.0 NaH_2PO_4, bubbled with 95% O_2/5% CO_2, unless otherwise noted. A cut was made between CA1 and CA3 to ensure that transmission was monosynaptic.

Stimulation and recording techniques were similar to those in Frerking et al., (2001). Briefly, field EPSPs (fEPSPs) were recorded using a patch pipette filled with aCSF that was placed in stratum radiatum. fEPSPs were evoked using bipolar stimulating electrodes, driven at a frequency of 0.1 Hz to monitor synaptic function. fEPSPs were recorded at a sampling frequency of 5 kHz and a filtering frequency of 1–2 kHz. fEPSP slopes were calculated using 1–2 ms after the fiber volley. For experiments in which field responses were strongly depressed (low calcium experiments in Fig. 3, adenosine and baclofen occlusion experiments in Fig. 4), fEPSP slope measurements were taken from averaged fEPSPs after subtraction with the AMPAR antagonist NBQX. For experiments in which protein kinase inhibitors were used, slices were preincubated for 4–8 h with the inhibitor before transfer to the recording chamber. Data was analyzed on-line using IgorPro software, and after acquisition using SigmaPlot.

All data are presented as mean ± S.E.M. Data were compared using the Student's *t*-test or the Mann–Whitney Rank Sum test, depending on whether or not the data were normally distributed. Significance was assessed at $P < 0.05$.

3. Results

3.1. ATPA depresses glutamate release via activation of Glu_{K5}-containing KAR heteromers

Previous studies have reported that ATPA, at concentrations that are selective for Glu_{K5}-containing KARs (<10 μM), can depress glutamate release at Schaffer-collateral synapses in the hippocampus (Clarke and Collingridge, 2002). Consistent with these reports, we found that 2 μM ATPA caused a significant depression of the fEPSP recorded in s. radiatum of area CA1 (Fig. 1A, B; 46 ± 2%, $n = 16$). This depression was associated with a significant change in paired-pulse facilitation (Fig. 1C; $n = 16$), verifying previous reports and suggesting that ATPA reduces the probability of release. We also found that the effect of ATPA was not obviously dependent on

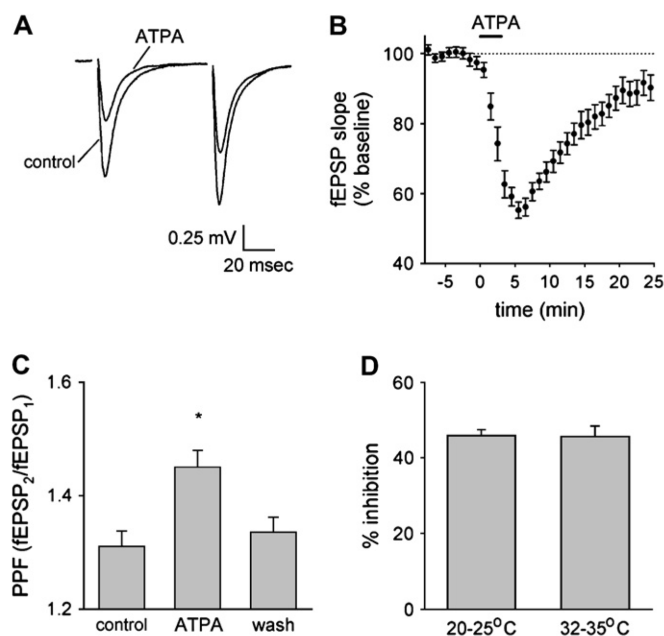

Fig. 1. ATPA induces a presynaptic depression of transmitter release. (A) Bath application of 2 μM ATPA reduces the size of the fEPSP and increases paired-pulse facilitation in a representative experiment. (B) The time course of the effect of ATPA is shown. (C) ATPA reversibly increases paired-pulse facilitation, indicating a presynaptic mechanism. Asterisk indicates a significant difference from control conditions. (D) The inhibition induced by ATPA is insensitive to the temperature of the recordings.

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