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Review

Presynaptic kainate receptor-mediated bidirectional modulatory actions: Mechanisms

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ABSTRACT

Kainate receptors (KARs) are members of the glutamate receptor family, which also includes two other ionotropic subtypes, i.e. NMDA- and AMPA-type receptors, and types I, II and III metabotropic glutamate receptors. KARs mediate synaptic transmission postynaptically through their ionotropic capacity, while presynaptically, they modulate the release of both GABA and glutamate through operationally diverse modus operandi. At hippocampal mossy fiber (MF)-CA3 synapses, KARs have a biphasic effect on glutamate release, such that, depending on the extent of their activation, a facilitation or depression of glutamate release can be observed. This modulation is posited to contribute to important roles of KARs in short- and long-term plasticity. Elucidation of the modes of action of KARs in their depression and facilitation of glutamate release is beginning to gather impetus. Here we will focus on the cellular mechanisms involved in the modulation of glutamate release by presynaptic KAR activation at MF-CA3 synapses, a field that has seen significant progress in recent years.

Contents

1. Introduction

Glutamate receptors of the kainate-type (KARs) mediate synaptic transmission postsynaptically, and presynaptically modulate neurotransmitter release at many different synapses (Lerma et al., 2001; Huettner, 2003). At the same time, KARs play roles in short- and long-term plasticity (Bortolotto et al., 1999; Contractor et al., 2001; Lauri et al., 2001a; Schmitz et al., 2000, 2001;

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Negrete-Díaz et al., 2007; Lyon et al., 2011; Andrade-Talavera et al., 2012). In their modulatory role, KARs have been shown to be involved in the control of both GABA and glutamate release (Rodríguez-Moreno and Sihra, 2007a,b; Jane et al., 2009 for review). Although original studies on the regulatory role(s) of presynaptic KARs pointed to a depressive action on neurotransmitter release, ensuing investigations indicated that these receptors have a biphasic effect, with relatively "low" agonist concentrations mediating an increase/facilitation and higher concentrations mediating a decrease/depression of neurotransmitter release. Thus, pioneering reports with GABAergic synapses in the hippocampus described KAR-mediated decrease of GABA release (Rodríguez-Moreno et al., 1997; Clarke et al., 1997), with pursuant reports then also describing a facilitation of GABA release (Cossart et al., 2001), this dichotomy likely reflecting diverse KARs with different subunit composition, and potentially differential subcellular localization (Rodríguez-Moreno et al., 2000). The elucidation of the modulation of glutamate release by KARs has followed a similar pattern, with some reports describing a depressive effect (Vignes et al., 1998; Contractor et al., 2000; Kamiya and Ozawa, 2000; Schmitz et al., 2000; Contractor et al., 2003; Negrete-Díaz et al., 2006, 2007; Lyon et al., 2011), and others indicating a facilitation of glutamate release (Bortolotto et al., 1999; Lauri et al., 2001a,b, 2003; Contractor et al., 2001; Rodríguez-Moreno and Sihra, 2004; Breustedt and Schmitz, 2004; Pinheiro et al., 2007; Scott et al., 2008; Fernandes et al., 2009; Andrade-Talavera et al., 2012), but see Kwon and Castillo (2008).

The inhibitory and facilitatory effects of KARs have been most extensively studied in relation to the modulation of glutamate release at the synapses established between the axon terminals (mossy fibers, MF) of the granular cells in the dentate gyrus and the principal cells in the CA3 region of the hippocampus (MF-CA3 synapses), where the expression of KARs is notably high (Represa et al., 1997; Darstein et al., 2003). Trains of granule cell firing are required to drive CA3 pyramidal neurons via MF terminals, determining both the latency and probability of postsynaptic activity (Henze et al., 2002). Presynaptic KARs may therefore play a fundamental role in patterning in CA3 physiology. Aberrations due to either reduction (or indeed increase) in spike transmission at MF-CA3 pyramidal cell synapses, brought about by inappropriate KAR activity, might lead to impairment in the pattern of place cell activity and in the definition of spatial fields in the CA3 region. This would be predicted to affect hippocampus-dependent behavioral tasks related to CA3 invoked working memory (Kesner, 2007).

MF-CA3 synapses are well characterized with respect to activity dependent modulation, showing distinctive forms of short-term and long-term plasticity (Henze et al., 2000; Nicoll and Schmitz, 2005). Thus, together with a modulatory role in glutamate release, KARs have been described to play a fundamental part in the very robust paired-pulse facilitation (PPF) and frequency facilitation (FF) evinced at these synapses (Salin et al., 1996; Nicoll and Schmitz, 2005). In addition to this short-term plasticity, intriguingly, MF-CA3 synapses also manifest long-term plasticity processes, including long-term potentiation (LTP) and long-term depression (LTD) (Bortolotto et al., 1999; Contractor et al., 2001; Lauri et al., 2001a; Schmitz et al., 2000, 2001, 2003; Negrete-Díaz et al., 2007; Lyon et al., 2011; Andrade-Talavera et al., 2012). Unusually, the LTP at MF synapses is found to be independent of NMDA receptors (Harris and Cotman, 1986), in stark contrast to observations at other synapses. Understanding the intracellular mechanisms involved in the evidently coexisting facilitatory and depressive actions of KARs has started to be completed with studies over the last few years. Here we summarize the current knowledge of these mechanisms.

2. Role of KARs in the depression of glutamate release at MF-CA3 synapses (Fig. 1)

KARs have an autoreceptor role in modulating the release of glutamate. Thus, MF terminals release glutamate which activates presynaptic KARs, sensing glutamate levels at these synaptic contacts to modulate subsequent release. The ability of synaptically released glutamate to facilitate or depress its own release might, in principle, explain the high sensitivity of the CA3 region of the hippocampus to epileptiform activity and excitotoxicity (Nadler et al., 1978; Sloviter and Damiano, 1981). Fig. 1

A general consensus exists at present that one of the functions of presynaptic KARs at MF-CA3 synapses is to depress the release of glutamate when the receptors are activated by relatively high (>100 nM) concentrations of the agonist kainate (KA) (Vignes et al., 1998; Contractor et al., 2000; Kamiya and Ozawa, 2000; Schmitz et al., 2000; Contractor et al., 2003; Negrete-Díaz et al., 2006, 2007; Lyon et al., 2011).

2.1. Mechanisms of KAR-mediated depression of glutamate release

The decrease of glutamate release produced by high KA concentrations has, on the one hand, been attributed to the canonical ionotropic mode of KAR activation, but on the other hand, the modulation evinces metabotropic characteristics. The frugal explanation for depression by KAR activation may be that the strong depolarization, produced by high concentrations of agonist, inactivates Na^+ and/or Ca^{2+} channels and/or promotes electrical shunting, and thereby reduces terminal excitability to depress evoked glutamate release (Kamiya and Ozawa, 2000; Schmitz et al., 2001). While the modulation by KARs may, in part, be due to these mechanisms, the depression of glutamate release at MF-CA3 synapses has also been shown to be underpinned by a metabotropic mechanism (Negrete-Díaz et al., 2006). In the latter mode of operation, KAR activation altered PPF and increased the number of failures of evoked EPSCs to change the $1/CV^{-2}$ in a manner consistent with a presynaptic locus of action (Negrete-Díaz et al., 2006). Furthermore, consistent with a metabotropic mechanism, the effect of KA was found to be long-lasting, with a slow recovery, as opposed to the previously proposed ionotropic mechanism of KAR-mediated modulation at MF-CA3 synapses, where the change and the recovery of KA-evoked holding current was fast (Kamiya and Ozawa, 2000). Crucially, supporting a metabotropic inhibition of glutamate release by KARs at MF-CA3 synapses was the observation that depression was sensitive to treatment with the $G_{i/o}$ inhibitor, pertussis toxin (PTX). Indeed, as for the facilitatory

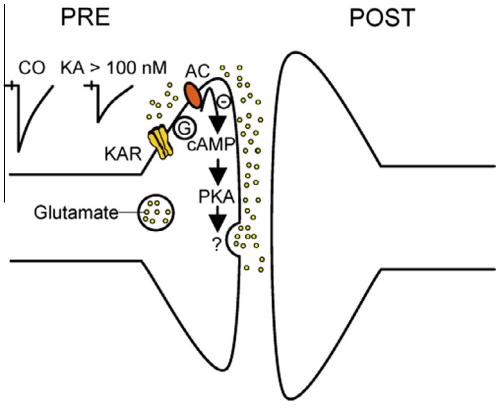

Fig. 1. Mechanism of KAR-mediated depression of glutamate release at MF-CA3 synapses. Kainate (KA) > 100 nM depresses glutamate release by activating KARs followed by the activation of a G protein and the modulation of adenylate cyclase (AC) and PKA activity.