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Review

Kainate Receptors and Mossy Fiber LTP

Zuner A. Bortolotto [2,*], Robert Nistico [2], Julia C. More [1], David E. Jane [1], Graham L. Collingridge [2]

[1] *MRC Centre for Synaptic Plasticity, University of Bristol, Department of Pharmacology, School of Medical Sciences, University Walk, Bristol BS8 1TD, UK*

[2] *MRC Centre for Synaptic Plasticity, University of Bristol, Department of Anatomy, School of Medical Sciences, University Walk, Bristol BS8 1TD, UK*

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Abstract

There is considerable interest in understanding long-term potentiation (LTP) of glutamatergic synaptic transmission because the molecular mechanisms involved in its induction and expression are believed to be critical for learning and memory. There are two distinct forms of LTP. One type is triggered by synaptic activation of NMDA receptors and the other is NMDA receptor-independent. The latter type of LTP has been mostly studied at mossy fiber/CA3 synapses. Here we summarise some of our recent studies concerning the mechanisms of the induction of the NMDA receptor-independent form of LTP at these CA3 synapses. This form of LTP is triggered by the synaptic activation of kainate receptors. We also address the importance of Ca^{2+} availability in the extracellular environment and the release of Ca^{2+} from intracellular stores for this form of LTP.

Keywords: Mossy fiber LTP; Kainate receptor; CA3 synapses; Ca^{2+} stores

Contents

INTRODUCTION

The ability of synapses to modify their function in response to an appropriate stimulus is a fundamental property of the nervous system network and it may represent an essential component of learning and memory (Bliss and Collingridge, 1993). Since its discovery, long-term potentiation (LTP) has been the most accepted and used model to explore synaptic functions at excitatory synapses underlying learning and memory processes.

L-Glutamate is the main excitatory neurotransmitter in the vertebrate nervous system. Pharmacological studies have identified three distinct classes of ionotropic glutamate receptors known as: AMPA, NMDA and kainate receptors (Watkins and Evans, 1981). Recent work using molecular cloning revealed the existence of five kainate receptor subunits (Bettler and Mulle, 1995). According to the IUPHAR nomenclature the subunits are named as: GLU_{K5}, GLU_{K6}, GLU_{K7}, GLU_{K1} and GLU_{K2} (Lodge and Dingledine, 2000). They are more commonly known as GluR5, GluR6, GluR7, KA-1 and KA-2. They can form homomeric and heteromeric assemblies. While AMPA and NMDA receptors are predominantly located postsynaptically, kainate receptors are also located presynap-

* Corresponding author. Tel.: +44 9546463; fax: +44 9291687.
E-mail address: Z.A.Bortolotto@bris.ac.uk (Z.A. Bortolotto).

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tically at many synapses, where they can modulate transmitter release (Lerma, 2003).

Kainate receptors have been shown to have a variety of roles in the hippocampus; both in excitatory and inhibitory transmission (Lerma, 2003). Nevertheless, very little is known about the role of kainate receptors in LTP. Key roles in synaptic plasticity have been identified for two of the ionotropic glutamate receptors. At many synapses in the brain, transient activation of NMDA receptors leads to a persistent modification in the strength of synaptic transmission mediated by AMPA receptors (Bear and Abraham, 1996; Bliss

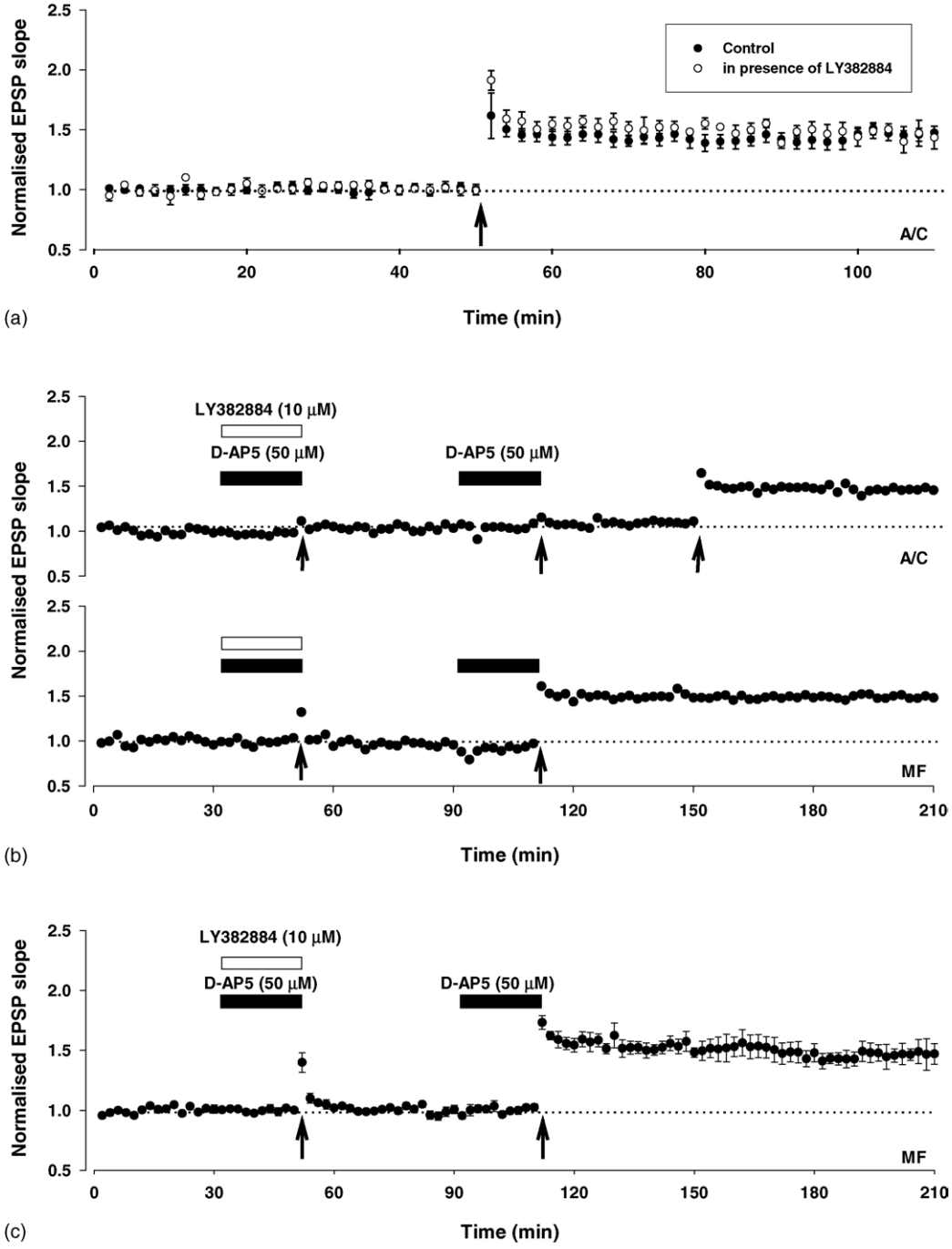

Fig. 1. LY382884 selectively blocks mossy fiber LTP. (a) Pooled data showing NMDA receptor-dependent LTP at CA3 synapses, evoked by tetanic stimulation of the associational commissural (A/C) fibers, under control conditions ($n = 6$) and in the presence of the Glu_{K5} antagonist LY382884 ($n = 3$). In this and subsequent plots, each point represents the slope average of four successive field EPSP responses. Note, in this and subsequent figures, that tetanic stimulation (100 Hz, 1s, test intensity, arrows) at mossy fiber pathway was always delivered in the presence of the NMDA receptor antagonist D-AP5. The duration of drug administration is indicated by the bars. (b) A single example to illustrate the reversible block of mossy fiber LTP by LY382884. (c) Pooled data (mean ± S.E. mean) of seven experiments showing that LY382884 fully blocks the induction of LTP in a reversible manner (from: Bortolotto et al., 1999).