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Invited review

The role of phosphodiesterases in hippocampal synaptic plasticity

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ABSTRACT

Phosphodiesterases (PDEs) degrade cyclic nucleotides, signalling molecules that play important roles in synaptic plasticity and memory. Inhibition of PDEs may therefore enhance synaptic plasticity and memory as a result of elevated levels of these signalling molecules, and this has led to interest in PDE inhibitors as cognitive enhancers. The development of new mouse models in which PDE subtypes have been selectively knocked out and increasing selectivity of PDE antagonists means that this field is currently expanding. Roles for PDE2, 4, 5 and 9 in synaptic plasticity have so far been demonstrated and we review these studies here in the context of cyclic nucleotide signalling more generally. The role of other PDE families in synaptic plasticity has not yet been investigated, and this area promises to advance our understanding of cyclic nucleotide signalling in synaptic plasticity in the future.

This article is part of the Special Issue entitled 'Glutamate Receptor-Dependent Synaptic Plasticity'.

1. Introduction

Synaptic plasticity is a hugely important property of neurons that is thought to underlie learning and memory (Bliss and Collingridge, 1993; Collingridge et al., 2010; Malenka and Bear, 2004). Following the seminal discovery that long-term potentiation (LTP), the activity induced strengthening of synapses, is dependent on NMDA receptor activity (Collingridge et al., 1983) the list of signalling molecules involved in synaptic plasticity has increased at a phenomenal rate. One class of signalling that is important for both LTP and long-term depression (LTD), the activity induced weakening of synapses, is cyclic nucleotide signalling. This form of signalling is mediated by adenosine and guanosine 3′, 5′ cyclic monophosphate (cAMP and cGMP, respectively) and an expanding area of research focuses on the role of enzymes that degrade these signalling molecules, the phosphodiesterases (PDEs). Here, we review the current understanding of how these molecules regulate synaptic plasticity in the most highly studied synapses in the brain, those in area CA1 of the hippocampus.

PDEs belong to a large family of phosphohydrolases that have varying properties and expression profiles that have only been partially investigated (reviewed extensively in Bender and Beavo, 2006). There are 11 classes of PDE, the products of 21 genes, however due to alternative transcriptional start sites and mRNA splicing there are many more PDE protein products. To date synaptic plasticity has been modulated by manipulations that block the activity of PDE2, 4, 5, and 9 (Table 1). However it is possible that additional untested PDEs may also play a role in synaptic plasticity, and we will highlight the case for PDE1 and PDE8. In order to understand the effect that PDE inhibitors have at the molecular level we believe it is necessary to view them in the context of the large body of work published on cyclic nucleotide signalling, which is itself highly complex. This review will therefore start with a brief introduction to this category of intracellular signalling in synaptic plasticity. A full account of cyclic nucleotide signalling is beyond the scope of this review, and the reader is referred to several excellent reviews referenced in the text for further information. PDE inhibitors have also received attention as cognitive enhancers and this has been a significant motivation for PDE research (Blokland et al., 2012; Menniti et al., 2006). It is beyond the scope of this review to discuss PDEs in the context of behavioural measures of cognition and we refer the reader to a review that more directly deals with this area for further information (Reneerkens et al., 2009).

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Table 1
Summary of studies that have investigated the role of PDEs in synaptic plasticity.

PDE	Mouse model	Drug	Cyclic nucleotide	Effect on LTP	Effect on LTD	Effect on DP	Induction protocol	Reference
PDE2	–	Bay 60-7550	cGMP and cAMP	Enhanced	–	–	Weak theta (2 pulses at 100 Hz repeated 4 times at 0.2 Hz)	Boess et al., 2004
PDE4	–	Rolipram	cAMP	Enhanced	–	–	Tetanus (100 Hz for 1 s)	Barad et al., 1998
PDE4	–	Rolipram	cAMP	Converts E-LTP to L-LTP	–	–	Weak tetanus (21 pulses at 100 Hz, intensity set at the pop spike threshold)	Navakkode et al., 2004
PDE4	–	Rolipram	cAMP	–	Converts E-LTD to L-LTD	–	E-LTD: 900 pulses at 1 Hz	Navakkode et al., 2005
PDE4D	PDE4D−/−	–	cAMP	Enhanced	No effect	–	Theta (4 pulses at 40 or 100 Hz repeated 10 times at 0.2 Hz), weak tetanus (25 pulses at 50 Hz), strong tetanus (20 pulses at 100 Hz repeated 5 times at 10 s intervals)	Rutten et al., 2008
PDE4B	PDE4B−/−		cAMP	No effect	Enhanced	–	Theta (4 pulses at 40 or 100 Hz repeated 10 times at 0.2 Hz), weak tetanus (25 pulses at 50 Hz), strong tetanus (20 pulses at 100 Hz repeated 5 times at 10 s intervals)	Rutten et al., 2011
PDE5 AND 6	*rd* mutation (PDE6B inactive)	Zaprinast at 10 μM	cGMP	–	Induced	Induced	Chemical LTD: zaprinast	Kuenzi et al., 2003
PDE5 AND 6		Zaprinast at 0.5 and 2 μM	cGMP	Decreased	–	–	Strong tetanus (100 pulses at 100 Hz times 3)	Monfort et al., 2002
PDE5 AND 6		Zaprinast at 20 μM	cGMP	–	Induced in the presence of PKA antagonist	–	Chemical LTD: zaprinast plus PKA inhibition	Santschi et al., 1999
PDE9A	–	Bay 73-6691	cGMP	Enhanced	–	–	Weak theta (2 pulses at 100 Hz repeated 4 times at 0.2 Hz)	van der Staay et al., 2008
PDE9	–	PF-04447943	cGMP	Enhanced	–	–	Weak tetanus (50 Hz 0.5 s, no effect seen when theta burst used)	Hutson et al., 2011
PDE9A	–	Bay 73-6691	cGMP	Enhanced, converts E-LTP to L-LTP	–	–	Weak Tetanus (20 pulses at 100 Hz) and Strong tetanus (100 pulses at 100 Hz times 3)	Kroker et al., 2012

2. cAMP signalling in synaptic plasticity

Research into cAMP signalling in synaptic plasticity has largely centred on two classes of enzyme, those that catalyse its synthesis and those that mediate its effects. The synthesising enzymes are adenylate cyclases (ACs), of which in mammals there are 9 membranous isoforms and 1 soluble isoform expressed differentially throughout the body (Seifert et al., 2012). cAMP dependent protein kinase (PKA) is a powerful signalling molecule activated by cAMP (Beavo et al., 1974; Miyamoto et al., 1969; Reimann et al., 1971; Walsh et al., 1968) and many of the effects of cAMP in synaptic plasticity discovered to date are thought to be mediated by this kinase. At a simple level enhanced synaptic transmission as a result of cAMP signalling has been shown to be possible in hippocampal slices as this can be induced by application of the AC activator forskolin or the cAMP analogue Sp-cAMPS (Chavez-Noriega and Stevens, 1992; Huang and Kandel, 1994; Pockett et al., 1993; Slack and Pockett, 1991) and these effects are blocked by PKA antagonists (Trudeau et al., 1996; Woo et al., 2002). During experimentally induced LTP, production of cAMP can be induced by specific isoforms of AC that are activated by Ca^{2+}/calmodulin (AC1 and AC8) as a result of calcium entry through NMDA receptors (Chetkovich et al., 1991; Chetkovich and Sweatt, 1993; Collingridge et al., 1983; Eliot et al., 1989), and this has been shown to be relevant to LTP and behaviour as mice that lack these isoforms of AC have impairments in hippocampal dependent forms of memory as well as in LTP (Wong et al., 1999).

The role of PKA in LTP has been found to be complex and to depend on certain specific conditions (reviewed extensively in Nguyen and Woo, 2003). PKA has been found to be involved in LTP only when recruited by specific stimulation protocols. LTP induced by multiple high frequency tetani (100 Hz for 1 s each) spaced more than 5 min apart or by theta bursts is blocked by PKA antagonists (Blitzer et al., 1995; Duffy and Nguyen, 2003; Frey et al., 1993; Huang and Kandel, 1994; Lu et al., 1999; Matsushita et al., 2001; Matthies and Reymann, 1993; Woo et al., 2000, 2003). However, if the tetani are repeated after a shorter time (e.g. 20 s) LTP is not blocked by PKA antagonists (Woo et al., 2003), suggesting that an interval between each high frequency tetanus with a critical time threshold is essential for the engagement of PKA. Also, if there is no repeat of the tetanus at all (i.e. only a single tetanus is applied) LTP is similarly insensitive to PKA antagonism (Blitzer et al., 1995; Duffy et al., 2001; Duffy and Nguyen, 2003; Huang and Kandel, 1994; Woo et al., 2000 however see Otmakhova et al., 2000; Yasuda et al., 2003). It is important to note that problems with the selectivity of PKA antagonists should be considered when interpreting these findings. LTP induced by stronger multi tetanic stimulation protocols is also termed late LTP (L-LTP), persist for many hours in hippocampal slices and is defined as being dependent on new protein synthesis in addition to PKA (Frey et al., 1993; Huang and Kandel, 1994). This longer lasting form of LTP is often distinguished from early LTP (E-LTP) induced by weaker single tetanus induction protocols, which is reported to decay more quickly.

A second important factor defining the involvement of PKA in LTP is the molecular composition of its subunits. Inactive PKA is a tetramer composed of 2 catalytic subunits (either Cα, Cβ, or Cδ) that are bound to and inhibited by 2 regulatory subunits (either RIα, RIβ, RIIα or RIIβ). Binding of cAMP to the regulatory subunits results in their dissociation from the catalytic subunits permitting their activity (Doskeland et al., 1993; Gibbs et al., 1992; Taylor et al., 1990; Wang et al., 1991). Different PKA subunits are activated by different LTP stimulation protocols. For example, deletion of Cβ1 results in