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Invited review

Investigations into the involvement of NMDA mechanisms in recognition memory

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ABSTRACT

This review will focus on evidence showing that NMDA receptor neurotransmission is critical for synaptic plasticity processes within brain regions known to be necessary for the formation of object recognition memories. The aim will be to provide evidence concerning NMDA mechanisms related to recognition memory processes and show that recognition memory for objects, places or associations between objects and places depends on NMDA neurotransmission within the perirhinal cortex, temporal association cortex medial prefrontal cortex and hippocampus. Administration of the NMDA antagonist AP5, selectively into each of these brain regions has revealed that the extent of the involvement NMDA receptors appears dependent on the type of information required to solve the recognition memory task; thus NMDA receptors in the perirhinal cortex are crucial for the encoding of long-term recognition memory for objects, and object-in-place associations, but not for short-term recognition memory or for retrieval. In contrast the hippocampus and medial prefrontal cortex are required for both long-term and short-term recognition memory for places or associations between objects and places, or for recognition memory tasks that have a temporal component. Such studies have therefore confirmed that the multiple brain regions make distinct contributions to recognition memory but in addition that more than one synaptic plasticity process must be involved.

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

1. Introduction

The judgement of prior occurrence has multiple potential component aspects involving, for example, different modalities, individual items and associations, objects, places and scenes, familiarity, recency and recollection. This review will concern what is known of the involvement of NMDA receptors in judgement of prior occurrence, recognition memory, for objects, places and associations between object and places in rats. Thus information concerning NMDA mechanisms related to recognition memory processes will be the focus of this review. The first part of the review will focus upon mechanisms of synaptic plasticity in those brain regions we know to be critical for recognition memory, notably the perirhinal cortex, hippocampus, and medial prefrontal cortex (mPFC) and the second part of the review will focus on behavioural evidence of the critical role of NMDA neurotransmission, from genetic studies, but more specifically from pharmacological manipulations of NMDA receptors, within these brain regions in the formation of recognition memory.

2. Plasticity mechanisms

Memory requires there to be changes in neuronal connectivity that are maintained across time. The leading hypothesis is that such changes involve synaptic plasticity. The involvement of NMDA receptors in synaptic plasticity has been widely investigated ever since the seminal paper by Collingridge et al. (1983), Herron et al. (1986). The selective antagonist, AP5, of the NMDA receptor allows common mechanisms for inducing plasticity to be targeted without affecting normal low-frequency synaptic transmission (though high frequency transmission may be affected) (Bliss and Collingridge, 1993). Thus NMDA receptor activation has been shown to be necessary for the most common (though not all) forms of long-term potentiation (LTP) and long-term depression (LTD) in the hippocampus (Bashir and Collingridge, 1992; Malenka and

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Nicoll, 1993). Importantly, NMDA receptors are involved in the induction rather than maintenance of such plasticity (Collingridge et al., 1983). The details of NMDA receptor-dependent plasticity induction mechanisms are beyond the scope of this review. Moreover, reported effects will be restricted to those applicable to adult rather than immature cortex; the plasticity mechanisms are correspondingly more easily related to mnemonic rather than developmental processes. It should be noted that most detailed studies of synaptic plasticity have used brain slices and that the precise conditions within local networks during plasticity induction are not necessarily exactly those pertaining during memory formation in the intact brain. In particular, experimental induction of LTD requires stimulation with low frequency electrical pulses over many seconds while, at least in perirhinal cortex, reductions in neuronal responsiveness can be produced rapidly, in even <1 s (Brown and Xiang, 1998; Fahy et al., 1993; Miller et al., 1993). Moreover, importantly, NMDA receptor antagonism may have effects relating to the summation and synchronisation of action potentials in addition to blocking the induction of common forms of LTP and LTD. Accordingly, AP5 (and other NMDA receptor antagonists) may have effects on information processing and transmission as well as plasticity (Daw et al., 1993; Schiller and Schiller, 2001; Larkum and Nevian, 2008; Augustinaite and Heggelund, 2007; Hunt and Castillo, 2012): the behavioural effects (including amnesia) of blocking NMDA receptors, cannot therefore be attributed with certainty to blocking LTP and LTD. With these caveats in mind there have been a number of studies which have provided evidence that LTP and LTD-like mechanisms mediate the formation of distinct learning and memory processes including fear conditioning (Whitlock et al., 2006) and memory for object-location configurations (Kemp and Manahan-Vaughan, 2012; Goh and Manahan-Vaughan, 2013). Further weak synaptic plasticity has been shown to be strengthened by a concomitant learning event, suggesting that the same cellular mechanisms may underlie both synaptic plasticity and learning (Goh and Manahan-Vaughan, 2012).

What is known of the role of NMDA receptors in plasticity mechanisms in brain regions implicated in recognition memory processes will now be considered. There is strong evidence for the involvement of the perirhinal cortex, hippocampus, temporal association cortex and mPFC in aspects of recognition memory (Ennaceur et al., 1996; Mumby and Pinel, 1994; Bussey et al., 1999; Norman and Eacott, 2004; Barker et al., 2007; Barker and Warburton, 2011; Hannesson et al., 2004a; Ho et al., 2011). Other contributions in this volume review in detail the role of NMDA receptors in the hippocampus (references in this issue). Antagonism of NMDA receptors by AP5 blocks induction of both LTP and LTD in the adult perirhinal cortex (Bilkey, 1996; Banks et al., 2012; Cho et al., 2000; Griffiths et al., 2008; Ziakopoulos et al., 1999). However, the induction of LTD in adult perirhinal cortex maintained in vitro also involves mGlu receptor activation (Cho et al., 2000), so that differences have been established between basic plasticity mechanisms in hippocampus and perirhinal cortex. Presumably evolution would make possible the exploitation of such plasticity differences to effect different memory processes in different cortical structures.

Notably, in both hippocampus and perirhinal cortex, LTP and depotentiation (the reversal of previously induced LTP) are dependent on NMDA receptors containing GluN2A subunits, whereas LTD is dependent on NMDA receptors containing GluN2B subunits (Bartlett et al., 2007; Liu et al., 2004; Massey et al., 2004; Morishita et al., 2007). Thus antagonists that have selective actions on NMDA receptors containing GluN2A or GluN2B subunits may potentially be used to investigate the dependency of recognition memory on either LTP-like or LTD-like mechanisms.

The NMDA-receptor dependency of plasticity mechanisms has not been studied in temporal association cortex in the rat. In rat mPFC, however, both LTP and LTD have been demonstrated (Hirsch and Crepel, 1990, 1992; Izaki et al., 2003). Interestingly while LTP induction in the mPFC is NMDA receptor-dependent (Hirsch and Crepel, 1991; Huang et al., 2004; Jay et al., 1995; Vickery et al., 1997), only NMDA receptor-independent mechanisms of LTD have been found in this region (Banks et al., 2012; Caruana et al., 2011; Hirsch and Crepel, 1991; Huang and Hsu, 2010; Lafourcade et al., 2007).

3. Behavioural studies

Behavioural studies relating recognition memory processes to NMDA receptor mechanisms will now be reviewed. In the rat, recognition memory has been extensively studied by using the species' instinctive tendency to explore novelty. Such procedures based on preference for novelty have the advantage that differential association with reinforcement is avoided when novel and familiar situations are compared. The effects of NMDA receptor antagonism have been studied using four such recognition memory procedures – involving objects locations objects associated with particular places and temporal order. The procedures involve an acquisition or sample phase, a delay and a choice or test phase (for temporal order there are two or more sample phases and delays). In each of these procedures a rat familiarises itself with one or more objects and/or places during the acquisition phase through spontaneous exploration. At test, following a variable retention delay, exploration of what has been familiarised is compared with exploration of something newly introduced (Ennaceur and Delacour, 1988).

3.1. Object recognition memory

In the standard object recognition memory task (OR) two objects are shown in the acquisition phase and during the test phase exploration of a familiar and a novel object is compared (see Fig. 1A). A number of studies now show that hippocampal or fornix lesions produce no effect in object recognition (Bussey et al., 2000; Mumby et al., 2002; Winters et al., 2004; Forwood et al., 2005; Good et al., 2007; Langston and Wood, 2010) although other studies have reported significant impairments (Clark et al., 2000, 2001). A recent study in our laboratory has established that both perirhinal cortex and the hippocampus are necessary for task solution if the two objects explored in the acquisition phase are different (G.R.I. Barker unpublished); however, only perirhinal cortex and not the hippocampus is required if the two objects explored at acquisition are identical copies of each other (Barker and Warburton, 2011; Winters et al., 2004). It is this latter (two rather than three object) version of the task that has been used, in the main, to study perirhinal NMDA receptor involvement in recognition memory.

Systemic and intracerebral administration of NMDA receptor antagonists have been shown to produced impairments in OR. Thus pre-training or post-training systemic administration of the non-competitive NMDA receptor antagonist MK801 impaired memory at 90 min and at 24 h suggesting that NMDA receptors are critical for both acquisition and consolidation (deLima et al., 2005). Similarly systemic administration of the competitive NMDA receptor antagonist (6)-3-(2-Carboxypiperazin-4-yl)-propanephosphonic acid (CPP) has been shown to block object familiarisation (Goh and Manahan-Vaughan, 2013) OR was also impaired when localised infusion of AP5 via cannulae placed bilaterally in perirhinal cortex was used to antagonise NMDA receptors during acquisition, with memory measured after a 3 h or 24 h delay (Barker et al., 2006; Winters and Bussey, 2005). However, the effect of AP5 on consolidation is equivocal as immediately post-acquisition intra-