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Distinct roles of the hippocampus and perirhinal cortex in $GABA_A$ receptor blockade-induced enhancement of object recognition memory

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ABSTRACT

It is well known that the hippocampus plays a role in spatial and contextual memory, and that spatial information is tightly regulated by the hippocampus. However, it is still highly controversial whether the hippocampus plays a role in object recognition memory. In a pilot study, the administration of bicuculline, a $GABA_A$ receptor antagonist, enhanced memory in the passive avoidance task, but not in the novel object recognition task. In the present study, we hypothesized that these different results are related to the characteristics of each task and the different roles of hippocampus and perirhinal cortex. A region-specific drug-treatment model was employed to clarify the role of the hippocampus and perirhinal cortex in object recognition memory. After a single habituation in the novel object recognition task, intra-perirhinal cortical injection of bicuculline increased and intra-hippocampal injection decreased the exploration time ratio to novel object. In addition, when animals were repeatedly habituated to the context, intra-perirhinal cortical administration of bicuculline still increased exploration time ratio to novel object, but the effect of intra-hippocampal administration disappeared. Concurrent increases of c-Fos expression and ERK phosphorylation were observed in the perirhinal cortex of the object with context-exposed group either after single or repeated habituation to the context, but no changes were noted in the hippocampus. Altogether, these results suggest that object recognition memory formation requires the perirhinal cortex but not the hippocampus, and that hippocampal activation interferes with object recognition memory by the information encoding of unfamiliar environment.

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1. Introduction

Recognition memory, which is a subcategory of declarative memory, is the ability to recognize previously encountered things, whether they are individual stimuli or whole events (Brown and Aggleton, 2001). As with other declarative memories, recognition memory consists of a variety of putative cognitive processes. The recognition process is generally thought to be composed of at least two components: recollection and familiarity. Recollection is thought to be a slower, more effortful process that requires conscious access to information about previously encountered experiences. In contrast, judgment of familiarity is thought to be a fast and relatively automatic process (Henson et al., 1999; Prull et al., 2006).

It is well known that recognition memory depends on the medial temporal lobe (MTL) and it plays a critical role in declarative memory. Previously, clinical and in vivo studies revealed that damage to the MTL caused impairment of performance in recognition memory tasks (Lee et al., 2003; Squire et al., 2007). In addition, recognition memory is commonly impaired in patients who are affected by brain injury or neurodegenerative diseases such as Alzheimer's dementia or schizophrenia (Grady et al., 2001; Pinkham et al., 2007). Therefore, understanding the brain regions affecting recognition memory may provide insight into the mechanisms of cognitive performance. Within the MTL, many studies have demonstrated that the perirhinal cortex is involved in recognition memory. Evidences from neuronal recording systems, immediate-early gene imaging, and animal lesion studies have revealed the role of the perirhinal cortex in recognition memory (Brown and Xiang, 1998; Winters et al., 2004; Zhu et al., 1995). However, the role of the hippocampus, the most important brain region in mammalian memory, in recognition memory is still highly controversial. For example, some studies using region-specific inactivation or protein synthesis inhibition demonstrated that the hippocampus is involved in object recognition memory (de Lima et al., 2006; Rossato et al., 2007). In contrast, other reports suggested that object recognition is impaired by perirhinal cortical lesions, but not by hippocampal lesions (Good et al., 2007; Winters et al., 2004). These inconsistencies are thought to be associated with differing contextual information among different studies.

Recently, we observed that intraperitoneal administration of bicuculline enhanced memory in the passive avoidance task in a dose-dependent manner (Kim et al., 2012), which is consistent with other reports (Luft et al., 2004; McGaugh and Roozendaal, 2009). Interestingly, in a pilot study, we did not observe any effect of intraperitoneal administration of bicuculline in the novel object recognition (data not shown). It is well known that spatial and contextual memory is tightly regulated by the hippocampus, while the perirhinal cortex is the most important brain region with regard to object recognition memory (Squire and Zola-Morgan, 1991; Winters et al., 2004). Several reports have suggested that the passive avoidance task is strongly linked to contextual and spatial information while the novel object recognition task involves information about the identity of the object (Burwell and Amaral, 1998; Winters et al., 2004). Therefore, we hypothesized that the different effects of bicuculine in the passive avoidance task and object recognition task are related to the characteristics of each task and the different roles of hippocampus and perirhinal cortex.

To test our hypothesis, we examined whether the effect of bicuculline on the object recognition memory is different when bicuculline is administered specifically in the perirhinal cortex or hippocampus using region-specific injections into each brain region. In addition, both a single habituation and a repeated habituation for 5 consecutive days before training were used in the novel object recognition task to investigate whether the degree of contextual familiarity could influence object recognition memory. And to investigate the role of the perirhinal cortex and the hippocampus in the different behavioral paradigms, we also investigated the changes in the expression level of c-Fos and the phosphorylation level of extracellular signal-regulated kinase (ERK) using Western blotting. Immediate-early genes such as c-Fos play roles in memory consolidation and are used as neuronal activation markers (Kim et al., 2012; Yasoshima et al., 2006). ERK is a key effector of the mitogen-activated protein kinase (MAPK) pathway and is necessary for the development of several forms of memory, including spatial memory and recognition memory (Giovannini, 2006; Kyosseva, 2004).

2. Results

2.1. *Effects of intra-perirhinal cortical or intra-hippocampal administration of bicuculline on the novel object recognition task after single habituation*

To investigate the effects of region-specific bicuculline treatment to the hippocampus or perirhinal cortex in the general novel object recognition paradigm, we employed a 1-day habituation paradigm (Fig. 2A). In the intra-perirhinal cortical treatment cohort, the exploration time ratio to the novel object and the discrimination index was significantly increased in the bicuculline-treated group compared with the vehicle-treated control group. [exploration time ratio, $t\ (11)=2.343$, $P<0.05$; discrimination index, $t\ (11)=2.343$, $P<0.05$, Fig. 2B]. However, in the intra-hippocampal treatment cohort, the exploration time ratio to the novel object and the discrimination index were decreased in the bicuculline-treated group compared with the vehicle-treated control group [exploration time ratio, $t\ (13)=2.312$, $P<0.05$; discrimination index, $t\ (13)=2.312$, $P<0.05$, Fig. 2C].

2.2. *Effects of intra-perirhinal cortical or intra-hippocampal administration of bicuculline in the novel object recognition task after repeated habituation*

Learning information about the context box could reportedly affect the encoding of object recognition in the novel object recognition task, and familiarization to the context could minimize this influence (Etkin et al., 2006; Oliveira et al., 2010). Therefore, to minimize the influence of contextual information on the animals, we employed a repeated habituation paradigm in the novel object recognition task (Fig. 3A). Rats were repeatedly exposed to the context for 5 days, and exploratory time in the box was measured as an index of familiarity to the context (Eichenbaum, 1996; Platel and Porsolt, 1982). On days 1 through 4, the exploratory time of rats in the context box consistently decreased compared