Available online at www.sciencedirect.com
ScienceDirect
Neurobiology of Learning and Memory 87 (2007) 583–596
Neurobiology of Learning and Memory
www.elsevier.com/locate/ynlme

Immediate early gene activation in hippocampus and dorsal striatum: Effects of explicit place and response training

Kathryn M. Gill, Ilene L. Bernstein, Sheri J.Y. Mizumori *

University of Washington, Department of Psychology, Box 351525, Guthrie Hall, Seattle, WA 98195, USA

Received 11 September 2006; revised 26 December 2006; accepted 29 December 2006
Available online 21 February 2007

Abstract

Evidence from lesion, electrophysiological, and neuroimaging studies support the hypothesis that the hippocampus and dorsal striatum process afferent inputs in such a way that each structure regulates expression of different behaviors in learning and memory. The present study sought to determine whether rats explicitly trained to perform one of two different learning strategies, spatial or response, would display disparate immediate early gene activation in hippocampus and striatum. c-Fos and Zif268 immunoreactivity (IR) was measured in both hippocampus and striatum 30 or 90 min following criterial performance on a standard plus-maze task (place learners) or a modified T-maze task (response learners). Place and response learning differentially affected c-Fos-IR in striatum but not hippocampus. Specifically, explicit response learning induced greater c-Fos-IR activation in two subregions of the dorsal striatum. This increased c-Fos-IR was dependent upon the number of trials performed prior to reaching behavioral criterion and accuracy of performance during post-testing probe trials. Quantification of Zif268-IR in both hippocampus and striatum failed to distinguish between place and response learners. The changes in c-Fos-IR occurred 30 min, but not 90 min, post-testing. The synthesis of c-Fos early in testing could reflect the recruitment of key structures in learning. Consequently, animals that were able to learn the response task efficiently displayed greater amounts of c-Fos-IR in dorsal striatum.

Keywords: c-Fos; Zif268; Place learning; Response learning; Hippocampus; Dorsal striatum; T-maze

1. Introduction

Damage to individual brain regions can cause selective behavioral impairments that are often attributed to functional specializations as independent memory systems. Hippocampus (HPC) and dorsal striatum (DS) are examples of two brain structures that have been categorized based on their proposed involvement in distinct memory systems. Animals with HPC damage are typically impaired on tasks requiring effective use of spatial context information. For instance, HPC lesions impair an animal's ability to utilize spatial landmarks to associate a location with either food reward, as in the plus-maze task, or safety, as in the Morris water maze (McDonald & White, 1993; Packard & McGaugh, 1996). In contrast, the association between discrete stimuli, irrespective of any relationship with spatial cues, and explicit behavioral responses learned through reinforcement outcomes in similar testing conditions appear to rely more on an intact DS (Devan, McDonald, & White, 1999; Featherstone & McDonald, 2005).

In certain instances, there appears to be competition between HPC and DS to regulate behavioral output (reviewed in Mizumori, Yeshenko, Gill, & Davis, 2004). Inactivation, or lesion, of HPC can cause simultaneous impairment of spatial learning and facilitation of acquisition of a response task (Chang & Gold, 2003). In conflict with the proposal that DS mediates only stimulus–response behaviors, lesions of a specific subregion, dorsomedial (DM) of DS can interfere with spatial and response learning. (Devan, Goad, & Petri, 1996; Whishaw, Mittleman, Bunch, & Dunnett, 1987). This would suggest that the functional division of HPC and DS into completely separate memory systems may be too restrictive.

* Corresponding author. Fax: +1 206 685 3157.
E-mail address: mizumori@u.washington.edu (S.J.Y. Mizumori).

1074-7427/$ - see front matter © 2007 Elsevier Inc. All rights reserved.
doi:10.1016/j.nlm.2006.12.011

At even greater odds with the multiple memory systems theory, single-unit recordings in HPC and DS have illustrated remarkable similarities in terms of spatial representation. Both regions contain neurons that exhibit spatially selective neural activity (Gill & Mizumori, 2006; Mizumori, Cooper, Leutgeb, & Pratt, 2000; Ragozzino, Leutgeb, & Mizumori, 2001; Yeshenko, Guazzelli, & Mizumori, 2004). Location-specific firing in both HPC and STR is sensitive to alterations in the visual testing environment independent of whether animals are performing a place or response task (Yeshenko et al., 2004). Despite the similarities in HPC and DS response to contextual changes, differences in how these areas respond to dopaminergic manipulations suggest that each region is differentially regulated by dopamine (Gill & Mizumori, 2006).

In addition to single unit analysis, measurement of immediate early gene (IEG) activation across brain regions provides a means of visualizing the pattern of neural activation resulting from specific behaviors in the intact animal. Detecting changes in the pattern of IEG activation in HPC and DS provides a different level of analysis for identifying changes in neural plasticity associated with learning. Activation of certain IEGs, such as *c-fos* and *zif268* (Krox-24, NGFI-A, EGr1, and ZENK) has been implicated during the consolidation of memory (Hall, Thomas, & Everitt, 2001; Huff et al., 2006; Weitemier & Ryabinin, 2004). The degree to which a structure displays differential amounts of IEG activation during different learning paradigms, such as place or response learning, could indicate their relative contribution to behavior. HPC IEG expression is induced after spatial learning (Guzowski, Setlow, Wagner, & McGaugh, 2001; Vann, Brown, Erichsen, & Aggleton, 2000).

Traditional views of multiple memory system function, originating primarily from lesion studies, hypothesize that disparate neural systems operate independently to regulate behavior. This perspective appears at odds with the apparent collaboration among systems based on similarities in neural processing. However, it could be that differences in responsiveness to neuromodulators such as dopamine underlie the distinct mnemonic functionality of different regions. If this were the case, IEG activation could likewise be differentially regulated by neuromodulatory activity. Accordingly, it would be expected that HPC should be selectively active during HPC-dependent tasks, while DS should become selectively active during striatal-dependent tasks. Consistent with this prediction, Colombo, Brightwell, and Countryman (2003) demonstrated that differences in HPC c-Fos expression 1 h after T-maze training correlated with a place strategy employed during a post-criterion probe trial. However, response strategy use did not induce the expected analogous increase in c-Fos in DS. Nevertheless, the observed structure-specific changes in IEG response to different behavioral paradigms could support the participation of these regions in separate memory systems.

The failure to find differential IEG activation in DS in previous studies may have been a result of insufficient task demands, or the potential differences were masked by simultaneous activation within HPC and DS. It is possible that explicit response testing could increase DS IEG expression above threshold for measurable activation, or sufficient response learning could cause IEG expression to diminish in other regions while DS levels remain constant. This study sought to determine whether explicit place and response testing on the radial maze would lead to differential IEG activation in the HPC or DS, respectively. To accomplish this, a new behavioral paradigm was developed to allow validation of IEG activation related to learning a specific cognitive strategy. Rats were trained on either a place or response task, and HPC and DS IEG activation was compared.

It was uncertain what the temporal pattern of activation of Zif268 and c-Fos immunoreactivity (IR) would be. Typically, IEG protein products are quantified approximately 1–2 h after exposure to experimental conditions (Chaudhuri, Nissanov, Larocque, & Rioux, 1997; reviewed in Guzowski et al., 2005; Morgan, Cohen, Hempstead, & Curran, 1987). The tasks used in this study require 60–90 min of testing. Therefore, one possibility is that structures are engaged at the onset of testing, with peak expression occurring shortly after the 60–90 testing session. Alternately, reaching behavioral criterion, or accurate levels of performance, may signal optimal activation of the brain regions engaged during learning and trigger IEG activation at this timepoint. Subsequently, peak expression would occur 90 min after behavioral criterion had been reached. Therefore, the present study compared c-Fos-IR and Zif268-IR in DS and HPC at two different timepoints, 30 or 90 min after animals reached behavioral criterion.

2. Methods

2.1. Animals

Subjects were male Long-Evans rats ($N = 32$; Charles River, Raleigh, NC) individually housed within a temperature-controlled environment (21 °C) in Plexiglas cages and maintained on a 12-h light–dark cycle. All behavioral testing occurred during the light portion of the cycle. Food and water were available ad libitum for 7 days upon arrival. Subsequently, prior to testing, animals were handled daily and food was restricted to maintain animals at 80% of their initial ad-lib weight. Animals had free access to water throughout the experiment. All methods described were in compliance with the University of Washington Institutional Animal Care and Use Committee and National Institutes of Health guidelines for the care and use of animals in research.

2.2. Behavioral testing

2.2.1. Apparatus

All animals were trained on a semi-automated modified eight arm radial maze, consisting of eight black Plexiglas runways (58 × 5.5 cm) that extended from a central platform (19.5 cm in diameter) and raised to a height 79 cm from the floor. Each runway was hinged in the center so that each arm could be raised or lowered independently. Place testing required a plus maze configuration. A rotating T-maze configuration was utilized for response testing, summarized in further detail below. The maze was