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The role of the ventral dentate gyrus in anxiety-based behaviors

Christy S.S. Weeden [1], Jared M. Roberts [2], Allison M. Kamm, Raymond P. Kesner *

Department of Psychology, University of Utah, Salt Lake City, USA

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ABSTRACT

Dorsoventral lesion studies of the hippocampus (HPP) indicate that the dorsal axis is important for spatial processing and the ventral axis is important in anxiety and olfactory processes. There is some evidence that ventral CA3 and ventral CA1 subregions are important for cued retrieval in fear conditioning, which supports a ventral-anxiety relationship. However, the role of the ventral dentate gyrus (DG) in anxiety-based behaviors is less understood. Therefore, we used elevated plus and open field mazes to investigate the role of the ventral DG in the ability to modify behavior in potentially dangerous conditions and to clarify a few previous reports that ventral HPP lesions may induce hyperactivity. Rats with ventral DG lesions spent significantly more time in the open arms of the elevated plus maze and inner zone of the open field test than did controls and rats with dorsal DG lesions. Locomotor measures indicate that all rats traveled at similar rates in enclosed arms, as well as in open arms of the elevated plus maze and all groups traveled at similar rates in the open field test, which indicates that differences in exploration were not likely due to hyperactivity. The present study findings indicate that the ventral DG plays an important role in anxiety-based behaviors, such as preference for safer environments and the ability to modify exploratory behavior when in potentially dangerous environments and that the dorsal DG is not importantly involved in anxiety.

1. Introduction

Moser and Moser (1998) demonstrated that the dorsal hippocampus (HPP) is important for spatial information processing. For example, rats with large lesions to the dorsal HPP were impaired in learning a simple maze task, but rats with lesions to the ventral HPP successfully learned to locate the escape platform. Subsequent investigations have revealed that the ventral portion of the HPP is important for processing odor information as well as anxiety-based behaviors (Bannerman et al., 1999, 2002, 2004; Kesner, Hunsaker, & Ziegler, 2011). Rats previously trained on a delayed-matching-to-sample working memory odor choice task failed to discriminate following dorsal HPP lesions, yet were able to successfully learn to select a rewarded odor when two odors were repeatedly presented together in a simple discrimination task (Kesner et al., 2011). Though it can be involved, the ventral HPP is not critical for spatial processing, especially when learning takes place after lesions or inactivations (Bannerman et al., 1999, 2002, 2003, 2004).

Gray and McNaughton (2000) have provided a rich context and extensive experimental repertoire of lesion studies to demonstrate hippocampal involvement in anxiety and to show that anxiety is distinctly different from fear, which has been shown to be amygdala-dependent (Gray & McNaughton, 2000). Anxiety has been described as a state that results from cognitive management of competing goals to avoid possible (but not directly present) danger and to engage in and explore the environment, whereas fear has been described as a near-instinctual, behavioral response to move away from a source of explicit danger. Several lesion and pharmacological investigations have used the elevated plus maze to demonstrate key differences between fear and anxiety. Rats treated with benzodiazepines or with ventral HPP lesions are faster to enter and remain in anxiety-provoking locations in a successive alleys maze than sham and amygdala lesioned rats, yet direct infusion of benzodiazepines into the amygdala fail to increase anxiogenic exploration (Bannerman et al., 2002; Gonzalez, Andrews, & File, 1996; McHugh, Deacon, Rawlins, & Bannerman, 2004; Pellow, Chopin, File, & Briley, 1985; Pesold & Treit, 1994).

Ventral HPP connections indicate that the structure is well-suited to support anxiety-based behaviors. For example, connections to the amygdala may facilitate a close relationship between fear and

* Corresponding author at: Department of Psychology, 380 S 1530 E BEHS 502, Salt Lake City, UT 84112, USA.
E-mail address: ray.kesner@psych.utah.edu (R.P. Kesner).
[1] Present address: The Unit on Neuroplasticity, National Institute of Mental Health, National Institutes of Health, Bethesda, MD, USA.
[2] Present address: Department of Neurobiology and Behavior, University of California, Irvine, CA, USA.

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anxiety behaviors, and direct ventral HPP projections to the hypothalamus impact the hypothalamic-pituitary adrenal axis (HPA), which is important for feeding, motivation, stress, and emotional state regulation (Dedovic, Duchesne, Andrews, Engert, & Pruessner, 2009; Felix-Ortiz & Tye, 2014; Lasseter, Xie, Ramirez, & Fuchs, 2010; Van Groen & Wyss, 1990). Interestingly, the ventral HPP also makes exclusive connections with the prefrontal cortex, which is important for many higher-order cognitive functions (Jay & Witter, 1991).

Individual subregions of the ventral HPP have been implicated in anxiety-based behaviors. For example, lesion studies show that the ventral CA3 is important for retrieval of contextual fear conditioning and the ventral CA1 is important for retention of trace fear conditioning (Hunsaker & Kesner, 2008; Rogers, Hunsaker, & Kesner, 2006). Excitation of ventral DG granule cells has been shown to suppress anxiety-based behaviors, and adult-born granule cells of the ventral DG have recently been implicated in anxious behaviors (Kheirbek et al., 2013; Wu & Hen, 2014). Additionally, a body of subregional behavioral studies indicates that all of the dorsal subregions of the HPP are important for individual processing roles, including the dorsal DG for pattern separation of highly overlapping spatial information and ventral DG for pattern separation for odor information (Gilbert, Kesner, & Lee, 2001; Kesner, 2013; Lee & Kesner, 2004; Weeden, Hu, Ho, & Kesner, 2014). Because lesion studies have provided evidence that the ventral CA3 and CA1 carry out specialized roles in anxiety-based behaviors, and due to the impact the DG has on hippocampal information, as well as evidence that all other dorsal and ventral subregions support specialized processing functions, there is a credible basis to suggest that the ventral DG may play a critical role in manifestation of anxiety-based behaviors in anxiety-provoking situations.

Lesion studies to the ventral HPP or entire HPP have revealed conflicting reports of hyperactivity (Bannerman et al., 1999, 2002; Kjelstrup et al., 2002; Lanier & Isaacson, 1975). For example, two different observations were reported using the Morris water maze: in one experiment, rats with lesions to the ventral HPP had faster swim speeds but in a different water maze experiment, did not (Bannerman et al., 1999, 2002). To meet criteria for hyperactivity, behaviors of experimental groups are typically compared to those of the control group. In other words, the definition of what constitutes "hyperactive" is actively impacted by control group behaviors – even if a treatment group's behaviors remain stable. Several measures of anxiety involve reduced locomotion; therefore, the measures of hyperactivity in anxiety-inducing tasks serve to confound the relationship between anxiety-based behaviors and assessments of locomotion. It is quite possible that previous mixed reports of hyperactivity may reflect changes in the behaviors of controls when moved from a non-anxiety situation (e.g., home cage) to one that is designed to provoke a range of anxiety levels (e.g., elevated plus maze). In fact, subjects from those reports failed to demonstrate hyperactivity in the home cage (Bannerman et al., 1999, 2003).

The elevated plus maze and open field are widely accepted as classical behavior tests used to measure context reactivity and anxiety-based behaviors (Ramos, Berton, Mormède, & Chaouloff, 1997; Walsh & Cummins, 1976). The open field test is sensitive to a multitude of behaviors and is most commonly associated with locomotion in terms of both quantity (distance traveled) and quality (location of travel) (Gould, Dao, & Kovacsics, 2009). Though it may be impossible to fully disentangle activity from anxiety, a strength of the elevated plus maze paradigm is the ability to directly compare behavior in two conditions that occur within the same test: open versus closed arm exploration. Therefore, an evaluation can be made between control and treatment groups, but also a direct comparison of each group's performance in open and closed arms can be examined (Ennaceur, 2014; Walf & Frye, 2007). Though the ability to directly compare arm exploration is valuable, the structure of the elevated plus maze greatly limits animal movement. A key feature of the open field test is that it provides a large arena that is less restrictive to animals' unique exploratory patterns. Genetic models and individual trait studies have reported both similar and dissimilar results from these two paradigms, and although some studies indicate exposure to multiple tests influences subsequent results, testing in both the elevated plus maze and open field have generally been reported as standard practice for investigation of anxiety-based behaviors and the strengths of each test may serve to clarify sensitive behavioral measures of anxiety (Walf & Frye, 2007). In order to investigate a potential role for the ventral DG in anxiety-based behaviors, an elevated plus maze and open field test were administered to rats with dorsal DG, ventral DG, and sham lesions.

2. Materials and methods

2.1. Subjects

Eighteen male Long-Evans rats (Simonsen Laboratories, Inc., Gilroy, CA), weighing 250–350 g were used as subjects. Rats were housed individually in plastic cages that were located in a colony room with a 12:12 h light/dark cycle. Subjects were free-fed and had ad libitum access to water. Testing was individually conducted for each rat during the light phase of the light/dark cycle. Subjects had been previously used in an unrelated spatial paradigm in which rats were placed on a cheeseboard and allowed to freely explore for 5 min. The testing room was different than the anxiety testing rooms (dimly-lit, wire mesh on walls, absence of extra-maze plush cues) and this session took place two weeks prior to surgical assignment. All subjects were used in both experiments; first in the elevated-plus maze experiment (Experiment 1) followed by the open field test experiment (Experiment 2). Although hyperactivity in a second paradigm has been reported in some cases, it is common practice to test rats in successive anxiety paradigms (Pellow et al., 1985; Walf & Frye, 2007). All procedures and animal care were in compliance with the National Institutes of Health, Institute for Animal Care and Use Committee of the University of Utah guidelines, and conformed to AAALAC protocols.

2.2. Surgical procedures

Rats were randomly assigned to control ($n = 6$), ventral DG ($n = 6$), or dorsal DG ($n = 6$) lesion groups. Rats in the ventral DG and dorsal DG lesion groups received bilateral intracranial infusions of colchicine (2.5 mg/ml, 0.8 µl/site) into the ventral DG or dorsal DG. Half of the control subjects ($n = 3$) received bilateral intracranial infusions of saline-hydrochloride solution (2.5 mg/ml, 0.8 µl/site) into the ventral DG and the other half of control subjects ($n = 3$) received the same solution into the dorsal DG. Prior to surgery, animals were administered atropine sulfate (0.54 mg/kg, i.m.). Subjects were anesthetized by exposure to isoflurane gas and positioned in a stereotaxic apparatus (David Kopf Instruments, Tujunga, CA). For the duration of the procedure, subjects remained anesthetized with a continuous flow of isoflurane (2–4%) and medical air (≈1.5 l/min) mixture. Hair covering the surgical site was removed with a rechargeable Conair trimmer (Shelton, CT). Antiseptic measures were carried out: a surgical drape was positioned to expose only the shaved area, which was swabbed three consecutive times with betadine. The skin covering the skull was incised and retracted to expose the skull. Bregma was identified and burr holes were drilled through the skull at injection sites. Injections were made by lowering a 7 µl Hamilton GasTight syringe (Hamilton Company, Reno, NV) that was attached to a

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