

The influence of NMDA receptors in the dorsomedial striatum on response reversal learning

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Abstract

In mammals, the dorsomedial striatum is one brain area shown to be critical for the flexible shifting of response patterns. At present, the neurochemical mechanisms that underlie learning during a shift in response patterns are unknown. The present study examined the effects of NMDA competitive antagonist, DL-2-amino-5-phosphonopentanoic acid (AP-5), injected into the dorsomedial striatum on the acquisition and reversal of a response discrimination. Male Long-Evans rats were tested across two consecutive days in a modified cross-maze. Rats received an infusion of either saline or AP-5 (5 or 25 nmol) 5 min prior to each test session. In the acquisition phase rats learned to turn in one direction (right or left) to receive a cereal reinforcement. In the reversal learning phase rats learned to turn in the opposite direction as in the acquisition phase. In both phases, criterion was achieved when a rat made 10 consecutive correct trials. Infusions of AP-5 did not impair acquisition, but impaired reversal learning of a response discrimination in a dose-dependent fashion. The reversal learning deficit induced by AP-5 resulted from reversion back to the originally learned response pattern following the initial shift. These results suggest that activation of NMDA receptors in the dorsomedial striatum are critical for the flexible shifting of response patterns by enhancing the reliable execution of a new response pattern under changing task contingencies.

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1. Introduction

One idea about the role of the striatum in learning and memory is that it has a unitary function supporting the acquisition of stimulus–response associations or “egocentric” response learning (Colombo, Davis, & Volpe, 1989; Cook & Kesner, 1988; Kesner, Bolland, & Dakis, 1993; Knowlton, Mangels, & Squire, 1996; McDonald & White, 1993; Mishkin, Malamut, & Bachevalier, 1984; Packard, Hirsh, & White, 1989; Packard & McGaugh, 1992; Potegal, 1969; Potegal, Copack, de Jung, Krauthamer, & Gilman, 1971). More recent studies indicate that the dorsolateral striatum, in particular, may be an area critical for the learning of arbi-

trary stimulus–response associations (Devan, McDonald, & White, 1999; Featherstone & McDonald, 2004a, 2004b; Jog, Kubota, Connolly, Hillegaart, & Graybiel, 1999; Packard & McGaugh, 1996; Packard, 1999; Reading, Dunnet, & Robbins, 1991; White & McDonald, 2001; Yin, Knowlton, & Balleine, 2004). For example, rats with dorsolateral striatal lesions are impaired in learning a conditional discrimination, which requires associating a specific visual or auditory stimulus with a particular lever press response (Featherstone & McDonald, 2004a, 2004b; Reading et al., 1991). Furthermore, recording from neurons in the rat dorsolateral striatum during the acquisition of a tone–response conditional discrimination indicate this area is critical for learning of stimulus–response associations (Jog et al., 1999). As performance improved in acquisition of the tone–response discrimination there was a

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concomitant increase in the percentage of neurons that showed correlated firing to a particular aspect of the task, e.g., initiation of movement or tone presentation. In addition, this selective activation of dorsolateral striatal neurons to different aspects of the learned stimulus–response association remained stable for weeks (Jog et al., 1999). Thus, findings from recording of dorsolateral striatal neurons and lesions of this area suggest that the dorsolateral striatum may be crucial for stimulus–response learning.

In contrast to the dorsolateral striatum, the dorsomedial striatum does not appear critical for the learning of stimulus–response associations, but supports learning when conditions require the flexible use of response patterns or a shift in strategies (Kolb, 1977; Livesey & Muter, 1976; Pisa & Cyr, 1990; Ragozzino, Jih, & Tzavos, 2002a; Ragozzino, Ragozzino, Mizumori, & Kesner, 2002b; Ragozzino & Choi, 2004; Tzavos, Jih, & Ragozzino, 2004). Activity of neurons in the dorsomedial striatum is correlated when conditions require the flexible shifting of navigational patterns (Mizumori, Cooper, Leutgeb, & Pratt, 2000; Wiener, 1993). Furthermore, lesions or temporary inactivation of the dorsomedial striatum do not impair the initial learning of different types of discrimination, but do impair place, visual cue or response reversal learning (Kirkby, 1969; Kolb, 1977; Pisa & Cyr, 1990; Ragozzino et al., 2002b; Ragozzino & Choi, 2004; Van Golf Racht Delatour & El Massioui, 1999). This pattern of findings suggests that the dorsomedial and dorsolateral striatum may be involved in distinct behavioral processes to enable learning.

Although there is accumulating evidence that the dorsomedial striatum supports learning when conditions require a flexible shift in response patterns there is not a clear understanding of the neurochemical mechanisms that underlie this type of learning. Considerable evidence indicates that NMDA receptors play a central role in striatal synaptic plasticity (Charpier & Deniau, 1997; Lovinger & Tyler, 1996). NMDA receptor activity is critical for the induction of corticostriatal long-term potentiation (Charpier & Deniau, 1997; Pisani et al., 2001). Long-term potentiation is a type of synaptic plasticity that may underlie different forms of learning and memory (Goosens & Maren, 2002; Kandel, 2001). Besides evidence suggesting that NMDA receptors are critical for certain forms of striatal synaptic plasticity, NMDA antagonists infused into the dorsomedial striatum impair performance in a task that requires the flexible shifting of different response sequences (Cory-Slechta, O'mara, & Brockel, 1999) and the learning of the win-shift version in the radial-arm maze (Smith-Roe, Sadeghian, & Kelley, 1999). These findings suggest that NMDA receptors in the dorsomedial striatum may enable learning when conditions demand a shift in response patterns.

To further explore this idea, the present experiment determined whether NMDA receptors in the dorsomedial striatum are involved in learning when task contingencies are reversed. Specifically, the present investigation examined the effects of microinjections of the NMDA antagonist, AP-5 into the dorsomedial striatum during the acquisition and reversal learning of a response discrimination task.

2. Methods

2.1. Subjects

The experimental subjects were 40 adult male hooded Long-Evans rats (Charles River Laboratories, Indianapolis) weighing between 310 and 370 grams at the initiation of the experiment. The subjects were housed individually in thick transparent plastic cages (54 cm × 20 cm × 29 cm), inside a temperature (24 °C) and humidity (~30%) controlled room. The room was kept on a 12 h light–dark cycle with the lights on at 7 a.m. Animal care and use was in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals, and was approved by the Institutional Laboratory Animal Care and Use Committee of the University of Illinois at Chicago.

2.2. Handling

Prior to surgery all rats were food restricted to maintain their weight at 85% of their ad libitum weight. One week before surgery each rat was handled for 10–15 min every day for a total of seven days. Rats were also given Froot Loops cereal while being handled (Kellogs, Battle Creek, MI, USA).

2.3. Surgery

Atropine sulfate (0.2 ml of a 250 µg/ml solution) was administered to each rat 15 min before the injection of the general anesthetic (sodium pentobarbital, 50 mg/kg i.p.). After being placed on the stereotaxic apparatus, a midsagittal incision was made to retract the scalp and expose the cranium. Eight-mm stainless steel cannulas were implanted bilaterally aimed towards the dorsomedial striatum (stereotaxic coordinates: 1.1 mm anterior to bregma, ±2.8 lateral to midline Paxinos & Watson, 1997). The nose bar was set at 3.3 ± 0.4 below horizontal zero to level the skull. The cannulas were implanted at a 10° angle. Four stainless steel jeweler screws (2 mm) were secured on the skull that served as anchors. Stylets were screwed securely into the cannulas to prevent obstruction. Following recovery, each rat was placed in its home cage and received ground rat chow and sugar made into a mash solution for two days.

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