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Research report

The time-dependent and persistent effects of amphetamine treatment upon recovery from hemispatial neglect in rats

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HIGHLIGHTS

- The effects of amphetamine treatment were tested in rats with hemispatial neglect.
- Amphetamine treatment resulted in fewer days to reach recovery.
- Accelerated recovery occurred even with a delay in amphetamine treatment.
- Recovery persisted for at least 60 days.
- Recovery is likely to be long term.

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ABSTRACT

Neglect is a neuropsychological disorder characterized by the failure to report or respond to stimuli presented to the side of the body opposite a brain lesion and occurs in approximately 40% of right hemisphere strokes. The need for effective therapies to treat neglect in humans has led to the development of a rodent model. Unilateral destruction of medial agranular cortex (AGm), which is part of a cortical network for directed attention, produces severe multimodal neglect with deficits similar to those seen in humans. Amphetamines have previously been investigated for inducing plasticity and recovery of function following brain damage. Amphetamine treatment has been shown to produce recovery from visual, frontal, and sensorimotor cortex damage in animals and this recovery may be the result of axonal growth originating from the opposite, unlesioned hemisphere. The purpose of this study was to investigate whether amphetamine treatment would induce recovery from neglect produced by unilateral AGm destruction, the time frame in which amphetamine must be administered in order to be effective, and the permanence of recovery following treatment. The results indicated that subjects injected with 2 mg/kg of D-amphetamine on days 0, 2, and 5 recovered in significantly fewer days than saline-treated controls, even when administration was delayed by 2 and 7 days. Additionally, these studies indicated that recovery persisted for at least 60 days suggesting that recovery is likely to be long term.

1. Introduction

Hemispatial neglect is a neuropsychological disorder that occurs in approximately 40% of right hemisphere stroke patients and is characterized by the failure to respond to stimuli presented to the side of the body opposite a brain lesion [25]. Neglect is a complex spatial-attentional disorder that cannot be explained by more elementary sensory-motor deficits [25,30]. For stroke patients, the single best predictor of a poor outcome is the continued presence of neglect deficits at 52 days post-stroke [14,25]. Patients are often unaware of their neurological deficit [21] and as a result, patients with lasting neglect deficits are often unable to live independently due to an inability to complete tasks such as driving a car or safely crossing the street [25]. Rehabilitation treatment for neglect rarely generalizes outside the therapeutic setting and drug therapies have not been used because the mechanism through which they work is not well understood [21].

The need for effective therapies has led to the development of a rodent cortical model of neglect, which focuses on a network for directed attention involving the rodent analog of the frontal eye fields, the medial agranular cortex (AGm) and posterior parietal cortex (PPC) [7,24,37]. Complete unilateral lesions of left AGm

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result in deficits similar to those seen in humans, severe neglect of visual, tactile, and auditory stimuli. Spontaneous recovery has been shown to occur, but it occurs slowly and is rarely complete [11,26,27]. Temporary recovery, however, can be induced by systemic injections of apomorphine [11], whereas, more permanent recovery can be induced through infusion of anti-Nogo-A antibodies or an environmental manipulation of 48 h of light deprivation [5,8,13].

AGm projects bilaterally to the dorsal central striatum (DCS), which is also a convergence zone for striatal afferents from PPC [9,24,36,40,41,50]. Lesions of DCS result in severe neglect that does not recover spontaneously and render interventions such as light deprivation and apomorphine ineffective [42,43]. Previous studies have found that recovery from left AGm-induced neglect is correlated with alterations in immediate early gene expression in the dorsolateral striatum and increases in NMDA and kainate receptors in the ipsilesional dorsolateral striatum [45]. These results have led to the conclusion that the striatum is vital for recovery from neglect and also suggest that increasing corticostriatal plasticity into the DCS may be a viable treatment option.

Studies investigating recovery following cortical injury have shown motor improvements associated with corticospinal, corticorubral and corticopontine axonal plasticity following amphetamine treatment [31,34]. Additionally, recovery with amphetamines has been correlated with increases in GAP-43 and synaptophysin suggesting that behavioral recovery correlates with neuronal remodeling and synaptic changes [38]. More recent work indicates that rats with severe stroke as a result of an embolic middle cerebral artery occlusion showed dose dependent improvement when treated with methamphetamine compared to saline [24] The effects of amphetamine treatment on recovery vary widely and may depend largely on the location and extent of the brain injury, the amphetamine dosing regimen, and the behavioral assessment used [1–3,20,31,34,38].

While amphetamines have been used with varying degrees of success in motor systems, few studies have looked at whether it will promote improvements in cognitive function following injury. Because of this the present study was designed to investigate the effectiveness of short-term administration of amphetamine upon recovery from neglect, as well as the time window for maximally induced recovery. Very little is known about how long a treatment's effectiveness lasts beyond demonstrating signs of improvement. Further, few studies that look at induced recovery have even focused upon how persistent of an effect the treatment has upon behavioral improvement. Therefore, as an additional object we also sought to determine whether recovery was permanent by testing subjects long after the recovery was initially demonstrated.

2. Methods

2.1. Subjects

All procedures were approved by the Northern Illinois University Institutional Animal Care and Use Committee. Fifty male Long Evans hooded rats 3–5 months of age were handled daily for 2 weeks to sufficiently gentle them for behavioral testing. Throughout the experiment, subjects were individually housed with free food and water and kept under a standard 12:12 h light/dark cycle at all times.

2.2. Surgery

The subjects were anesthetized with a ketamine–xylazine mixture (87 mg/ml: 13 mg/ml) at a dosage of .87 ml/kg i.p and placed in a stereotaxic device. A “skull window” was removed over the left hemisphere from 5.0 mm rostral to 2.5 mm caudal and 0.0 mm to 2.5 mm lateral to Bregma. The medial agranular cortex (AGm) of the left hemisphere was removed by gentle subpial aspiration down to the white matter by use of a fine-gauge pipette and the lesion gently packed with Gelfoam. The incision was closed with sterile wound clips. Subjects were kept warm and monitored prior to behavioral testing.

2.3. Drug injections

Six groups received i.p. injections of (+) D-amphetamine sulfate (2 mg/kg) (Sigma–Aldrich, St. Louis, MO) or 0.9% saline on days 0, 3, 6 ($n = 16$ amph, $n = 14$ saline); days 2, 5, 8 ($n = 7$ amph, $n = 3$ saline) or days 7, 10, 13 ($n = 7$ amph, $n = 3$ saline) [16,17,34]. The animals were first tested a four hours post-surgery to establish the presence of neglect, as prior research by our lab has shown that neglect at this time point is an indicator of future deficits. Twice per week behavioral tests were spaced such that testing and drug injections occurred at a minimum of 24 h apart in order to avoid the subject being under the influence of the drug during testing.

2.4. Behavioral testing

2.4.1. Circling

Circling behavior was assessed because the tendency to consistently circle in the ipsi- or contralesional direction might confound the interpretation of the behavioral measures. Subjects were place in their home cage on a testing platform for 2 min of observation of circling behavior prior to behavioral testing for neglect. The number of ipsi- and contralesional turns was counted to the nearest 1/2 turn. All testing was conducted during the light phase of the light/dark cycle in a room with standard overhead fluorescent lighting and the experimenter blind to the experimental treatment.

2.4.2. Orientation testing

Subjects were tested for the presence of neglect 4–6 h after neglect surgery and then twice a week for 8 weeks during the light phase of the light/dark cycle with the experimenter blind to the subjects' conditions. Neglect testing was a modification of the testing procedure developed by Crowne and Pathria [12] and is described in detail in previous publications [11,40,44]. Following observation of circling behavior, subjects were taken out of their cage and placed directly on the testing platform. The testing platform contained markings delineating angles of 0°, 30°, 45°, and 60° in either direction from a central line running the length of the testing platform. The subjects were gently restrained by hand from behind without restricting head movement and the head aligned with the centerline. Stimuli were presented only when there was no evidence of struggling, no asymmetry of body posture, and when the head was oriented in direct line with the body. The animal's body sometimes needed to be realigned several times during testing [6,40].

Visual, auditory, and tactile stimuli were presented in turn. The visual stimulus consisted of the presentation of a silver metallic rod 10.0 cm in length, which was waved in a small circle (approximately 5.0 cm in diameter) five times within the animal's visual field at a distance of 7.5–10.0 cm from the animal at a rate of approximately one revolution/second. The auditory stimulus was a single 114-dB (SPL) click generated by a clicking device held at mid-body, approximately 5 cm from the subject. The tactile stimulus was a single caudal-to-rostral stroke through the vibrissa with a 15-cm wooden Puritain applicator (Harkwood Products, No. 807).

Each test session was composed of three cycles of testing, with each cycle consisting of a single presentation of each of the three stimuli to each side of the body in order: Visual, tactile, and then auditory. The order of stimulus presentation has been shown to