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Research report

Noradrenergic antagonists mitigate amphetamine-induced recovery

M.J. Hylin[a,*], M.M. Brenneman[b], J.V. Corwin[c]

[a] Neurotrauma and Rehabilitation Laboratory, Department of Psychology, Southern Illinois University, Carbondale, IL, United States
[b] Department of Psychology, Coastal Carolina University, P.O. Box 261954, Conway, SC, United States
[c] Department of Psychology, Northern Illinois University, DeKalb, IL, United States

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ABSTRACT

Brain injury, including that due to stroke, leaves individuals with cognitive deficits that can disrupt daily aspect of living. As of now there are few treatments that shown limited amounts of success in improving functional outcome. The use of stimulants such as amphetamine have shown some success in improving outcome following brain injury. While the pharmacological mechanisms for amphetamine are known; the specific processes responsible for improving behavioral outcome following injury remain unknown. Understanding these mechanisms can help to refine the use of amphetamine as a potential treatment or lead to the use of other methods that share the same pharmacological properties. One proposed mechanism is amphetamine's impact upon noradrenaline (NA). In the current, study noradrenergic antagonists were administered prior to amphetamine to pharmacologically block α- and β-adrenergic receptors. The results demonstrated that the blockade of these receptors disrupted amphetamines ability to induce recovery from hemispatial neglect using an established aspiration lesion model. This suggests that amphetamine's ability to ameliorate neglect deficits may be due in part to noradrenaline. These results further support the role of noradrenaline in functional recovery. Finally, the development of polytherapies and combined therapeutics, while promising, may need to consider the possibility that drug interactions can negate the effectiveness of treatment.

1. Introduction

Currently the treatments for stroke are very limited and patients are often left with disabilities, such as hemispatial neglect, that leave them unable to care for themselves and reliant upon others [1]. Various treatments following stroke have sought to improve outcomes by targeting specific mechanisms that underlie functional recovery. Drugs that enhance long-term recovery differ from those that offer neuroprotection or promote reperfusion [2]. While amphetamine has been used in the clinical treatment of stroke, clinical trials have been met with mixed success [3–11].

There is a paucity of studies that have investigated the putative mechanisms that underlie amphetamine-induced recovery. Prior research has shown that drugs that increase noradrenergic activity promote motor recovery from experimental stroke [12]. More recently, Wolf, et al. found that FGF-2 is increased in pyramidal neurons following amphetamine treatment of motor deficits [13]. Further, *in vitro* experiments found that FGF-2 expression was increased by β- and α1-receptor activity suggesting that the increased noradrenaline (NA) activity with amphetamine treatment may underlie its effects upon recovery. Recently, Brenneman, et al. found that amphetamine treatment results in permanent stable recovery from hemispatial neglect [14]. Amphetamine-induced recovery from neglect was observed within a few weeks and was thought to be long-lasting, since animals tested at 2 months following recovery still demonstrated behavioral improvement [14]. The results of the Brenneman et al. (2015) study are similar to prior studies examining amphetamine's effects upon motor recovery following experimental stroke [13,15–19]. Although it is not completely understood how amphetamine results in behavioral improvement following injury, it has been suggested that the increase in neuromodulators such as NA may be responsible [20,21]. Support for this comes from several studies that have demonstrated that increasing NA promotes functional recovery following a cortical injury [12,22–28]. NA agonists impact the rate of recovery similar to amphetamine treatment [20,21]. Conversely, drugs that specifically block or decrease NA negate recovery [20,27,29–31]. In addition, NA antagonits have also been found to reinstate deficits following spontaneous motor recovery, potentially suggesting that the maintenance of recovery is also influenced by NA [16,30]. However, no studies to date have examined noradrenaline's role in amphetamine-induced recovery via directly blocking NA prior to amphetamine treatment.

Given the demonstrated role of noradrenaline in recovery

* Corresponding author at: Neurotrauma and Rehabilitation Laboratory, Department of Psychology, Southern Illinois University, Carbondale, IL United States.
E-mail address: mhylin@siu.edu (M.J. Hylin).

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[26,28,32–34], the present study was designed to specifically examine whether amphetamine-induced recovery from neglect involves activation of noradrenergic receptors. Prior research has demonstrated that noradrenaline's effects upon recovery are primarily mediated by α-adrenergic receptor activity [16,30]. However, β-adrenergic receptors are involved in synaptic plasticity [35–38] and are associated with the synthesis and release of trophic factors [39–41]. Therefore, in the current study, α- and β-adrenergic antagonists were used to pharmacologically block noradrenergic receptors prior to amphetamine treatment.

2. Methods

2.1. Subjects

The subjects (n = 60) were male Long Evans hooded rats 120–180 days of age that were bred from stock purchased from Harlan (Indianapolis, IN). Throughout the duration of the study, the subjects were individually housed with food and water freely available. The subjects were kept on a 12:12-h light/dark cycle with all behavioral testing done in the light portion of the cycle. To gentle the subjects for behavioral testing, they were handled for 1–2 min per day for a period of 3 weeks prior to surgery and subsequent behavioral testing.

2.2. Surgical procedures

Following the handling procedures, all subjects received surgery. All surgical manipulations were carried out under aseptic conditions and per the approval of the N.I.U. Institutional Animal Care and Use Committee. Subjects were anesthetized using a ketamine-xylazine mixture (87:13 mg/ml) at a dosage of 0.87 mL/kg, ip. When the subject was unresponsive, as determined by the absence of a corneal reflex and response to a mild tail pinch, the scalp was shaved and was placed into a stereotaxic apparatus using blunt-tipped ear bars. Using a surgical microscope, an incision was made along the midline of the scalp to reveal the skull. The pericranium was retracted and held into place using hemostatic forceps. A craniotomy on the left side of the skull was performed using a dental drill. The following coordinates was used in creating the skull window: 5.0 mm rostral to bregma, 2.5 mm caudal to bregma, and 2.5 mm lateral to the sagittal suture. The skull window (7.5 mm X 2.5 mm) was then gently removed as not to disturb the dura mater. An incision was made in the dura mater extending the length of the skull window to expose the underlying medial agranular cortex (AGm). Then, the AGm was removed by gentle aspiration down to the white matter with the use of a fine-gauge pipette attached to a suction pump [14,42,43]. Following hemostasis, gelfoam was gently placed into the lesion cavity. The incision was closed using wound clips and treated with topical Neomycin C. The subjects were closely monitored in their home cage under a heating lamp for the hour following surgery as they recovered from anesthesia and were then placed back in the colony. All subjects survived the surgical manipulations.

The aspiration procedure was utilized as it has reliably resulted in severe neglect deficits in the animal model for the past few decades [42–49]. While photothrombotic and endothelin models have been used to examine stroke deficits; neglect produced using this model results in reliable long-term deficits with little to no spontaneous recovery when there is complete removal of the AGm [14,44,50]. Therefore, this results in a reliable model for examining induced recovery. Furthermore, the recent publication by Brenneman, et al. [14] utilized this surgical technique to examine the effect of amphetamine upon recovery from neglect. Because the aim of this study was to examine the mechanisms surrounding recovery the same surgical procedures were used to replicate the findings of the Brenneman, et al. [14] to examine the role of noradrenaline in amphetamine-induced recovery. Because the purpose of the study was to examine these drugs in brain damaged animals, shams were not included as a part of the study design to reduce the number of animals used.

2.3. Behavioral procedures

2.3.1. Pretreatment

Prior to subjects being assigned to a treatment group, but following surgery, behavioral testing was conducted to establish whether the subject had severe neglect. To be included in the study the subject had to demonstrate severe neglect four hours following surgery. This criterion was used because prior studies have demonstrated that the presence of neglect at 4–6 h post-surgery is an excellent predictor (.98) that the rats will continue to demonstrate severe neglect in subsequent tests and do not typically spontaneously recover without treatment [14,42,46]. Only subjects demonstrating severe unilateral neglect (Total Neglect Score ≤ 0.33) were included in this study. Approximately 40% of all subjects that received unilateral AGm lesions demonstrated severe unilateral neglect on their first test following the lesion. Because the purpose of this study was to understand impact of amphetamine treatment and noradrenergic antagonists upon severe neglect, only subjects demonstrating severe unilateral neglect were used in the study. Subjects failing to demonstrate severe neglect typically had incomplete removal of the caudal AGm.

2.3.2. Circling

Prior to orientation testing, circling behavior was monitored to determine whether the lack of response to the contralateral stimuli later in testing is due to neglect rather than due to strong tendency to turn or circle toward the ipsilateral side of space [45]. The number of ipsilateral and contralateral turns was recorded to the nearest half-turn for a period of two minutes.

2.3.3. Orientation testing

Immediately after assessment of circling behavior orientation testing was conducted. Orientation testing is a modified version of the one used by Crowne and Pathria and has been used in previous studies of neglect [45,47,51]. A testing session began by bringing the subject into the testing room in its home cage and placing it upon the testing platform. The subject was then allowed two minutes of adaptation to the environment during which circling behavior was monitored, after which the subject was taken out of its cage and placed upon the testing platform. The platform contained markings which were used to indicate 0°, 30°, 45°, and 60° angles in both directions of which the 0° is the center marking. The markings were used to rate the degree of orientation to the stimulus presented. The subject was gently restrained without restriction of head movement to align the subject's snout with the 0° (center) marking. Stimuli were presented only when there was no struggling, no asymmetry of posture, and the head was aligned with the rest of the body. For consistency, presentation of the stimuli occurred in the following order: visual, tactile, and auditory. However, prior work has shown that the order of stimulus presentation has no significant effect upon the behavioral results [49].

The visual stimulus consisted of a 10 cm silver, metallic rod (8 mm width) that was moved in small circles (approximately 5 cm in diameter) 7.5–10 cm from the animal. Care was taken to not stimulate the vibrissa. The tactile stimulus consisted of a caudal-to-rostral stroke through the vibrissa using a Puritan applicator (15 cm length) (Hardwood Products Co., No.807). It is important to note that even though this stimulus has a visual aspect; similar results have been found when subjects were tested under red light conditions (Corwin, unpublished results). The auditory stimulus consisted of a single 114-dB (SPL) click produced by a clicking device. To minimize visual contact with the stimulus, the click was presented at the midbody approximately 5 cm from the subject. All three stimuli were presented to both sides of the subject's body. The initial side of stimulation was determined in a quasi-random fashion. All three stimuli were presented three separate times during a testing session. The degree of head

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