Behavioural Brain Research 260 (2014) 148–154

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Beta-adrenergic antagonist effects on a novel cognitive flexibility task in rodents

Patrick M. Hecht[a,b,c,1], Matthew J. Will[a,b,d,e,1], Todd R. Schachtman[a,e,2], Lauren M. Welby[e,1], David Q. Beversdorf[a,b,c,e,f,g,*]

[a] Interdisciplinary Neuroscience Program, University of Missouri, Columbia, MO 65211, USA
[b] Thompson Center for Autism and Neurodevelopmental Disorders, University of Missouri, Columbia, MO 65211, USA
[c] Center for Translational Neuroscience, University of Missouri, Columbia, MO 65211, USA
[d] Christopher Bond Life Sciences Center, University of Missouri, Columbia, MO 65211, USA
[e] Department of Psychological Sciences, University of Missouri, Columbia, MO 65211, USA
[f] Department of Radiology, University of Missouri, Columbia, MO 65211, USA
[g] Department of Neurology, University of Missouri, Columbia, MO 65211, USA

HIGHLIGHTS

- This addresses the gap between human and animal studies of cognitive flexibility.
- We developed a novel unconstrained cognitive flexibility task for study in rodents.
- Treatment with propranolol had no effect on the attentional set shifting tasks.
- Propranolol improved performance on the unconstrained cognitive flexibility task.

ARTICLE INFO

Article history:
Received 28 October 2013
Received in revised form
23 November 2013
Accepted 24 November 2013
Available online 1 December 2013

Keywords:
Noradrenergic
Propranolol
Problem solving
Creativity
Cognitive flexibility
Attentional set-shifting

ABSTRACT

Previous work examining animal models of cognitive flexibility have focused on tasks where animals are required to shift between cues in order to reach a food reward from among a limited set of choices. Performance by nonhuman animals on these tasks, including reversal learning, intradimensional set-shifting, and extradimensional set-shifting, are affected by pharmacological action on serotonergic, dopaminergic, and alpha-adrenergic, but not beta-adrenergic receptors. However, beta-adrenergic antagonists, such as propranolol, are widely utilized for conditions such as test anxiety. Propranolol improves performance in humans during cognitive flexibility tasks where there is a broad set of potential solutions. The current investigation utilized a digging task where the rodent must develop a novel solution in order to obtain a reward. Similar to the effects observed in humans, propranolol improved performance on this task, while not affecting performance on set-shifting tasks, as with previous animal studies. This may allow future investigation of the neurobiological mechanism by which propranolol affects context-specific anxiety, and could provide insight into the neurobiology of creativity.

1. Introduction

Cognitive flexibility is the capacity to inhibit a dominant response when it represents a non-optimal or inappropriate solution and to enable access to more remote alternatives [1]. Deficits in various aspects of cognitive flexibility have been noted in a variety of neuropsychiatric disorders such as schizophrenia [2], autism [3], and obsessive compulsive disorder [4]. Identifying the neural correlates and molecular mechanisms of cognitive flexibility will aide in advancing treatments for these disorders. To date, rodent models have examined this executive function with the use of the attentional set-shifting task (ASST). This task assesses the ability of a rat to discriminate between cues across several

Abbreviations: ASST, attentional set-shifting task; SD, simple discrimination; CD, compound discrimination; IDS, intradimensional set shift; EDS, extradimensional set shift.

* Corresponding author at: Department of Radiology, DC069.10, One Hospital Drive, Columbia, MO 65212, USA. Tel.: +1 573 882 6081.
E-mail addresses: pmhp6d@mail.missouri.edu (P.M. Hecht), willm@missouri.edu (M.J. Will), schachtmant@missouri.edu (T.R. Schachtman), lmwy9b@mail.missouri.edu (L.M. Welby), beversdorfd@health.missouri.edu (D.Q. Beversdorf).
[1] Address: 1201 Rollins Street, Room 347, Columbia, MO 65211, USA.
[2] Address: 109 McAlester Hall, Columbia, MO 65211, USA.

0166-4328/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.bbr.2013.11.041

perceptual modalities in order to obtain a food reward [5]. By pairing rewarded and non-rewarded cues with two feeding bowls it is possible to assess reversal learning and set-shifting with this task. During reversal learning, the previously non-rewarded cue becomes a rewarded cue and the previously rewarded cue becomes non-rewarded, requiring a switch in behavior within the task. Set-shifting can be further subdivided into intradimensional set-shifting (IDS) and extradimensional set-shifting (EDS). Both forms of set-shifting involve training the subjects with one rule and then shifting them to a new rule; however, IDS involves applying the new rule to cues within the same stimulus modality, whereas EDS involves applying the new rule to cues from an entirely different stimulus modality [6].

Previous studies have begun to investigate the neuropharmacological influences on reversal learning and set shifting tasks. Rats with depleted levels of serotonin showed an impaired performance in reversals during the ASST [7]. Similarly, in a series of experiments in marmosets, depletion of serotonin has been shown to have a significant impact on reversal learning while having no effect on either IDS or EDS [8–10]. This has further been demonstrated in the clinical population by reducing central 5-HT with tryptophan depletion [11,12]. Crofts et al. [13] showed that IDS performance, where the specific stimuli are changed when the animal is transferred ('shifted') from one discrimination task to another, but the modality along which the stimuli differ remains the same for both discriminations [14] (e.g. still responding to odor, but there are two new odors), was significantly impaired by decreasing dopamine levels in the prefrontal cortex. Extradimensional set-shift performance, requiring a shift in responding to a different stimulus modality from the discrimination task upon which the animals were previously tested [14] (e.g. switching from odor to digging material), has been shown to be modulated by the noradrenergic system [15] with action at the α-adrenergic receptors in the prefrontal cortex improving performance [16]. None of these tasks, though, are affected by drugs acting on β-adrenergic receptors [16].

Problem solving in humans is not restricted to shifting between a constrained set of options, but also involves complex situations in which there is a broader, unconstrained set of possible solutions, or unconstrained cognitive flexibility, requiring a novel solution. The use of anagrams and the Compound Remote Associates task are common measures of unconstrained cognitive flexibility in the human population. Anagrams have been used as a method of assessing creativity [17–19] and the Compound Remote Associates task is reported to measure insight-based problem solving by accessing lexical/semantic and associative networks [20]. Previous research has shown a beneficial effect of the β-adrenergic antagonist, propranolol, on these unconstrained flexibility tasks in humans [1,21–23]. β-adrenergic antagonists have long been used for the treatment of test anxiety and performance anxiety [24,25]. This contrasts with the facilitation of EDS in animals with increased adrenergic activity acting on the α-adrenergic receptors and the lack of effects with β-adrenergic antagonists on the ASST [16]. We hypothesize that propranolol will significantly improve performance on a novel problem solving task in a rodent model of unconstrained cognitive flexibility while having no effect on set-shifting performance.

2. Materials and methods

2.1. Animals

Twenty-eight adult male Sprague Dawley rats (Harlan Laboratories, Indianapolis, IN) were housed in pairs on a 12:12 light/dark cycle with lights on at 0600 hours. Rats were acclimated to the colony for a minimum of 7 days during which they received food and water ad libitum. After this period, rats were food restricted to 85% of their free-feeding weight before initial training and were maintained at this weight throughout the experiment. Rats were randomly assigned to receive either 1 mg/kg propranolol (Bedford Laboratories, Bedford, OH) or saline treatments via intraperitoneal (i.p.) injection. All procedures were approved by the Institutional Animal Care and Use Committee of the University of Missouri, Columbia.

2.2. Apparatus

The testing apparatus was a custom built white Plexiglas arena, measuring 40 cm × 70 cm × 30 cm ($w \times l \times h$), as shown in Fig. 1, which was placed directly under bright fluorescent light during testing. A removable white divider separated one-third of the arena and this area was used as a start box. The rat was placed in the start box following each trial to allow the apparatus to be cleaned with diluted Alconox (White Plains, NY, USA) and reward pots to be switched. At the opposite end of the arena, a divider separated two reward pots that were used for the attentional set-shifting task. The divider consisted of a 13 cm wide wall that was closed with a removable Plexiglas wall. The divider could be opened to reveal a digging tunnel measuring 13 cm × 95 cm × 40 cm that was an adaptation of the apparatus used in Thompson et al. [26]. When the divider was opened, the tunnel was exposed revealing two ramps at either end that sloped downward toward the center. An additional Plexiglas insert was placed in the middle of the ramp allowing 9 cm of open space from the bottom of the ramp.

2.3. Attentional set-shifting task

The procedure was modified from previously described protocols [5,16]. In this task the rat discriminated between olfactory, tactile, and visual cues to obtain a food reward. The reward pots consisted of terra-cotta pots with an internal rim diameter of 7 cm and a depth of 6 cm. Reward pots were defined by a distinct odor and digging medium as shown in Table 1. To scent the pots, 20 μL of scented oil (Frontier Natural Products Co-op, Norway, IA, USA) was applied to the rim of the pot 5 days before its use. Then 5 μL was reapplied the day before testing to reinforce the scent. Only one odor was applied to a given pot and a different bowl was used for each combination of odor and digging medium. The food reward was a ¼–½ Honey Nut Cheerio (General Mills Cereals, Minneapolis, MN, USA) and was placed at the bottom of the reward pot and covered with the appropriate digging material. To avoid responses due to the rats being able to smell the reward in the baited pot, a small amount of powdered Cheerio was sprinkled onto the digging material of all pots. Before all training and testing procedures, the experimental rat was transferred to the testing room and allowed to habituate for 30 min prior to training and testing. Rats were then transferred into the start box. Each trial began when the start box was opened. Digging was defined as an active attempt to retrieve the buried reward by moving the digging medium. If the rat began to dig in the incorrect pot, the rat was transferred back to the start box and the trial was marked as an error.

The procedure required a total of 4 days to complete for each rat, consisting of two training days and two testing days. Testing was divided into two days (day 3 and day 4) due to the 2-h half-life of propranolol in rat brain [27].

2.4. Day 1: training 1

Rats were first trained in their home cage to reliably dig in an unscented pot for a food reward under an increasing amount of sawdust. The rats were then transferred to the testing