Neuroscience Letters 678 (2018) 62–67

Contents lists available at ScienceDirect

Neuroscience Letters

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

Research article

Effects of systemic cholinergic antagonism on reinforcer devaluation in macaques

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ARTICLE INFO

Keywords:
Acetylcholine
Nicotinic receptor
Muscarinic receptor
Behavioral flexibility

ABSTRACT

The capacity to adjust actions based on new information is a vital cognitive function. An animal's ability to adapt behavioral responses according to changes in reward value can be measured using a reinforcer devaluation task, wherein the desirability of a given object is reduced by decreasing the value of the associated food reinforcement. Elements of the neural circuits serving this ability have been studied in both rodents and nonhuman primates. Specifically, the basolateral amygdala, orbitofrontal cortex, nucleus accumbens, and mediodorsal thalamus have each been shown to play a critical role in the process of value updating, required for adaptive goal selection. As these regions receive dense cholinergic input, we investigated whether systemic injections of non-selective nicotinic or muscarinic acetylcholine receptor antagonists, mecamylamine and scopolamine, respectively, would impair performance on a reinforcer devaluation task. Here we demonstrate that in the presence of either a nicotinic or muscarinic antagonist, animals are able to shift their behavioral responses in an appropriate manner, suggesting that disruption of cholinergic neuromodulation is not sufficient to disrupt value updating, and subsequent goal selection, in rhesus macaques.

1. Introduction

Throughout the course of daily life, associations between environmental cues, actions, and outcomes do not remain constant, but rather shift over time. The ability to alter behavioral strategies in the face of shifts in reward value is thus a key survival mechanism. One family of tasks that has been particularly well characterized in this context in nonhuman primates are reinforcer devaluation tasks [1–16].

Across species, an experimentally induced decrease in reward value results in a shift in action selection away from items associated with the devalued reward. In macaques, the typical devaluation study pairs two sets of objects with two different foods (e.g., peanuts and fruit snacks). Over the course of repeated sessions of visual discrimination learning trials, animals learn incidentally which objects are associated with a particular food reward. On subsequent test days, animals are allowed to freely consume one of the food items prior to task onset. Once the task session begins, animals are allowed to choose between objects associated with the now devalued food and objects associated with the non-devalued food. Monkeys will typically shift their choices away from the objects associated with the devalued (pre-fed) food and toward those associated with the non-devalued food. The same pattern of adjusting goal selection in response to reinforcer devaluation has been reported across multiple species, including mouse, rat and human [17–20].

Making such adaptive shifts to new information about the reinforcer critically relies on interactions between the amygdala and orbitofrontal cortex [21], as well as information processed by the mediodorsal thalamus [22]. Through a series of lesion and pharmacological inactivation studies, the roles of these regions in (i) adjusting reward value during selective satiation and (ii) guiding behavioral choices during task performance have been elucidated. Both the amygdala and orbitofrontal cortex are necessary for adjusting reward value, whereas the orbitofrontal cortex is also needed for guiding behavioral choices [12,13,16].

Acetylcholine is a prominent neuromodulator across multiple cortical regions as well as within the amygdala [23,24] and mediodorsal thalamus [25]. Cholinergic manipulations in these structures lead to reduction of task-related neuronal activity in an operant task (amygdala) and impairments in a mnemonic rule-guided saccade task (prefrontal cortex) [26,27]. Surprisingly, cholinergic deafferentation of the frontal cortex is without effect on reinforcer devaluation [28]. However, the contribution of cholinergic signaling in other brain regions to devaluation performance is yet unknown. As a first step to address this question, we systemically administered two non-selective cholinergic ligands, the nicotinic acetylcholine receptor (nAChR) antagonist, mecamylamine, and the muscarinic acetylcholine receptor (mAChR)

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https://doi.org/10.1016/j.neulet.2018.05.003
Received 26 January 2018; Received in revised form 27 April 2018; Accepted 1 May 2018
Available online 02 May 2018
0304-3940/ Published by Elsevier B.V.

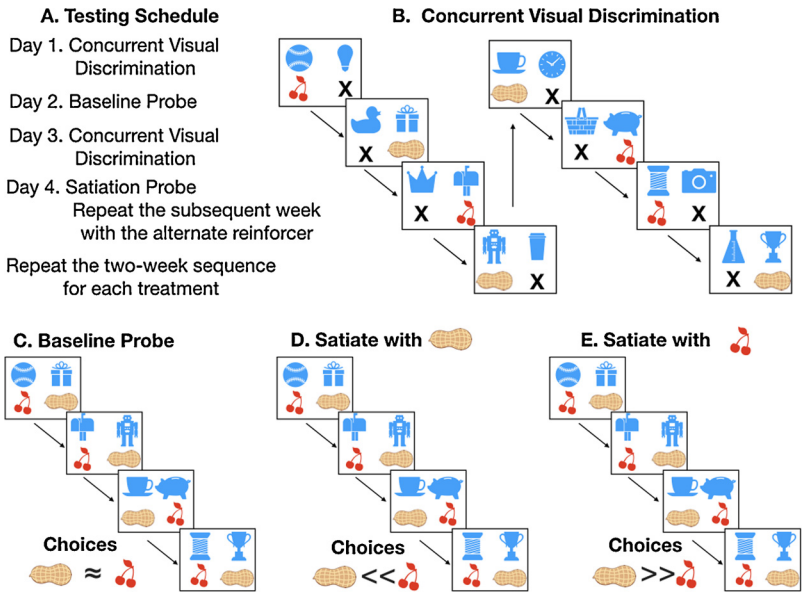

Fig. 1. Schematic of the Reinforcer Devaluation Task. (A) Weekly schedule of testing sessions. (B) Concurrent visual discrimination to create association between a specific primary reinforcer (fruit snack or peanut) and its associated secondary reinforcer. (C) Baseline probe trials to establish animals' baseline preferences for the two primary reinforcers. (D) Probe session following satiation with primary reinforcer (peanut). (E) Probe session following satiation with primary reinforcer (fruit snack).

antagonist, scopolamine, and evaluated the impact on reinforcer devaluation processes.

2. Methods

2.1. Subjects

Four adult, male, rhesus monkeys (Macaca mulatta) were used in this study. These animals had previously been tested on a within-session concurrent discrimination learning task [29]. Their weights ranged from 8.2–9.8 kg at the start of the present study. These animals were housed with visual access to conspecifics and access to enrichment toys.

Water was available ad libitum in the home cage. Meals (LabDiet #5049), supplemented with fresh fruit, were provided twice daily. The first meal was always scheduled after cognitive testing occurred. The study was conducted under a protocol approved by the Georgetown University Animal Care and Use Committee, in accordance with the Guide for the Care and Use of Laboratory Animals, and adhering to guidelines for animal care delineated in the EC Directive 86/609/EEC.

2.2. Drugs and treatment

Scopolamine hydrobromide and mecamylamine hydrochloride were obtained from Sigma-Aldrich and Alamone Labs, respectively. Drug solutions were prepared in sterile saline at a concentration of 138 μg/ml and 10 mg/ml. Drugs were administered in a volume of 0.1 ml/kg to deliver 13.8 μg/kg of scopolamine or 1 mg/kg of mecamylamine. Drug treatments occurred 20 min prior to the initiation of selective satiation. We selected pre-satiation treatment with these drugs as it provided the most robust test of our hypothesis. In this way, drug was present during both the satiation procedure and the instrumental task.

Drug doses were similar to those used in previous studies [29–34]. Several studies have reported dose-dependent cognitive impairment after systemic administration of scopolamine with doses ranging from 1 to 32 μg/kg [31,35,36]. In these studies, impairments were evident at doses similar to that which we employed. These studies found impairments evident for as long as 40–60 min after scopolamine administration. It is worth noting that our testing never exceeded 50 min from injection to completion of behavioral testing. These data are also consistent with a human study, which showed binding of scopolamine in high muscarinic receptor regions of the brain up to two hours post IV injection of the drug [37].

Cognitive impairment has also been reported following systemic mecamylamine injection (0.32–1.78 mg/kg), with deficits evident after doses as low as 0.32 mg/kg and impairment clearly evident following a dose of 1 mg/kg, which is what we employed in the present study [34]. In this study, mecamylamine was administered 15 min prior to a 40–50 min long testing session, which again exceeds the total duration of testing in the present study.

For these reasons, we selected doses of both drugs that sufficiently disrupted behavior in previous studies and are confident of their action throughout our total 50 min of experimentation.

2.3. Apparatus and materials

The monkeys were trained in a Wisconsin General Testing Apparatus located in a darkened, sound-shielded room. The test tray, which was located at the level of the floor of the monkey transport cage, contained three food wells spaced 18 cm apart (center to center) on the midline of the tray. The wells were 25 mm in diameter and 5 mm deep. For the present task, only the two outer wells were used. The stimuli were 80 junk objects that differed widely in shape, size, color, and texture.

2.4. Food reinforcers

We selected two highly palatable foods that are commonly used as reinforcers across laboratories for this task: fruit snacks and peanuts [1,6,21]. Food 1 was a fruit snack (Sharkbites; General Mills) and food 2 was half of a honey roasted peanut (Planters; Kraft Foods). Animals did not receive these food reinforcers outside of the context of this task (e.g., as enrichment or reinforcers in other tasks).

2.5. Object discrimination training

All monkeys were trained on a task as described previously by Málková and colleagues [1,6]. Briefly, the animals were first trained on a set of 40 object-discrimination problems (Fig. 1b). The objects were placed over the food wells; the monkey could only see and retrieve the food by displacing an object. In each of the 40 object pairs, one object (S+) was baited with a food reinforcer and the other was unbaited (S−). Half of the S+ objects (20) were baited with fruit snacks and the other half baited with peanuts, intermixed within a session. The S+ and S− assignment of the objects, the order of the object pairs, and the food reinforcer paired with particular objects remained constant across days; however, the left–right positions of the S+ object were