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Research report

Role of dopamine D1 receptors in novelty seeking in adult female Long-Evans rats

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Abstract

Adult Long-Evans ovariectomized female rats received injections of the DA D1 antagonist SCH 23390 (0, 0.03 and 0.3 mg/kg, i.p.) and were observed in an open field apparatus (OFA) with a novel object. Results indicate that a significant effect of SCH 23390 was found on several measures of novelty seeking and activity, with the high dose producing a significant decrease in (1) approaches to and (2) rears while approaching the novel object, (3) latency to interact with the novel object, (4) in time interacting with the novel object, (5) anxious behavior (as measured by rears) and (6) locomotor activity (LMA), as compared to both the saline and low dose. Interestingly, the effects of SCH 23390 on approaches and rears were not significant when LMA was factored into the analysis (repeated measures ANCOVA), however, marked results were still found on time interacting with the novel object. These data demonstrate that SCH 23390 produced dose-dependent effects on novelty seeking that were independent of LMA, implicating D1 receptors in the incentive-motivational aspect of novelty seeking in adult gonadectomized female rats.

Keywords: Novel object; Sensation-seeking; Rats; Dopamine antagonists; Forced novelty; Open field; SCH 23390

1. Introduction

The trait of novelty seeking is associated with many clinical disorders, including substance abuse [9,13,16,17], bulimia nervosa [14], conduct disorder [25], borderline personality disorder [21] and other cluster B personality disorders [20]. Reduced levels of novelty seeking are correlated with obsessive–compulsive disorder [19] and cluster C personality disorders [20]. Understanding the neural mechanisms underlying novelty seeking may be an important component to treating some of these clinical disorders.

In addition to humans, a number of species (*e.g.*, rats) have been shown to reliably display behaviors, such as exploration, approach and responsiveness to novel objects and/or places, which map onto the human personality dimension of novelty seeking [23]. Therefore, rats can provide a model for novelty seeking because they naturally show an interest in novel objects and can readily be tested in responses to novel objects. Exposing rats to novel objects induces interaction with the object and play-like behavior in all ages after first causing typical anxiety-related behaviors, such as rearing and grooming [11]. Quite interestingly, rats that have been exposed to novel objects and allowed to interact and play with them subsequently display reduced anxiety in the elevated plus maze, without showing any effect on activity level. There are some distinctions across the age axis, as adolescent rats show the strongest preference for novel objects, but this attraction is also present in adults [12], though observed most readily in females [4]. This enduring novelty seeking behavior has been demonstrated in intact females, and yet research has shown differences between gonadectomized and intact females in younger animals. Therefore, it was of interest, in the present study, to determine if novelty seeking would be enduring in adult gonadectomized females.

The conditioned place preference (CPP) paradigm has been established as a method to examine the incentive-motivational aspects of novelty [5]. In a choice situation (no novel objects), rats that were initially given free access to novel objects in a distinct environment chose the novel-paired environment. Other research has investigated the role of dopamine (DA) in mediating novelty, given its role in several incentive-motivational models.

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The D2 antagonist, haloperidol, produced dose-dependent disruption of novelty seeking behavior in a free choice test between novel and familiar environments at doses that impeded locomotion [1]. Intraperitoneal injections of the D1 antagonist SCH 23390, the D1 agonist SKF 38393, and the D2 agonist quinpirole eliminated novelty-maintained place-preference task, but only SCH 23390 did so at a dose (0.03 mg/kg) that had no significant effect on locomotor activity [2]. At that dose, SCH 23390 also blocked expression of learned novelty-maintained preference when administered before post-conditioning preference test [6] and blocked an increase in place preference without interfering with object interaction [3].

Taken together, existing research has shown that D1 antagonists reduce the expression of learned preferences related to novel objects but do not interfere with novel object detection [4]. However, much of this work has been accomplished in adolescent and young adult male rodents with little work exploring intact and gonadectomized females. Therefore, the present study set out to examine the impact of the D1 antagonist SCH 23390 on novelty seeking behaviors, such as latency to interact with novel object, and total time spent with the novel object in an open field apparatus (OFA) in mature gonadectomized female rats.

2. Materials and methods

2.1. Animals and surgery

Ten adult females (250–300 g) were derived from Long-Evans rats purchased from Charles River Breeding Labs (Wilmington, MA). The animals were housed in pairs in Plexiglas cages with free access to water and food with lights on 07:00–19:00 h, and all testing was conducted during the light phase. All procedures were approved by the University of Massachusetts Boston Institutional Animal Care and Use Committee and adhered to the NIH *Guide for the Care and Use of Laboratory Animals* (1996).

All animals were ovariectomized bilaterally using standard procedures as described previously [7] in order to avoid effects of stage of estrus on novelty testing. Briefly, under sodium pentobarbital (40 mg/kg, i.p., Abbott Laboratories, Chicago, IL) anesthesia, each animal was shaven bilaterally 20 cm from the base of the rib cage. A 1.5 cm incision was made through the skin and the abdominal wall to expose the peritoneal cavity and locate the ovary. The ovary was clamped, the top of the uterine horn was ligated with 3–0 suture and a surgical blade was used to excise the ovary. After, the abdominal wall was sutured and the skin closed with surgical staples. Animals were given topical antibiotics and allowed to recover for a minimum of 1 week.

2.2. Drugs

Two doses of SCH 23390 (Research Biochemical, Inc., Natick, MA) were used in this study (0.03 and 0.3 mg/kg, i.p.) and were counterbalanced with isotonic saline to avoid order bias. SCH 23390 and saline were always administered a full 30 min prior to the onset of testing. Animals were injected and returned to their home cage until the onset of testing.

2.3. Equipment

A plastic box measuring 5 cm × 5 cm × 5.5 cm covered in wrapping paper served as the novel object for the experiment. Three colors of wrapping paper were used, and animals were exposed to each color of wrapping paper only once to ensure the novelty of the stimulus across trials [18]. The paper colors were paired with equal frequency with each drug manipulation. Paper texture and other factors were held constant to reduce potential confounds. Activity level, arousal, approach and interaction with the novel object were recorded in an open field apparatus (OFA). The OFA was constructed of formica-laminated plywood cut into a 75 cm × 75 cm × 30 cm box. Inside the box, a matrix divided into twenty-five 15 cm × 15 cm grids allowed the experimenter to record movement within the OFA.

Table 1
Description of animal behaviors coded by investigators during OFA experimental trials

Coding term	Behavior observed
Grid entry	The placement of at least two paws inside one of the OFA grids.
Approach grid entry	Entry into one of the four grids adjacent to the grid containing the novel object.
Rears in the OFA	Rears occurring within the entire OFA, including the approach grids.
Rears in the approach grid	Rears occurring only within one of the approach grids.
Total time interacting with novel object	Time spent by the animal per trial touching, sniffing or ripping the paper on the object or exploring within 2 cm of the object [10].
Time until first interaction	Time elapsed from the start of trial until the animal interacts with the object [24].
Anxious behavior	Fecal boli, grooming, squealing and unusual behaviors [15].

2.4. Procedure

Animals were habituated to the OFA for two sessions for 10 min on two separate days prior to forced novelty testing. On the habituation and trial days, animals were placed in the center grid of OFA and on trial days, the novel object was secured to the center grid on the floor of the OFA with double-sided tape and the animal initially placed in a peripheral grid. Each testing bout lasted for 10 min and there was a 48 h inter-trial interval. All testing was performed by two trained investigators: the first recorded grid entries, approach grid entries, and rears (see Table 1 for descriptions of coded behaviors), and the second recorded the time until first interaction with the novel object [24], the total time interacting with the novel object [10], and signs of anxiety [15]. Grid entries from the open field were tallied to obtain both the total number per test session and the number of entries in the four grids adjacent to the novel object, which was used as a measure of frequency of approaches to the novel object.

2.5. Statistical analyses

SPSS (v 13) for Windows was used for all statistical analyses. Inter-rater reliability was assessed using Pearson correlation coefficients for paired samples from each investigator for measures from habituation sessions of number of entries into the center nine cells of the grid, the number of entries into the 16 peripheral cells, and rears in each location. Each dependent measure was analyzed with a repeated measures ANOVA with SCH 23390 dose (three levels). Where appropriate, Tukey's HSD was used to ascertain specific pair-wise differences adequate for significance at $p < 0.05$, $p < 0.01$ and $p < 0.001$. All analyses were performed on absolute values for the indices measured for novelty seeking (see Table 1).

3. Results

3.1. Inter-rater reliability

The data elements evaluated for inter-rater reliability (entries in center grids, entries into peripheral grids during OFA habituation trials) produced paired sample correlations ranging from 0.990 to 0.999, $p < 0.001$, between investigators' coding of the