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Lewis and Fischer 344 rats as a model for genetic differences in spatial learning and memory: Cocaine effects

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ABSTRACT

Lewis (LEW) and Fischer 344 (F344) rats are considered a model of genetic vulnerability to drug addiction. We previously showed important differences in spatial learning and memory between them, but in contrast with previous experiments demonstrating cocaine-induced enhanced learning in Morris water maze (MWM) highly demanding tasks, the eight-arm radial maze (RAM) performance was not modified either in LEW or F344 rats after chronic cocaine treatment. In the present work, chronically cocaine-treated LEW and F344 adult rats have been evaluated in learning and memory performance using the Y-maze, two RAM protocols that differ in difficulty, and a reversal protocol that tests cognitive flexibility. After one of the RAM protocols, we quantified dendritic spine density in hippocampal CA1 neurons and compared it to animals treated with cocaine but not submitted to RAM.

LEW cocaine treated rats showed a better performance in the Y maze than their saline counterparts, an effect that was not evident in the F344 strain. F344 rats significantly took more time to learn the RAM task and made a greater number of errors than LEW animals in both protocols tested, whereas cocaine treatment induced deleterious effects in learning and memory in the highly difficult protocol. Moreover, hippocampal spine density was cocaine-modulated in LEW animals whereas no effects were found in F344 rats.

We propose that differences in addictive-like behavior between LEW and F344 rats could be related to differences in hippocampal learning and memory processes that could be on the basis of individual vulnerability to cocaine addiction.

1. Introduction

It has been suggested that chronic cocaine exposure produces spatial learning and memory deficits (Bashkatova et al., 2005; Melnick et al., 2001; Quirk et al., 2001; Santucci et al., 2004). However, a recent study concludes that post-training cocaine administration can facilitate learning, but this effect is highly dependent on the dose and the type of task employed (Rkieh et al., 2014). In this sense, our previous studies have demonstrated no effects of cocaine in hippocampal-dependent spatial learning in the radial arm maze (RAM; Fole et al., 2011) accordingly to results obtained by other authors (Kantak et al., 2005). On the contrary, we have observed a better performance of spatial learning when animals were submitted to difficult tasks in the Morris water maze (Del Olmo et al., 2006a; Del Olmo et al., 2007), an improvement that could be related to cocaine-induced hippocampal LTP facilitation (Del Olmo et al., 2006b; Thompson et al., 2002; Thompson et al., 2004; Thompson et al., 2005).

Lewis (LEW) and Fischer 344 (F344) rat strains present several differences on a number of physiological characteristics, such as hypothalamic-pituitary-adrenal axis activity, behavioral tasks performance, including impulsivity (Aparicio et al., 2015) and drug reward assays, showing different behavioral effects in response to abused drugs, and are frequently used as an experimental model of vulnerability to drug addiction (Kosten and Ambrosio, 2002; see also Cadoni, 2016 for a more recent review). Our previous data showed significant differences in hippocampal synaptic plasticity and related spatial learning and memory in these two inbred strains of rats (Fole et al., 2011; Miguens et al., 2011; Prakash et al., 2009). In this sense, other authors have observed that F344 rats are less effective in spatial learning tasks performance (van der Staay et al., 2009).

Synaptic plasticity modulation involves dendritic-spine changes (see Stuart and Spruston, 2015 for a recent review). We previously found that cocaine increases dendritic spine density in the CA1 field of

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the hippocampus both in LEW and F344 rats (Fole et al., 2011) as it has been observed in other strains of rats after prenatal cocaine exposure (Frankfurt et al., 2009). Moreover, significant structural differences in CA1 pyramidal cells between LEW and F344 rats have been reported prior and after cocaine self-administration (Miguéns et al., 2015; Selvas et al., 2017).

Thus, in order to clarify whether chronic treatment with cocaine could modulate hippocampal-dependent learning and memory in LEW and F344 rats we used the Y-maze, two RAM protocols that differed in the difficulty of the tasks and a RAM-reversal protocol to study cognitive flexibility. Dendritic spine density was also studied to verify possible changes in neuron morphology as a consequence of cocaine treatment in both strains of rats.

2. Methods

2.1. Animals

Male LEW (n = 88) and F344 (n = 88) rats (Charles River, Spain) 8 weeks old at the beginning of the experiments were used (240–260 g and 220–240 g, respectively). They were housed in groups of 4 under a light/dark cycle (12 h/12 h), in a temperature controlled room (22 °C) with standard food and tap water ad libitum, in accordance with the European Communities Council Directive (86/609/EEC) for the care and use of laboratory animals. After 1 week of adaptation to the facility, animals were randomly divided into two groups with similar average body weight and assigned either to a cocaine or saline treatment. Animals were handled regularly for a week before experiments.

2.2. Drug administration

After one week of habituation, animals were i.p. injected with saline (0.9% NaCl) or cocaine chlorhydrate (15 mg/Kg in 0.9% NaCl) in 1 ml/kg of volume for consecutive days during all the protocol duration. Cocaine administration began 7 days before the beginning of the Y-maze or RAM protocols. Animals received cocaine/saline injections in the afternoon after conclude RAM daily sessions to avoid cocaine acute effects in the RAM performance. Furthermore, in order to enhance animal's motivation for food they were partially food restricted leading to 5–10% reduction of initial body weight in all RAM tasks. Food restriction was maintained until the end of the RAM procedures.

2.3. Behavioral procedures

2.3.1. Y-maze

We followed the procedure described in Conrad et al. (1996) with some modifications. The Y-maze apparatus consisted of three arms made of black plastic joined in the middle to form a "Y" shape (50 × 19 × 35 cm). The height of the wall of the arms allowed the rats to see distal spatial landmarks consisted of colored sheets of paper with different forms. The inside of the arms were identical, providing no intramaze cues. Seven days before setting the Y-maze protocol, animals were administered (i.p.) with cocaine (15 mg/Kg) or saline and 4 groups were obtained: LEW-SAL, LEW-COC, F344-SAL and F344-COC (n = 8 for each group). The Y-maze task consisted in two sessions with 4 h inter-trial interval. Rats were placed into one of the arms of the maze (start arm) and allowed to explore the maze with one of the arms closed for 15 min (novel arm) while the other arm remains open (other arm). After a 4-h inter-trial interval, rats were returned to the Y-maze by placing them in the start arm. Then, rats were allowed to freely explore all three arms of the maze for 5 min (test trial). In test sessions, the time exploring each arm was quantified. Discrimination ratios (DRs) for novel vs. other arm were calculated as the time exploring the novel arm divided by the time exploring the novel arm plus the other arm; and DRs for novel vs. start arms were calculated as the time exploring the novel arm divided by the time exploring novel arm plus the start arm. After each assay, the maze was cleaned with an ethanol solution (50%) to avoid odor cues.

2.3.2. Eight-arm radial maze

The eight-arm radial maze protocol was performed as previously described (Fole et al., 2011). The apparatus consisted of eight identical arms extending radially from an octagonal platform that was elevated 80 cm above the floor and surrounded by multiple external cues (posters, pictures, etc.). A cup containing food was placed at the end of each arm. We previously demonstrated that cocaine effects in spatial memory were related to the difficulty of the task (Del Olmo et al., 2006a; Del Olmo et al., 2007). Thus, in the present work we have used two different RAM protocols that differ in the degree of difficulty determined by the number of sessions and trials per session (protocol 1 and protocol 2). Moreover, we used a third protocol (reversal) to study cognitive flexibility. In all of these experiments, 4 groups were obtained: LEW-SAL, LEW-COC, F344-SAL, and F344-COC (n = 10–12 for each group).

For protocols 1 and 2, tests were performed in three phases: (1) habituation, this phase was identical for each protocol and consisted in placing chocolate pellets (Kellogg's chocolate wheat scoops) both at the end and at the entrance of all eight arms during two exploratory trials (5 min each) in just one session to prepare the animals for the maze; (2) acquisition, which consisted of two consecutive trials of 5 min each during 5 consecutive days (Protocol 1), or just one trial of 5 min (Protocol 2) performed once a day during 8 days (in acquisition sessions, only four arms were baited, and these same arms remained baited during all acquisition and retention session); and (3) retention tests, consisting of two consecutive 5 min trials that were carried out 48, 72 and 96 h after completion of the preceding session (Protocol 1), or one 5 min trial that were carried out after 48 and 72 h (Protocol 2). In summary, the two different protocols used for the experiments were as follows:

→ Protocol 1: difficult protocol
- Habituation: 2 exploratory trials in 1 session
- Acquisition: 2 consecutive trials every day during 5 consecutive sessions
- Retention tests: 2 consecutive trials carried out 48, 72 and 96 h after completion of the preceding session

→ Protocol 2: very difficult protocol.
- Habituation phase: 2 exploratory trials in 1 session
- Acquisition phase: 1 daily trial during 8 consecutive sessions
- Retention tests: 1 trial carried out 48 and 72 h after completion of the preceding session

An *arm entry* was counted when all four paws of the animal crossed the entrance of the arm. A *correct choice* was defined as the first-time entry into a baited arm followed by food consumption. Entries in a non-baited arm were considered as *reference memory errors* (e-reference), and the re-entries in a previously visited arm were considered as *working memory errors* (e-working). Total errors were the sum of both reference and working memory errors (e-total). Differences among groups in latency to reach the four baited arms, and differences in working, in reference and in total memory errors were evaluated in each trial. An observer recorded visited arms, correct choices performed by each rat, and the time taken to obtain all the available food pellets for each trial. Working memory, reference and total errors, as well as latencies to reach baited arms, were measured in each group during all acquisition and retention sessions. We have represented in graphs working memory errors to simplify the reading whereas relevant data in reference or total errors are presented in the text.

Other parameters as velocity and efficacy were extracted from these data. The velocity of animals moving inside the maze was calculated as the relationship between visited arms and latencies, and we considered efficacy as the capacity to visit the fewest number of arms to find the 4