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Effects of chronic cocaine treatment during adolescence in Lewis and Fischer-344 rats: Novel location recognition impairment and changes in synaptic plasticity in adulthood

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ABSTRACT

The use of Lewis (LEW) together with Fischer-344 (F344) rats has been proposed as an addiction model because of the addiction behavior differences of these two strains. We have previously suggested that these differences could be related to learning and memory processes and that they depend on the genetic background of these two strains of rats. Adolescence is a period of active synaptic remodeling, plasticity and particular vulnerability to the effects of environmental insults such as drugs of abuse. We have evaluated spatial memory using novel location recognition in LEW and F344 adult rats undergoing a chronic treatment with cocaine during adolescence or adulthood. In order to study whether synaptic plasticity mechanisms were involved in the possible changes in learning after chronic cocaine treatment, we carried out electrophysiological experiments in hippocampal slices from treated animals. Our results showed that, in LEW cocaine-treated rats, hippocampal memory was only significantly impaired when the drug was administered during adolescence whereas adult administration did not produce any detrimental effect in spatial memory measured in this protocol.

Moreover, F344 rats showed clear difficulties carrying out the protocol even in standard conditions, confirming the spatial memory problems observed in previous reports and demonstrating the genetic differences in spatial learning and memory.

Our experiments show that the effects in behavioral experiments are related to synaptic plasticity mechanisms. Long-term depression induced by the glutamate agonist NMDA (LTD-NMDA) is partially abolished in cocaine-treated animals in hippocampal slices from LEW rats. Hippocampal LTD-NMDA is partially inhibited in F344 animals regardless of whether saline or cocaine administration, suggesting the lack of plasticity of this strain that could be related to the inability of these animals to carry out the novel object location protocol.

1. Introduction

Adolescence is a period of heightened propensity to develop addiction in humans (Chambers, Taylor, & Potenza, 2003; Kandel, Yamaguchi, & Chen, 1992; Wong, Ford, Pagels, McCutcheon, & Marinelli, 2013) and, using animal models, we can provide insight into age-related neuropsychological consequences of drug exposure. Adolescence is also a period of development in which synaptic plasticity seems to facilitate the acquisition of learning and it is the most important period for initiation in drug abuse. Several reports show that adolescent rats take more of certain drugs of abuse than adult animals (Anker & Carroll, 2010; Schramm-Sapyta et al., 2011), whereas others show that adolescents and adults do not differ (Kerstetter & Kantak, 2007; Li & Frantz, 2009). In addition, cocaine administration during adolescence has recently been associated with increased stress responses when animals are exposed to new environments in adulthood (Stansfield & Kirstein, 2007). Furthermore, preclinical studies described that psychomotor effects induced by cocaine are dependent on the age of the individual (Caster, Walker, & Kuhn, 2005; Collins & Izenwasser, 2002; Frantz, O'Dell, & Parsons, 2007). In spite of these data, little is known about the long-term cognitive effects that cocaine use in adolescence could have on cognition in adulthood.

It has been suggested that drug addiction is related to learning and memory processes (Hyman, Malenka, & Nestler, 2006) and adolescence is a developmental period during which neural circuits are particularly susceptible to modification by experience

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(King, Pattwell, Glatt, & Lee, 2014). Specifically, it has been found that cocaine administration during adolescence causes deficits in spatial learning tested with the Morris Water Maze (MWM) protocol (Santucci et al., 2004). In this regard, some authors have highlighted the influence of cocaine on attentional behavior in recognition tasks such as novel objects in familiar environments (Carey, Damianopoulos, & Shanahan, 2008). Other studies demonstrate that repeated cocaine administration leads to attention and reversal learning deficits (Dalley et al., 2005; Jentsch, Olausson, De La Garza, & Taylor, 2002). Most of the studies involving the hippocampal-dependent tasks suggest that cocaine administration results in learning and memory deficits (Bashkatova, Meunier, Maurice, & Vanin, 2005; Melnick, Kubie, Laungani, & Dow-Edwards, 2001; Quirk, Richards, & Avery, 2001; Santucci et al., 2004) although our previous studies showed no effects of cocaine, or a cocaine-induced improvement or deficit in spatial learning depending on the difficulty and nature of the task (Del Olmo, Higuera-Matas, Miguens, Garcia-Lecumberri, & Ambrosio, 2007; Fole et al., 2011; Del Olmo et al., 2006).

The performance in hippocampal-dependent spatial learning tasks has been related to long-term potentiation (LTP) (Lynch, 2004), which is considered to be one cellular basis of learning and memory (Bliss & Collingridge, 1993). To date, the findings of existing studies on cocaine effects on LTP are contradictory. Some authors have shown that this drug is able to inhibit LTP in the hippocampus (Smith, Browning, & Dunwiddie, 1993), while others show that cocaine administration facilitates the hippocampal LTP (Del Olmo, Higuera-Matas et al., 2006; del Olmo et al., 2006; Thompson, Gosnell, & Wagner, 2002; Thompson, Swant, Gosnell, & Wagner, 2004).

It has to be assumed that other types of plasticity are involved in learning and memory processes such as long-term depression (LTD) and depotentiation of LTP (Jouvenceau et al., 2006; Nabavi et al., 2014). It is postulated that adolescence represents a phase of increased activity of LTD mechanisms that confer a predisposition to synaptic elimination and further that termination of this LTD-permissive phase marks the transition to adulthood (Selemon, 2013) revealing adolescence as a period of active synaptic remodeling and plasticity.

We have also previously shown significant genetic differences in hippocampal depotentiation in the two inbred strains of rats, Lewis (LEW) and Fischer-344 (F344) (Prakash, Ambrosio, Alguacil, & Del Olmo, 2009), that show different biochemical and behavioral effects in response to psychoactive drugs and are frequently used as an experimental model to study the vulnerability of drug addiction (Kosten & Ambrosio, 2002). Moreover, our previous experiments have demonstrated that F344 rats perform less effectively than LEW rats in the RAM test (Fole et al., 2011) in agreement with the findings of other authors (van der Staay, Schuurman, van Reenen, & Korte, 2009).

In this work, we aimed to study whether cocaine use during adolescence affects spatial memory and synaptic plasticity mechanisms that underlie memory in adulthood. To this end, spatial memory assessed by new location recognition task (novel location recognition, NLR) was studied in LEW and F344 rats. Since animals need to be in a familiar context to be attracted by the novelty caused by the inclusion of an object in a new location, we decided to evaluate whether the way the animals explored the new location within the familiar context may be altered by cocaine and whether such alterations were dependent on the genetic makeup of individuals. We also studied the possible changes in synaptic plasticity of hippocampal CA1 neurons in these same animals.

Our results demonstrate that the presence of cocaine during adolescence impairs location recognition memory in adult animals and that such impairment depends on the genetic background of animals. By contrast, no relevant effects were observed in adult cocaine-treated rats. This effect could be related to cocaine-induced changes in hippocampal synaptic plasticity.

2. Materials and methods

2.1. Animals

Male LEW and F344 adult rats (8 weeks old, 220–240 g, Harlan, Spain) and adolescent rats (3 weeks old, 90–110 g, Charles River, Spain) were housed in groups of 5 under a light/dark cycle (12 h/12 h), in a temperature controlled room (22 °C) with standard food and 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, animals were randomly divided into two groups with similar average body weight and assigned either to a cocaine or saline treatment as outlined in the next paragraph.

2.2. Drug administration

After one week of habituation, animals were administered daily i.p. injections of either saline (0.9% NaCl) or cocaine chlorhydrate (20 mg/kg) in two different periods: (1) some animals were injected in adolescence – P32-P45 – and (2) others when they reached adulthood – P56-P69. The experimental groups were LEW-SAL, LEW-COC, F344-SAL and F344-COC for both ages: adults (LEW-SAL = 6, LEW-COC = 7, F344-SAL = 9, F344-COC = 9) and adolescents (LEW-SAL = 7, LEW-COC = 6, F344-SAL = 6, F344-COC = 7). Regardless of treatment age, all animals performed the behavioral protocol, novel location recognition (NLR), at the age of P68-P70. Some of these animals were used for electrophysiological experiments after the behavioral protocol.

2.3. Novel location recognition protocol

Experiments were carried out in a version of the novel location recognition (NLR) that was adapted for rats – concretely – a version used by us in other experiments (Valladolid-Acebes et al., 2013). The hippocampus-dependent object location memory task exploits the observation that rodents prefer to explore an object when its relative position in a box is different from the position in which the animal encountered it during a previous experience (Save, Poucet, Foreman, & Buhot, 1992). The NLR test was chosen because it is specifically hippocampal-dependent (Barker, Bird, Alexander, & Warburton, 2007) and also because this test has been shown to be less stressful than other experimental paradigms used to evaluate learning performance (Lucas, Chen, & Richter-Levin, 2013). Four boxes (35 × 35 cm; 40 cm high) were used and two identical objects were placed in each one. The dimensions of the objects were 3 × 7 × 8 cm so that the animals could surround them and lean on them for a full scan. The system was placed in a room in which the floor and walls were painted black, with controlled conditions of humidity and temperature (22 °C). Light levels were sufficient for animals to carry out the protocol as a visual task. The stimuli presented were identical copies of objects composed of Lego pieces (Lego UK, Slough, UK) and were heavy enough to avoid displacement during testing. Animals did not receive any external cue during testing.

The test was organized into three sessions:

(i) During the "Habituation session" animals were allowed 10 min to freely explore the empty box, (ii) In the "Exploration session" animals were allowed 5 min to freely explore the box containing two objects, each placed 5 cm from the top left and right corners. From now on, these locations for objects will be referred to as familiar (F) and novel location object (NLO), respectively.