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Reserpine differentially affects cocaine-induced behavior in low and high responders to novelty

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ABSTRACT

Individuals are known to differ in their sensitivity to cocaine. Cocaine is known to inhibit the re-uptake of monoamines. The response to cocaine has also been found to depend on monoamines inside reserpine-sensitive storage vesicles. The present study examined the effects of reserpine (1–2 mg/kg) on cocaine-induced behavior (10–15 mg/kg) in Low Responders (LR) and High Responders (HR) to novelty rats. LR displayed less cocaine-induced walking, wall rearing, free rearing and stereotyped behavior than HR did. The dose of 1 mg/kg of reserpine decreased cocaine-induced walking, wall rearing, free rearing and stereotyped behavior in LR, but not in HR. A dose of 2 mg/kg of reserpine was required to inhibit cocaine-induced behavior in HR. Combining these behavioral findings with our previously reported neurochemical finding that a higher dose of reserpine was required to inhibit the accumbal dopamine response to cocaine in HR than in LR (Verheij et al., 2008), suggests that HR are more sensitive to the behavioral effects of cocaine than LR because cocaine can release more monoamines from storage vesicles in HR than in LR. Our behavioral data also demonstrate that the individual differences in sensitivity to reserpine are not only limited to the dopaminergic system of the nucleus accumbens.

1. Introduction

Individual differences in the susceptibility to psychostimulants have extensively been reported, both in humans (Ball et al., 1994; Gynther et al., 1995; Jaffe and Archer, 1987; van den Bree et al., 1998) and in animals (Mantsch et al., 2001; Piazza et al., 1989, 2000). In this study we focused on two types of rat that are known to differ in their acute response to cocaine (COC). These individuals, which co-exist in a normal outbred population of Wistar rats, are selected on the basis of their exploratory response in a novel environment and, accordingly, labeled low responders (LR) and high responders (HR) to novelty (Bevins et al., 1997; Cools et al., 1990; Cools and Gingras, 1998; Cools and Tuinstra, 2003; Dellu et al., 1996; Kabbaj, 2004; Piazza et al., 1989, 1991; Rouge-Pont et al., 1993; Verheij and Cools, 2008). These rats are generally referred to as an animal model for low and high sensation seeking in man (Ballaz et al., 2007a, 2007b; Cools and Ellenbroek, 2002; Dellu et al., 1996).

Previous studies have demonstrated that COC increases monoamine levels in the nucleus accumbens to a smaller degree in LR than in HR (Chefer et al., 2003; Hooks et al., 1991b; Verheij et al., 2008). In addition, the behavioral response to COC has been shown to be smaller in LR than in HR (Hooks et al., 1992, 1991a, 1991b). COC is known to inhibit the re-uptake of monoamines by blocking plasmalemmal monoamine transporters (Lee et al., 2001). However, both neurochemical and behavioral studies have demonstrated that the response to COC depends also on monoamines inside storage vesicles (Davis, 1985; Florin et al., 1995; Hurd and Ungerstedt, 1989; McMillen, 1983; McMillen et al., 1980; Pifl et al., 1995; Scheel-Kruger et al., 1977; Venton et al., 2006; Verheij et al., 2008). We have recently demonstrated that the monoaminergic storage pools of the nucleus accumbens of LR are smaller than the monoaminergic storage pools of the nucleus accumbens of HR (Cools and Verheij, 2002; Verheij and Cools, 2009b; Verheij et al., 2008). We have, therefore, proposed that LR are less sensitive to the neurochemical effects of COC than HR, because COC can release less monoamines from storage vesicles in LR than in HR (Verheij and Cools, 2008; Verheij et al., 2008).

In the present study we have used the indole alkaloid reserpine (RES). RES binds to vesicular monoamine transporters (Henry et al., 1998; Kirshner et al., 1963). After RES treatment, monoaminergic storage vesicles are known to become empty (Colliver et al., 2000; Dahlstrom et al., 1965; Gong et al., 2003; Pothos et al., 1998; Wagner, 1985). Following the dose of 1 mg/kg of RES, COC could still increase the levels of accumbal dopamine in HR, but not in LR rats (Verheij

Abbreviations: COC, cocaine; HR, High Responders to novelty; LR, Low Responders to novelty; RES, reserpine.

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et al., 2008). A higher dose of 2 mg/kg of RES was needed to inhibit the COC-induced increase of accumbal dopamine in HR (Verheij et al., 2008). The aim of the present study was to analyze whether these individual differences in the sensitivity to RES do exist not only at the neurochemical level, but also at the behavioral level. The expected RES-induced changes in behavior demonstrate that the RES-induced neurochemical changes are functional. Based on our neurochemical findings, we hypothesized that COC-treated LR are more sensitive to the behavioral effects of RES than COC-treated HR.

2. Methods

2.1. Subjects

Adult male LR ($n=41$) and HR ($n=64$) that were selected from the outbred strain of Nijmegen Wistar rats were used throughout the study. Apart from the assessment of the behavioral response to COC, these rats were also used to measure the COC-induced changes of accumbal dopamine (see Introduction). The results of this neurochemical analysis have been published in a separate paper (Verheij et al., 2008). All rats (weight = 180–220 g) were reared and housed in macrolon cages (42×26×15 cm; $n=3$–4 per cage) under a fixed 12/12 h light/dark cycle (lights on: 07.00 a.m.) in a temperature-controlled room (21±1.7 °C). Water and food pellets were available *ad libitum*. The experiments were performed in accordance with institutional, national and international guidelines for animal care and welfare. All procedures were in agreement with the NRC (National Research Council) 2003 guidelines for the care and use of mammals in neuroscience and behavioral research and the European communities council directive of 24 November 1986 (86/609/EEC). Every effort was made to minimize the number of animals used and their suffering.

2.2. Open-field selection

Rats were individually housed 3 days before the open-field selection procedure (Verheij et al., 2008). Testing took place between 09.00 h and 17.00 h in a room illuminated by white light of 170 lx. The rat was placed on a black, square table (160×160 cm) made of Perspex. This open-field is 95 cm elevated above the floor and surrounded by a white neutral background (270×270×270 cm). Behavior was recorded with a computerized automated tracking system for a period of 30 min. The objective parameters of ambulation and habituation time were used to select LR and HR (see also: Cools et al., 1990; Ellenbroek and Cools, 2002). Ambulation was defined as the overall distance (cm) traveled in 30 min. Habituation time was defined as the duration of the period (s) that started as soon as the rat began to explore the open-field and ended as soon as the locomotor activity stopped for at least 90 s. Rats that habituated in less than 480 s and walked less than 4800 cm in 30 min were labeled LR, whereas rats that habituated after 840 s and walked more than 6000 cm in 30 min were labeled HR (see also: Verheij et al., 2008). Habituation time in addition to ambulation was used as selection criterion, because traveled distance per se is not always a reliable criterion (Cools et al., 1997; Saigusa et al., 1999). To select extremes in ambulation we used fixed criteria, instead of a split that is based on mean ambulation, because the mean of ambulation may well differ between rats of different breeders (Ellenbroek and Cools, 2002). Typically, 40–50% of the rats within a Wistar population do not fit our criteria (see Results) and are excluded from analysis. Efforts were made to include these animals in other studies (Verheij et al., 2007).

2.3. Reserpine and cocaine treatment

At 12.00 h on the first day of the experiment, LR and HR were injected with RES or its solvent. After this systemic injection (volume: 1 ml/kg, i.p.), rats were returned to their home cage and left undisturbed. At 12.00 h on the second day of the experiment, a systemic injection (volume 1 ml/kg, i.p.) of COC or its solvent (saline) was given. Rats were exposed to a new cage immediately after their second injection. This novel cage was slightly larger than the home cage (new dimensions: 30×30×35 cm) and lacked sawdust on the floor.

2.4. Doses of reserpine

Both LR and HR were injected with 1 mg/kg of RES (Daiichi, Tokyo, Japan) on day 1 and 10 or 15 mg/kg of COC (Brocacef, Amsterdam, The Netherlands) on day 2. Because the dose of 1 mg/kg of RES was found to have no effect on the COC-induced neurochemical changes in HR (Verheij et al., 2008), an additional group of HR was pretreated with a

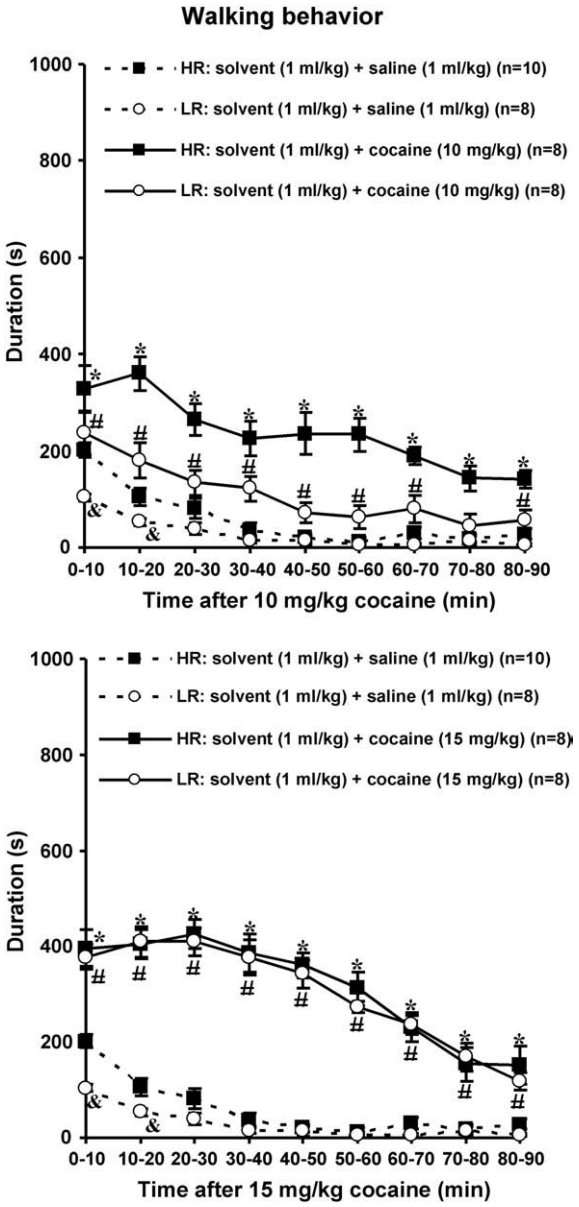

Fig. 1. Effects of saline (upper/lower panel), 10 mg/kg (upper panel) and 15 mg/kg (lower panel) of cocaine on the duration (s) of walking behavior in LR (circle) and HR (square). Cocaine-treated rats are represented by a filled line, saline-treated rats are represented by a dotted line. All rats were pretreated with the solvent of reserpine (=solvent) 24 h before saline or cocaine was given. Data are expressed as mean±SEM. LR = Low Responders to novelty, HR = High Responders to novelty. # = Significant difference between cocaine-treated and saline-treated LR (Student's *t*-test), * = Significant difference between cocaine-treated and saline-treated HR (Student's *t*-test), & = Significant difference between saline-treated LR and saline-treated HR (Student's *t*-test).