Dopaminergic mechanisms mediating the long-term expression of locomotor sensitization following pre-exposure to morphine or amphetamine

Abstract The role of dopaminergic mechanisms in opiate- and psychostimulant-induced long-term locomotor sensitization was investigated. To that aim, rats were behaviourally sensitized with morphine or amphetamine and 3 weeks after cessation of treatment challenged with various direct and indirect dopamine agonists. Both morphine- and amphetamine-pretreated rats displayed sensitization of the locomotor effects of amphetamine, cocaine, and the selective dopamine reuptake inhibitor GBR-12909. Sensitization of the locomotor stimulant effects of the dopamine D2/D3 receptor agonist quinpirole was observed in amphetamine- but not morphine-pretreated rats. In contrast, morphine-, but not amphetamine-pretreated rats appeared hyposensitive to the locomotor inhibitory effects of a low, presumably D2-autoreceptor selective, dose of quinpirole. Neither pretreatment induced sensitization to the dopamine D1/D2 agonist apomorphine or the dopamine D1 agonist SKF-82958. In fact, the locomotor stimulant effects of SKF-82958 appeared to be decreased in animals pre-exposed to amphetamine. These results suggest that functional changes in presynaptic dopamine release mechanisms represent common neuroadaptations involved in the long-term expression of morphine- and amphetamine-induced locomotor sensitization. Presynaptic dopamine D2 and postsynaptic D2 and/or D3 receptors are differentially involved in the expression of morphine- and amphetamine-induced locomotor sensitization. In a parallel study, we report that all of the drugs that elicited sensitized locomotor responses in morphine- or amphetamine-pretreated rats caused reinstatement of previously extinguished heroin- or cocaine-seeking behaviour, respectively. Taken together, these data suggest a marked relationship between drug-seeking behaviour and drug sensitization.

Key words Behavioural sensitization · Locomotor activity · Morphine · Amphetamine · Dopamine D1 receptor · Dopamine D2 receptor

Introduction

Upon repeated exposure to drugs of abuse, such as opiates and psychostimulants, their locomotor stimulant and positive reinforcing effects become persistently enhanced. This phenomenon, termed behavioural sensitization (Stewart and Badiani 1993), is thought to be involved in certain aspects of drug addiction, such as drug craving and compulsive drug-seeking behaviour (Robinson and Berridge 1993). Although it is generally assumed that upon pre-exposure to one drug, long-term sensitization to other drugs (cross-sensitization) also occurs, most studies investigating behavioural sensitization employ the same drug as pretreatment and challenge drug. As a result, information on the existence of long-term cross-sensitization is, in fact, quite scarce. Regarding the neuronal mechanisms involved, there is an overwhelming amount of data to suggest that the expression of long-term behavioural sensitization is dependent on hypersensitivity of nucleus accumbens (NAcc) dopamine (DA) nerve terminals (for review, see Pierce and Kalivas 1997a). However, the contribution of DA receptors in the expression of behavioural sensitization has only been investigated in a limited number of studies (see Pierce and Kalivas 1997a). Therefore, in the present study, we investigated the contribution of both pre- and postsynaptic DA mechanisms in the expression of long-term locomotor sensitization. To that aim, rats were repeatedly treated...
with morphine or amphetamine according to regimens that reliably elicit long-term behavioural sensitization in our laboratory (De Vries et al. 1996; Vanderschuren et al. 1997, 1999). Three weeks post-treatment, the locomotor responses of morphine- or amphetamine-pre-treated rats to various direct and indirect DA agonists were determined. Because of the suggested relationship between drug sensitization and compulsive drug-seeking behaviour (Robinson and Berridge 1993), the relevance of the present findings for drug-seeking behaviour was investigated in a parallel study (De Vries et al., 1999). In that study, the same challenge drugs used here were evaluated for their ability to evoke reinstatement of responding in rats with a history of heroin or cocaine self-administration.

Materials and methods

Animals and drug treatments

All experiments were approved by the Animal Care Committee of the Free University of Amsterdam. Male Wistar rats (Harlan, Zeist, The Netherlands), weighing 180–200 g at the beginning of drug treatment, were housed two per cage in Macrolon cages under controlled conditions (lights on from 0700 to 1900 hours) for 1 week before use. Food and water were available ad libitum. Animals were briefly handled on the 2 days preceding the beginning of drug treatment and on the 2 days preceding drug challenges. Pretreatment consisted of 14 daily injections with morphine (10 mg/kg, SC) (Vanderschuren et al. 1997) or five daily injections with amphetamine (2.5 mg/kg, IP) (De Vries et al. 1996). Control groups received vehicle injections.

Procedure

Horizontal motor activity was measured in Perspex cages (40 x 40 x 35 cm) using a video tracking system (EthoVision, Noldus Information Technology B.V., Wageningen, The Netherlands), which determined the position of the animal 5 times per second. All experiments were conducted between 9.30 a.m. and 4.30 p.m., in the light phase of the day/night cycle. White noise was used to minimize the influence of surrounding sounds. Three weeks after the last pretreatment injection, locomotor challenge tests were conducted as follows. Animals were allowed to habituate to the test cages for 2 h, during which activity was monitored. The rats then received an injection with saline (1.0 ml/kg, SC or IP, depending on the route of administration of the challenge drug) and activity was monitored for 1 h. Subsequently, animals were injected with SKF-82958 (1 mg/kg, SC), quinpirole (0.05 or 0.5 mg/kg, SC), apomorphine (0.3 mg/kg, SC), amphetamine (1 mg/kg, IP), cocaine (15 mg/kg, IP), or GBR-12909 (10 mg/kg, IP) and, depending on the drug used, activity was monitored for 30 min to 4 h. The challenge doses of the drugs were based on pilot studies, and represent doses inducing a submaximal stimulation of locomotor activity, except for the low dose of quinpirole, which was selected on basis of its locomotor inhibitory effect (Eilam and Szechtman 1989) (see Fig. 2A). Animals were challenged only once.

Statistics

Horizontal locomotor activity, expressed as travelled distance (cm) was calculated in 10 min intervals, except where indicated. Behavioural sensitization is most often defined as an absolute increase in the locomotor effects of a given dose of drug (Stewart and Badiani 1993). In addition, especially after challenges with psychostimulant drugs such as amphetamine and cocaine, behavioural sensitization can also involve an earlier onset of locomotion after drug injection, which will result in an increased locomotor effect during early phases of the test period (Stewart and Badiani 1993; Carey and Gui 1998). In parallel with the declining locomotor effect of the drug, pretreatment effects sometimes wear off during later phases of the challenge. In the present study, the length of the test periods was chosen to monitor the entire locomotor effects of the various challenge drugs. Locomotor activity was therefore analyzed using two-factor repeated measures analyses of variance (ANOVA) for time and pretreatment on the entire test period, in order to detect pretreatment-induced changes in the absolute locomotor effect of the various challenge drugs. In addition, two-factor repeated measures ANOVAs for time and pretreatment were also performed on the first 30 min of the test period, to detect pretreatment effects occurring during the onset and, in most cases, peak of the locomotor challenges. The effect of 0.05 mg/kg quinpirole in drug-naive animals was analyzed using a one-way ANOVA.

Drugs

Morphine-HCl, (+)-amphetamine-sulphate, cocaine-HCl, and apomorphine-HCl were purchased from O.P.G. (Utrecht, The Netherlands), and (±)-SKF-82958-HBr [(±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrobromide], GBR-12909-diHCl [(1-[2-bis(4-fluorophenyl)methoxy]ethyl)-4-[3-phenylpropyl]piperazine dihydrochloride], and (+)-quinpirole-HCl were purchased from Research Biochemicals (Natick, Mass., USA). All drugs were dissolved in sterile saline, except for GBR-12909, which was dissolved in distilled water.

Results

In none of the experiments was an effect of morphine or amphetamine pretreatment observed on locomotor activity during the habituation phase (data not shown) or saline challenge (Figs. 1A–1C).

Challenges with direct dopamine agonists

As shown in Fig. 1, an injection with the DA D1 receptor agonist SKF-82958 (1.0 mg/kg, SC) enhanced locomotion. The locomotor effect of SKF-82958 was not affected by pretreatment with morphine [entire period: F(pretreatment)(1,10) = 0.00, NS; first 30 min: F(pretreatment)(1,10) = 2.00, NS] (Fig. 1A). The locomotor effect of SKF-82958 appeared to be suppressed in animals pretreated with amphetamine. More precisely, in amphetamine-pretreated rats, SKF-82958-induced locomotor activity was decreased during the first 30 min of the test period [F(pretreatment)(1,23) = 4.33, P < 0.05], indicating a delayed onset of SKF-82958-induced locomotor activity, but over the entire test period, this effect was not statistically significant [F(pretreatment)(1,23) = 2.76, NS] (Fig. 1B).

Administration of 0.05 mg/kg quinpirole, SC, to drug-naive, habituated rats suppressed locomotor activity as compared to a saline challenge [F(1,13) = 4.76, P < 0.05] (Fig. 2A). Three weeks post-treatment,