ELSEVIER

Pharmacology, Biochemistry and Behavior 73 (2002) 697–702

PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR

www.elsevier.com/locate/pharmbiochembeh

Rotational behaviour in AA and ANA rats after repeated administration of morphine and cocaine

Janne A.V. Mikkola[a], Sanna Janhunen[a], Petri Hyytiä[b], Kalervo Kiianmaa[b], Liisa Ahtee[a,*]

[a]*Department of Pharmacy, Division of Pharmacology and Toxicology, University of Helsinki, P.O. Box 56, FIN-00014 Helsinki, Finland*
[b]*Department of Mental Health and Alcohol Research, National Public Health Institute, P.O. Box 33, FIN-00251 Helsinki, Finland*

Received 7 February 2002; received in revised form 10 May 2002; accepted 13 May 2002

Abstract

The purpose of the present study was to investigate the effects of repeated morphine and cocaine treatments on rotational behaviour in alcohol-preferring AA (Alko Alcohol) and alcohol-avoiding ANA (Alko Non-Alcohol) rats after unilateral 6-hydroxydopamine lesions of the ascending dopamine pathways. We administered saline, morphine (1 or 3 mg/kg) or cocaine (10 mg/kg) once daily for 4 days with an additional challenge 8 days after the repeated drug treatment. Ipsilateral rotations of the animals were monitored after each drug treatment. Both morphine (3 mg/kg but not 1 mg/kg) and cocaine induced more rotational behaviour in AA than in ANA rats over the 4-day drug treatment period. On Day 12, a challenge with 3 mg/kg morphine or cocaine induced significantly more rotations in the AA rats pretreated with morphine or cocaine when compared to saline-treated AA rats exposed to these drugs for the first time. This finding indicates that sensitization to the effects of morphine and cocaine occurs in the AA rats, while no clear sensitization was seen in the ANA rats. Collectively, these results suggest that morphine and cocaine activate the cerebral dopamine pathways to a greater extent in AA than in ANA rats.

Keywords: Alcohol-preference; Morphine; Cocaine; Rotational behaviour; 6-Hydroxydopamine

1. Introduction

It is well known that alcohol, opioids and psychostimulants increase synaptic concentrations of dopamine in the nucleus accumbens and caudate–putamen (Di Chiara and Imperato, 1988). Cerebral dopaminergic mechanisms appear to be involved in the locomotor activity stimulating effect, as well as in the reinforcing effects of drugs of abuse (Robinson and Berridge, 1993; Wise and Bozarth, 1987). To summarise these observations, opioids and psychostimulants, by elevating synaptic concentrations of dopamine, increase the locomotor activity of animals. Furthermore, after repeated drug treatment, the locomotor activity stimulating effects of opioids and psychostimulants becomes sensitized, an effect associated with increased dopamine release in the nucleus accumbens (for a review, see Kalivas and Stewart, 1991). After repeated administration of opioids to rodents, these drugs also induce stereotypies and gnawing, which are thought to be associated with overactivity of the nigrostriatal dopaminergic mechanisms (Ahtee and Attila, 1987).

Alcohol-preferring AA (Alko Alcohol) and alcohol-avoiding ANA (Alko Non-Alcohol) rat lines have been developed by selective outbreeding for differences in voluntary alcohol consumption (Eriksson, 1968, 1969). In addition to alcohol, the AA rats consume greater amounts of aqueous solutions of cocaine and etonitazene, a μ-opioid receptor agonist, suggesting that the rewarding properties of these drugs may be stronger in AA than in ANA rats (Hyytiä and Sinclair, 1993). AA rats also show more stimulation of locomotor activity after morphine administration than ANA rats. Furthermore, the morphine- or cocaine-induced stimulation of locomotor activity in AA rats became sensitized after 4 days treatment with morphine (1 mg/kg) or cocaine (10 mg/kg), an observation that is not seen in ANA rats (Honkanen et al., 1999a,b). One similarity between rats of these two lines is that acute morphine administration has been shown to stimulate dopamine release in the nucleus accumbens to the same extent,

* Corresponding author. Tel.: +358-9-191-59472; fax: +358-9-191-59471.
E-mail address: liisa.ahtee@helsinki.fi (L. Ahtee).

0091-3057/02/$ – see front matter © 2002 Elsevier Science Inc. All rights reserved.
PII: S0091-3057(02)00876-6

whereas the nigrostriatal dopaminergic mechanisms seem to be more sensitive to the effects of morphine in AA than in ANA rats (Honkanen et al., 1999a,b). This suggests that it is not the mesolimbic but rather the nigrostriatal dopaminergic mechanisms that may be responsible for mediating the discrepancies seen in the locomotor activities of the AA and ANA rats after acute morphine injection.

In this investigation, we have attempted to clarify the involvement of striatal dopaminergic mechanisms in morphine's and cocaine's effects by examining the behavioural differences induced by acute or repeated morphine or cocaine administration in AA and ANA rats. The effects of these drugs on rotational behaviour were measured in both lines of rats after unilateral 6-hydroxydopamine lesions of the striatal dopamine neurons had been performed. Drugs that activate the remaining dopamine pathways presynaptically should induce ipsilateral rotation, i.e., rotation towards the lesioned side (Ungerstedt and Arbuthnott, 1970). Previous studies have demonstrated that morphine and cocaine both induce ipsilateral rotation in such lesioned rats (Kimmel and Holtzman, 1997).

2. Method

2.1. Animals

Experimentally, naive male AA and ANA rats weighing 270–500 g, aged 3–6 months from generations F_{78}–F_{80}, were used. The rats were housed in groups of three to five rats of each line per cage under a 12/12-h light/dark cycle (lights on at 6 a.m.) at an ambient temperature of 22 °C. Tap water and rat chow (Altromin 1324, Chr. Petersen, Denmark) were available ad libitum. The animal experiments were approved by the local Institutional Animal Care and Use Committee and the chief veterinarian of the County Administrative Board, and were conducted according to the "European Convention for the Protection of Vertebrate Animals Used for Experimental and Other Scientific Purposes".

2.2. Stereotaxic surgery

Unilateral lesions of the right nigrostriatal tract were produced by injection of 6-hydroxydopamine (8 μg in volume of 2 μg/μl given 1 μl/min for 4 min) into the medial forebrain bundle of rats under halothane anaesthesia (3.5% during induction and 2% during surgery) with a 30-gauge needle. Upon completion, the injection needle was kept in place for an additional minute to minimize backflow of the solution. The coordinates used were A/P −4.4 mm, L/M +1.3 mm, D/V −8.2 mm relative to bregma according to the atlas of Paxinos and Watson (Paxinos and Watson, 1986). Prior to surgery, desipramine (15 mg/kg ip, 1 ml/kg) was administered to prevent the uptake of 6-hydroxydopamine into noradrenergic nerve endings, and thus protect these nerve terminals from destruction. After surgery, the rats were placed into individual cages for 1–2 days and then returned to the group cages. An additional period of 2 weeks was allowed after the surgery prior to any further experimental procedures being carried out.

2.3. Measurement of rotation

Rotational activity of the rats was measured in circular metal bowls (35 cm diameter and 15 cm high) with a transparent Plexiglas cylinder (40 cm high) surrounding the bowls. The rat was attached to a rotation sensor by means of a spring tether connected to a plastic belt around the neck of the rat. The rotation sensor detected full (360°) clockwise and counterclockwise turns. Rats were taken from group cages, given saline (1 ml/kg sc or ip), placed individually into test chambers and allowed to habituate to the chamber for 30 min. Thereafter, the rats were given morphine (1 or 3 mg/kg sc), cocaine (10 mg/kg ip) or saline (sc or ip) and rotations counted for 2 (cocaine), 3 (morphine 1 mg/kg) or 3.5 h (morphine 3 mg/kg). The rotations were measured at these time points based on the duration of action of the drugs found in our previous studies (Honkanen et al., 1999a,b; Mikkola et al., 2001a,b, 2000). Only the dose of 10 mg/kg of cocaine was studied because a difference in behavioural sensitization between AA and ANA rats was previously found only with this dose (Honkanen et al., 1999a,b). After the sessions, the rats were placed back into the group cages. The procedure was repeated on 4 consecutive days with an additional challenge session 8 days after the fourth session. In the challenge session, all rats, including those that had previously received saline, were given either morphine or cocaine.

2.4. Verification of 6-hydroxydopamine lesions

6-Hydroxydopamine lesions were verified by measuring the reduction in striatal dopamine concentration. One to two weeks after the experiments, the rats were decapitated, brains removed from the skull, placed on a glass plate and the striata dissected as described previously (Ahtee et al., 1989). The dissected samples were immediately frozen on dry ice and stored at −80 °C until assay. Samples were homogenized and purified as described earlier (Haikala, 1987). The samples were assayed for concentration of dopamine by high-performance liquid chromatography using a C-18 reverse-phase column (Spherisorb ODS2, 4.6×250 mm) and electrochemical detection (+780 mV, Waters Model 464 detector, Millipore, MA, USA). Only rats with a dopamine depletion of more than 95% in the lesioned right striatum as compared to the intact left striatum were included in the final data analysis. The mean striatal dopamine %depletion±S.E.M. of rats included in results were: AA 98.7±0.3%, ANA 99.4±0.3%. Additionally, we measured the mean dopamine %depletion in the limbic forebrain of seven randomly selected AA and ANA rats included in results: AA 89.6±1.3%, ANA 91.0±2.7%.

2.5. Drugs

Morphine- and cocaine-hydrochloride were obtained from the University Pharmacy (Helsinki, Finland), and 6-hydroxydopamine and desipramine from Sigma (St. Louis, MO). Morphine was administered subcutaneously and cocaine intraperitoneally. Both drugs were administered in a volume of 1 ml/kg dissolved in 0.9% NaCl solution (saline). Desipramine was dissolved in purified water and administered intraperitoneally, 15 mg/kg, 1 ml/kg. 6-OHDA was dissolved in 0.9% saline containing 0.02% ascorbic acid.

2.6. Statistical analysis

The total numbers of ipsilateral rotations during the four pretreatment sessions were analysed with two- or three-way repeated measures of analysis of variance (ANOVA) with rat line (AA, ANA) and treatment (saline, morphine or cocaine) as between-subjects factors and day (Days 1–4) as the within-subjects factor. Rotational activity on the challenge day was analysed with two-way (line, pretreatment) ANOVA. Simple effects analysis of drug treatments on individual experimental days were tested with ANOVA followed by Tukey's compromise post-hoc test.

3. Results

3.1. Morphine

The smaller dose of morphine (1 mg/kg) did not induce any significant changes in the number of rotations over the 4-day repeated treatment session [treatment effect: $F(1,25)=1.04$, $P=.32$, three-way ANOVA, Fig. 1]. However, there was a significant Treatment×Day interaction: $F(3,75)=3.17$, $P=.03$, three-way ANOVA, which apparently results from habituation of the saline-treated animals to the test situation. There were no differences in the effect of morphine between rat lines [Treatment×Rat Line interaction: $F(1,25)=0.41$, $P=.53$, three-way ANOVA] or between rat lines and days [Treatment×Rat Line×Day interaction: $F(3,75)=0.18$, $P=.91$, three-way ANOVA]. The effects of morphine (1 mg/kg) on the challenge day did not differ between saline- or morphine-pretreated rats [pretreatment effect: $F(1,25)=0.01$, $P=.91$, two-way ANOVA, Fig. 1] or between rat lines [rat line effect: $F(1,25)=0.004$, $P=.95$, two-way ANOVA].

However, the larger dose of morphine (3 mg/kg) induced significant ipsilateral rotations [treatment effect: $F(1,55)=17.60$, $P<.001$, three-way ANOVA, Fig. 1], which were higher in AA than in ANA rats [Treatment×Rat Line interaction: $F(1,55)=6.39$, $P=.01$, three-way ANOVA]. Further analysis conducted on individual experimental days showed that morphine significantly enhanced the rotational behaviour in AA but not in ANA rats and that, on Days 2–4, the 3 mg/kg morphine dose induced significantly more rotations in the AA than in the ANA rats (Fig. 1). Over the 4-day repeated treatment session, the effect of 3 mg/kg of morphine on ANA rats was found to be significant [treatment effect: $F(1,30)=12.08$, $P=.002$, two-way ANOVA]. The effect of morphine did not significantly change over the 4-day repeated treatment sessions [Treatment×Day interaction: $F(3,165)=1.59$, $P=.19$, three-way ANOVA]. The effect of repeated morphine treatment did not differ statistically significantly between rat lines and Days 1–4 [Treatment×Rat Line×Day interaction: $F(3,165)=1.51$, $P=.21$, three-way ANOVA].

On Day 12, when both saline- and morphine-pretreated rats were given the challenge dose 3 mg/kg of morphine, the effect of morphine was more pronounced in AA than in ANA rats [rat line effect: $F(1,55)=4.91$, $P=.03$, two-way ANOVA, Fig. 1]. The effect of morphine was stronger in the morphine-pretreated than in the saline-pretreated rats [pretreatment effect: $F(1,55)=5.74$, $P=.02$, two-way ANOVA]

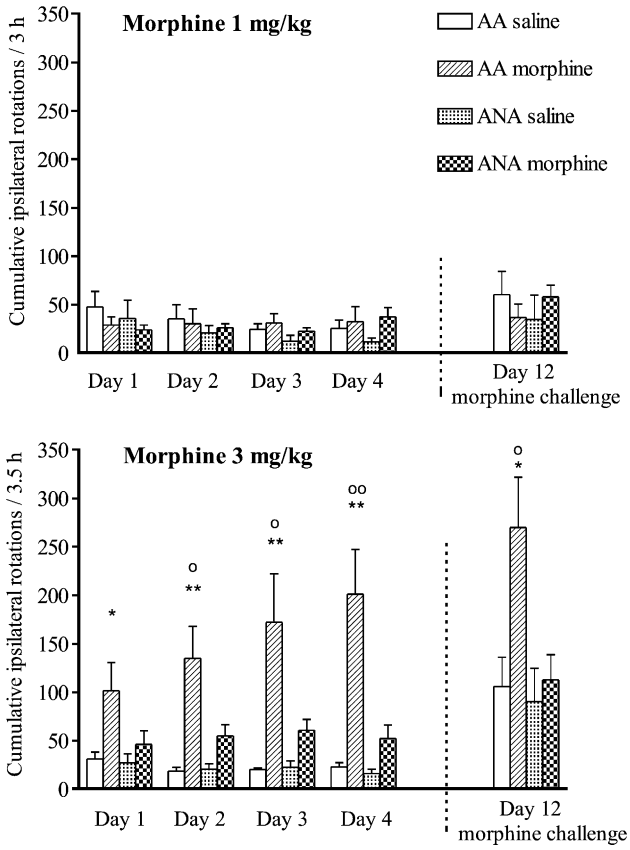

Fig. 1. Effects of repeated treatment with saline or morphine (1 or 3 mg/kg sc) on rotational behaviour in the alcohol-preferring (AA) and alcohol-avoiding (ANA) rats. Columns represent the means (±S.E.M.) of cumulative ipsilateral rotations; 6–9 rats per each group were used to study the effects of morphine 1 mg/kg and 10–16 those of morphine 3 mg/kg. On Days 1–4, some of the rats received saline subcutaneously and the rest received morphine (1 or 3 mg/kg sc), daily, before starting counting the rotations. On Day 12, all rats received a challenge with morphine. *$P<.05$ and **$P<.01$, in comparison with corresponding saline-pretreated rats, °$P<.05$ and °°$P<.01$, in comparison with corresponding ANA rats (ANOVA followed by Tukey's compromise post-hoc test).

indicating sensitization to morphine. Further analysis was conducted to clarify which group of rats was sensitized. This showed that AA but not ANA rats were significantly sensitized to repeated morphine, and that the 3 mg/kg challenge dose of morphine induced significantly more rotations in the AA rats pretreated with morphine than in the correspondingly pretreated ANA rats (Fig. 1). Finally, when the magnitude of the sensitization, i.e., the difference between the effects of the 3 mg/kg dose of morphine on morphine- and saline-pretreated rats, were compared between the rat lines, a P value of .08 was found [Pretreatment×Rat Line interaction: $F(1,55)=3.29$, $P=.08$, two-way ANOVA], suggesting stronger sensitization of AA rats.

3.2. Cocaine

Cocaine induced significant ipsilateral rotations [treatment effect: $F(1,30)=35.59$, $P<.001$, three-way ANOVA, Fig. 2], which were higher in AA than in ANA rats [Treatment×Rat Line interaction: $F(1,30)=5.35$, $P=.03$, three-way ANOVA]. When measured on individual experimental days, the results of cocaine treatment reached statistical significance only in AA rats (Fig. 2). Furthermore, on Days 3 and 4, cocaine induced significantly more rotations in AA than in ANA rats (Fig. 2). Over the 4-day repeated treatment session, cocaine's effect on ANA rats was found to be significant [treatment effect: $F(1,17)=16.54$, $P<.001$, two-way ANOVA]. The effect of cocaine did not change significantly over the 4-day repeated treatment sessions [Treatment×Day interaction: $F(3,90)=1.84$, $P=.15$, three-way ANOVA]. The effect of repeated cocaine treatment did not differ statistically significantly between rat lines and Days 1–4 [Treatment×Rat Line×Day interaction: $F(3,90)=0.60$, $P=.62$, three-way ANOVA].

The effect of cocaine on the challenge day did not differ between the rat lines [rat line effect: $F(1,30)=0.24$, $P=.63$, two-way ANOVA]. However, the effect of cocaine was stronger in the cocaine-pretreated than in the saline-pretreated rats [pretreatment effect: $F(1,30)=11.26$, $P=.002$, two-way ANOVA] indicating sensitization to cocaine. Further analysis was conducted to clarify which group of rats was sensitized. This showed that AA but not ANA rats were significantly sensitized to repeated cocaine (Fig. 2). Although this sensitization was significant only in AA rats, the magnitude of the sensitization did not differ between the rat lines [Pretreatment×Rat Line interaction: $F(1,30)=0.85$, $P=.36$, two-way ANOVA].

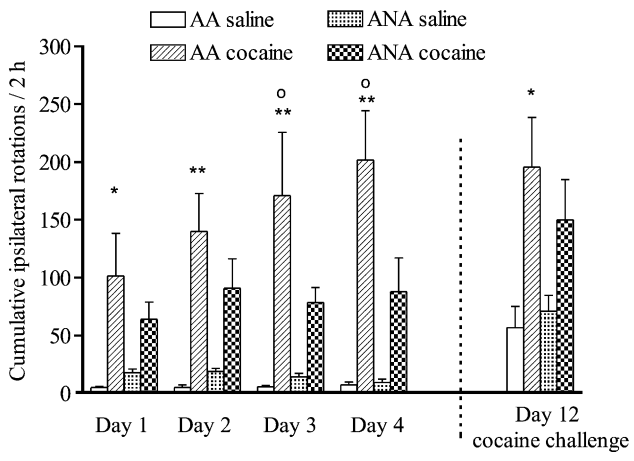

Fig. 2. Effects of repeated treatment with saline or cocaine (10 mg/kg ip) on rotational behaviour in the alcohol-preferring (AA) and alcohol-avoiding (ANA) rats. Columns represent the means (±S.E.M.) of cumulative ipsilateral rotations of 7–11 rats. On Days 1–4, some of the rats received saline intraperitoneally and the rest of the rats received cocaine (10 mg/kg ip), daily, before starting counting the rotations. On Day 12, all rats received the cocaine challenge. *$P<.05$ and **$P<.01$, in comparison with corresponding saline-pretreated rats, °$P<.05$ and °°$P<.01$, in comparison with corresponding ANA rats (ANOVA followed by Tukey's compromise post-hoc test).

4. Discussion

Both morphine and cocaine induced ipsilateral rotation in AA and ANA rats with unilateral striatal 6-hydroxydopamine lesions. Moreover, both morphine and cocaine generated more rotational behaviour in AA than in ANA rats. Neither the AA nor the ANA rats showed statistically significant sensitization to morphine- or cocaine-induced rotational behaviour during repeated 4-day treatment with these drugs, although the number of morphine- or cocaine-induced rotations increased by two-fold in the AA rats from Days 1 to 4. However, a challenge dose of morphine or cocaine 8 days after 4-day pretreatment with these drugs or saline provoked significantly more rotations in those AA rats pretreated with morphine or cocaine than in those AA rats that had received 4-day saline treatment. Such sensitization was not seen in the ANA rats. Furthermore, morphine induced significantly more rotations in the AA rats withdrawn for 8 days from repeated morphine than in the corresponding ANA rats. In contrast, the rotational responses of the AA and ANA rats challenged with cocaine 8 days after 4 days of repeated treatment did not differ.

In the present study, acute administration of the 3 mg/kg dose of morphine produced significant ipsilateral rotational activity in AA rats, but did not enhance such activity in ANA rats. This finding is in agreement with those previously reported by Honkanen et al. who found a larger degree of locomotor activity enhancement after acute morphine administration in AA rats than in ANA rats (Honkanen et al., 1999a,b), suggesting that morphine activates dopaminergic transmission to a greater extent in AA than in ANA rats. However, in that particular study, 1 mg/kg dose of morphine increased the locomotor activity of rats from both lines, whereas in the present study, this dose of morphine was not sufficient to enhance the rotational behaviour of either AA or ANA rats. It should be noted that the rotational behaviour measured in nigrostriatally 6-hydroxydopamine-lesioned rats mainly reflects the responses of dopaminergic striatal mechanisms, whereas opioids have also been shown to

increase the locomotor activity independently of dopamine, when administered directly into the nucleus accumbens (Kalivas et al., 1983; Pert and Sivit, 1977). Thus, in addition to the possible role of cerebral dopamine, nondopaminergic mechanisms might also be involved in producing the different locomotor responses to morphine observed in rats from these two lines. One possible explanation may come from findings that AA rats have a higher density of μ-opioid receptors in the shell subdivision of the nucleus accumbens when compared to ANA rats (de Waele et al., 1995; Marinelli et al., 2000).

On the fourth day of repeated daily treatment with 1 or 3 mg/kg morphine, no significant sensitization of rotational behaviour was found in rats of either line. In line with the responses of rotational behaviour determined in the present study, no significant sensitization of the locomotor activity enhancing effects of morphine could be detected previously in either AA or ANA rats during the 4-day treatment with a 3 mg/kg dose of morphine (Honkanen et al., 1999a,b). However, AA rats but not ANA rats were found to be sensitized to the locomotor activity stimulating effects of 1 mg/kg of morphine during the 4-day treatment (Honkanen et al., 1999a,b). If this sensitization of locomotor activity enhancing effect of 1 mg/kg of morphine resulted from enhanced dopaminergic transmission, at least some enhancement of rotational behaviour should have been observed in the AA rats after repeated treatment with this dose of morphine. As mentioned previously, opioids have also been shown to increase the locomotor activity in rodents independently of dopamine, when administered directly into the nucleus accumbens (Kalivas et al., 1983; Pert and Sivit, 1977). Thus, our behavioural studies suggest that morphine-induced cerebral dopamine release is not altered significantly during repeated 4-day treatment with morphine in either AA or ANA rats. This view agrees with other results obtained in our laboratory, that the dopamine releasing effect of acute morphine is not enhanced after a repeated 4-day treatment regime with the drug, either in the caudate–putamen or in the nucleus accumbens of rats from either line (Mikkola et al., 2000, 2001a,b). Additionally, in this study, when the rats were challenged with a 3 mg/kg dose of morphine 8 days after repeated saline or morphine pretreatment, it was found that AA but not ANA rats showed enhanced rotational behaviour as compared with saline-pretreated controls suggesting enhanced dopaminergic transmission. The idea that enhanced dopaminergic transmission was occurring in the challenge session in AA rats is in agreement with several studies showing sensitization of mesolimbic dopamine release after 3 or more days of withdrawal from repeated morphine administration (Kalivas and Stewart, 1991; Acquas and Di Chiara, 1992; Cadoni and Di Chiara, 1999; Spanagel et al., 1993). This suggests that a withdrawal period from chronic morphine treatment is needed to produce enhanced cerebral dopaminergic transmission in AA rats, but this phenomenon is absent in rats from the ANA line.

In the present study, morphine clearly induced more ipsilateral rotations in AA than in ANA rats over the 4-day treatment period. It is known that drugs that increase synaptic levels of dopamine in the striatum through a presynaptic mechanism induce ipsilateral rotation in rats after unilateral 6-hydroxydopamine lesion of the nigrostriatal dopamine system (Ungerstedt and Arbuthnott, 1970). Thus, the more pronounced morphine-induced rotational behaviour of AA rats as compared with ANA rats suggests that the effects of morphine on dopaminergic mechanisms are more evident in AA than in ANA rats. Indeed, it has been found that morphine seems to increase dopamine release and metabolism in the striatum more in AA than in ANA rats, whereas there appear to be no differences in the effects of morphine on mesolimbic dopaminergic mechanisms between these rats (Honkanen et al., 1999a,b; Mikkola et al., 2000, 2001a,b). AA rats have also been shown to have more μ-opioid receptors in the substantia nigra than ANA rats (Soini et al., 1998, 1999), which may account for the enhanced effect of morphine on the nigrostriatal dopamine mechanisms in these rats.

In the present study, cocaine induced rotational behaviour in both AA and in ANA rats, but this effect was more pronounced in AA rats, especially on Days 3 and 4 during repeated cocaine treatment. However, no significant differences in the effects of cocaine on Day 1 between the two lines of rats were found. This is consistent with our previous findings that the effects of acute cocaine administration on horizontal locomotor activity (Honkanen et al., 1999a,b) or on mesolimbic or nigrostriatal dopamine release (Mikkola et al., 2001a,b) do not differ between rats of these lines. After a repeated 4-day treatment with cocaine (10 mg/kg), its effects on locomotor activity and extracellular concentrations of dopamine in the nucleus accumbens are enhanced in AA but not in ANA rats (Honkanen et al., 1999a,b; Mikkola et al., 2001a,b). However, in the present study, repeated cocaine treatment did not induce significant enhancement of ipsilateral rotations in rats of either line. In agreement with the present results, sensitization of the effect of cocaine on extracellular dopamine concentration in the dorsal striatum was not previously observed in either AA or ANA rats (Mikkola et al., 2001a,b).

Another important factor that should be considered is that in the present study, only rats that showed a greater than 95% depletion of nigrostriatal dopamine were included in the data. However, as the 6-hydroxydopamine lesion was aimed to the medial forebrain bundle, depletion of mesolimbic dopamine may also occur. In fact, we also measured dopamine concentrations in the nucleus accumbens of some rats, and found approximately 90% depletion of mesolimbic dopamine. Therefore, any direct conclusions as to whether the rotational behaviour of the rats results from a depletion of mesolimbic or nigrostriatal dopamine cannot be made on the basis of these experiments. Thus, the findings of the present study correspond to our previous neurochemical findings, in that where there were

no changes in nigrostriatal dopamine release, no significant sensitization of rotational behaviour during repeated cocaine treatment occurred in rats of either line. The influence of the sensitization of mesolimbic dopamine release, previously found in the AA rats, can be seen in the more pronounced rotational behaviour in these rats on Days 3 and 4 when compared to the ANA rats. In the challenge session, 8 days after repeated cocaine treatment when all rats were given an acute dose of cocaine, cocaine pretreated AA but not ANA rats showed significant enhancement in the effect of cocaine as compared with saline-pretreated controls. This suggests, as in the case with morphine, that a withdrawal period of several days may show up or strengthen the sensitization phenomenon associated with cocaine.

In conclusion, both morphine and cocaine induced more rotational behaviour in the AA than in the ANA rats during the 4-day repeated treatment, suggesting that these drugs induce stronger activation of brain dopaminergic mechanisms in the AA than in the ANA rats. However, in a challenge session 8 days after repeated morphine or cocaine treatment, a sensitization to these drugs was induced in the AA but not in the ANA rats. The alcohol-preferring AA and alcohol-avoiding ANA rat lines have been developed by selective outbreeding for differences in voluntary alcohol consumption (Eriksson, 1968, 1969). Therefore, in theory, differences found between the rats of these lines could be related to differences in their voluntary alcohol consumption. Consequently, the differences determined in this study may have a role in the variations observed in voluntary alcohol consumption between the alcohol-preferring and alcohol-avoiding rat lines.

Acknowledgments

This study was supported by grants from the Finnish Foundation for Alcohol Studies to J.A.V. Mikkola and from the Yrjö Jahnsson Foundation to P. Hyytiä.

References

Acquas E, Di Chiara G. Depression of mesolimbic dopamine transmission and sensitization to morphine during opiate abstinence. J Neurochem 1992;58(5):1620–5.

Ahtee L, Attila LM. Cerebral monoamine neurotransmitters in opioid withdrawal and dependence. Med Biol 1987;65(2–3):113–9.

Ahtee L, Attila LM, Carlson KR, Haikala H. Changes in brain monoamine metabolism during withdrawal from chronic oral self-administration of morphine and in response to a morphine challenge in the withdrawn state. J Pharmacol Exp Ther 1989;249(1):303–10.

Cadoni C, Di Chiara G. Reciprocal changes in dopamine responsiveness in the nucleus accumbens shell and core and in the dorsal caudate–putamen in rats sensitized to morphine. Neuroscience 1999;90(2):447–55.

de Waele JP, Kiianmaa K, Gianoulakis C. Distribution of the mu and delta opioid binding sites in the brain of the alcohol-preferring AA and alcohol-avoiding ANA lines of rats. J Pharmacol Exp Ther 1995; 275(1):518–27.

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA 1988;85(14):5274–8.

Eriksson K. Genetic selection for voluntary alcohol consumption in the albino rat. Science 1968;159:739–41.

Eriksson K. Factors affecting voluntary alcohol consumption in the albino rat. Ann Zool Fenn 1969;6:227–65.

Haikala H. Use of a novel type of rotating disc electrode and a flow cell with laminar flow pattern for the electrochemical detection of biogenic monoamines and their metabolites after Sephadex gel chromatographic purification and high-performance liquid chromatographic isolation from rat brain. J Neurochem 1987;49(4):1033–41.

Honkanen A, Mikkola J, Korpi ER, Hyytiä P, Seppälä T, Ahtee L. Enhanced morphine- and cocaine-induced behavioral sensitization in alcohol-preferring AA rats. Psychopharmacology 1999a;142(3): 244–52.

Honkanen A, Hyytia P, Korpi ER, Ahtee L. Effects of morphine on metabolism of dopamine and serotonin in brains of alcohol-preferring AA and alcohol-avoiding ANA rats. Alcohol 1999b;18(1):3–10.

Hyytiä P, Sinclair JD. Oral etonitazene and cocaine consumption by AA, ANA and Wistar rats. Psychopharmacology 1993;111(4):409–14.

Kalivas PW, Stewart J. Dopamine transmission in the initiation and expression of drug- and stress-induced sensitization of motor activity. Brain Res Brain Res Rev 1991;16(3):223–44.

Kalivas PW, Widerlov E, Stanley D, Breese G, Prange AJ. Enkephalin action on the mesolimbic system: a dopamine-dependent and a dopamine-independent increase in locomotor activity. J Pharmacol Exp Ther 1983;227(1):229–37.

Kimmel HL, Holtzman SG. Mu opioid agonists potentiate amphetamine- and cocaine-induced rotational behavior in the rat. J Pharmacol Exp Ther 1997;282(2):734–46.

Marinelli PW, Kiianmaa K, Gianoulakis C. Opioid propeptide mRNA content and receptor density in the brains of AA and ANA rats. Life Sci 2000;66(20):1915–27.

Mikkola JAV, Honkanen A, Piepponen TP, Kiianmaa K, Ahtee L. Effects of repeated morphine on cerebral dopamine release and metabolism in AA and ANA rats. Pharmacol, Biochem Behav 2000;67(4):783–91.

Mikkola JAV, Honkanen A, Piepponen TP, Kiianmaa K, Ahtee L. Effects of repeated cocaine treatment on striatal dopamine release in alcohol-preferring AA and alcohol-avoiding ANA rats. Naunyn-Schmiedeberg's Arch Pharmacol 2001a;363(2):209–14.

Mikkola JAV, Honkanen A, Piepponen TP, Kiianmaa K, Ahtee L. Effects of repeated morphine treatment on metabolism of cerebral dopamine and serotonin in alcohol-preferring AA and alcohol-avoiding ANA rats. Alcohol Alcohol 2001b;36(4):286–91.

Paxinos G, Watson C. The rat brain in stereotaxic coordinates. 2nd ed. San Diego: Academic Press, 1986.

Pert A, Sivit C. Neuroanatomical focus for morphine and enkephalin-induced hypermotility. Nature 1977;265(5595):645–7.

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev 1993;18 (3):247–91.

Soini SL, Ovaska T, Honkanen A, Hyytia P, Korpi ER. Brain opioid receptor binding of [^{3}H]CTOP and [^{3}H]naltrindole in alcohol-preferring AA and alcohol-avoiding ANA rats. Alcohol 1998;15(3):227–32.

Soini SL, Honkanen A, Hyytiä P, Korpi ER. [^{3}H]Ethylketocyclazocine binding to brain opioid receptor subtypes in alcohol-preferring AA and alcohol-avoiding ANA rats. Alcohol 1999;18(1):27–34.

Spanagel R, Almeida OF, Shippenberg TS. Long lasting changes in morphine-induced mesolimbic dopamine release after chronic morphine exposure. Synapse 1993;14(3):243–5.

Ungerstedt U, Arbuthnott GW. Quantitative recording of rotational behavior in rats after 6-hydroxy-dopamine lesions of the nigrostriatal dopamine system. Brain Res 1970;24(3):485–93.

Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev 1987;94(4):469–92.