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ORIGINAL INVESTIGATION

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Evidence that mesoaccumbens dopamine and locomotor responses to nicotine in the rat are influenced by pretreatment dose and strain

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Abstract *Rationale*: Sensitisation of the mesoaccumbens dopamine response to nicotine has been implicated in the development of nicotine dependence. This study explored the doses of nicotine that elicit the response in two strains of rats that differ in their baseline levels of activity. *Methods*: Male Sprague-Dawley and Lister hooded rats were pretreated with daily subcutaneous injections of (–)-nicotine for 7 days at doses ranging from 0.03 mg/kg to 0.90 mg/kg. Microdialysis studies were performed on day 9 in conscious freely moving rats, placed in an activity box and challenged with 0.4 mg/kg nicotine. *Results*: The acute administration of nicotine to drug-naive rats stimulated dopamine overflow in the accumbal shell but not the core. Sprague-Dawley rats, pretreated with nicotine (0.03 mg/kg/day and 0.10 mg/kg/day) showed increased basal overflow of dopamine in the accumbal core. Pretreatment with 0.10 mg/kg/day or 0.30 mg/kg/day, but not 0.03 mg/kg/day or 0.90 mg/kg/day, also caused sensitisation of the response to a nicotine challenge on the test day. Sensitisation of the locomotor response to nicotine exhibited a simple dose–response relationship, with the largest sensitisation being observed in animals pretreated with 0.90 mg/kg/day. In Lister hooded rats, pretreatment with nicotine reduced basal dopamine overflow in the accumbal core and did not cause sensitisation to a subsequent challenge with nicotine. *Conclusions*: Sensitisation of the mesoaccumbens dopamine response to nicotine is influenced by pretreatment dose and the strain of rats used. It is not related directly to the expression of sensitised locomotor responses to the drug and, therefore, may be implicated in other psychopharmacological properties of the drug, including dependence.

Keywords Nicotine · Mesoaccumbens dopamine · Sensitisation · Locomotor activity · Rat · Sprague-Dawley · Lister hooded

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Introduction

Nicotine has a psychopharmacological profile that is characteristic of a psychostimulant drug of abuse. Behaviourally, it stimulates the locomotor activity of experimental animals, especially when given repeatedly (Clarke 1990), and can serve as a reinforcer in self-administration experiments (Corrigall and Coen 1989; Donny et al. 1995, 1999). There is convincing evidence that these properties of the drug depend on its ability to stimulate the dopamine (DA)-secreting neurones that project from the ventral tegmental area to the nucleus accumbens (Clarke et al. 1988; Nisell et al. 1994; Balfour et al. 1998; Louis and Clarke 1998).

The nucleus accumbens can be divided into two principal subdivisions, the core and the shell, which are innervated by and project to different areas of the brain (Heimer et al. 1991). The shell of the accumbens is an extension of a limbic structure, the amygdala, whereas the core sends major projections to areas of the brain concerned with the regulation of motor function. The acute administration of drugs of dependence, including nicotine, preferentially enhances DA overflow in the shell of structure (Cadoni and Di Chiara 2000; Cadoni et al. 2000), and it has been suggested that this is the primary response underlying the ability of these drugs to serve as reinforcers in self-administration experiments (Di Chiara 1998, 1999). Pretreatment with psychostimulant drugs of dependence results in sensitisation of their effects on locomotor activity and DA overflow in the accumbens (Kalivas et al. 1993), and it has been proposed that this process is also implicated in the neural

mechanisms underlying dependence (Robinson and Berridge 1993). Recent studies have demonstrated that the mesoaccumbens DA neurones that exhibit sensitisation to psychostimulants are those that project to core of the structure (Cadoni et al. 2000). Studies in this and other laboratories have shown that the DA response to nicotine, measured in the core of the accumbens, is also enhanced in rats that have been pretreated with drug for some days prior to the test day (Benwell and Balfour 1992; Balfour et al. 1998; Cadoni and Di Chiara 2000). In contrast, sensitisation is not observed in the shell of the accumbens of rats exposed to the same pretreatment paradigm (Cadoni and Di Chiara 2000). Thus, the effects of both acute and repeated nicotine on DA overflow in the shell and core the accumbens are consistent with those observed with other psychostimulant drugs of abuse.

The pretreatment paradigm used to elicit sensitised DA responses to nicotine also results in sensitisation of its effects on locomotor activity (Benwell and Balfour 1992; Cadoni and Di Chiara 2000). Other studies in our laboratory, however, have demonstrated a clear dissociation between the expression of sensitised mesoaccumbens DA responses to nicotine and sensitisation of the locomotor response to the drug (Shoaib et al. 1994; Balfour et al. 1996). This has led us and others to suggest that the sensitised DA response to the drug may be implicated in other psychopharmacological properties of the drug more closely related to the development of dependence (Balfour et al. 1998, 2000; Di Chiara 2000). The doses of nicotine that reinforce self-administration exhibit a bell-shaped dose–response relationship, higher doses being too aversive to serve as pharmacological rewards (Corrigall and Coen 1989). The primary objective of this series of experiments was to establish the relationship between pretreatment dose and the expression of sensitised mesoaccumbens DA and locomotor responses to nicotine.

Materials and methods

The experiments were performed on male Sprague-Dawley or Lister hooded rats (Charles River, UK). The animals weighed 300–350 g at the beginning of the experiment and were housed individually in shoebox cages. They were allowed free access to food (standard laboratory chow) and water except when they were in the activity boxes used for the dialysis experiments. The holding room lights were on between 0800 hours and 2000 hours daily. The animals were pretreated with daily subcutaneous injections of L-(–)-nicotine or saline for 7 days. Three hours after the last injection on day 7, the animals were anaesthetised with halothane and dialysis probes (Benwell and Balfour 1992) inserted stereotaxically into the core or the shell of the nucleus accumbens. The coordinates used for the probes located in the core were +1.7 mm in the AP plane and +1.5 mm laterally relative to Bregma and –7.1 mm vertically from the surface of the brain according to the atlas of Paxinos and Watson (1986). The coordinates used for the shell were +1.7 mm in the AP plane, +0.9 mm laterally and –7.1 mm vertically. The positions of the probes are shown diagrammatically in Fig. 1. The rats were left for 48 h to recover from surgery before being transferred to an activity box – 40-cm square with 40-cm high sides. The dialysis probe was connected to a syringe pump which delivered a balanced salt solution (NaCl 146 mM, KCl 4 mM, $CaCl_2$ 2 mM, $MgCl_2$ 1 mM) through a liquid swivel. The animals were left for 2 h to allow the system to equilibrate and the animals to habituate to the test environment before 3×15 dialysate samples were collected for analysis by means of high-performance liquid chromatography (HPLC) with electrochemical detection. The animals were given a control injection of saline and 5 further dialysate samples were collected and analysed. The animals then received a challenge dose of L-(–)-nicotine (0.4 mg/kg s.c.) or D-amphetamine (0.5 mg/g s.c.) and a further 5 samples were collected. During the experiment, the locomotor activity of the rats was monitored using infra-red photobeams arrayed at 13-cm intervals along two sides if the box. Locomotor activity was measured as the movement between the beams. At the end of the experiment, the animals were killed humanely and the position of the probe confirmed histologically in frozen sections. The results for rats in which the probes were found to be lying outside the predetermined coordinates were discarded from the analysis.

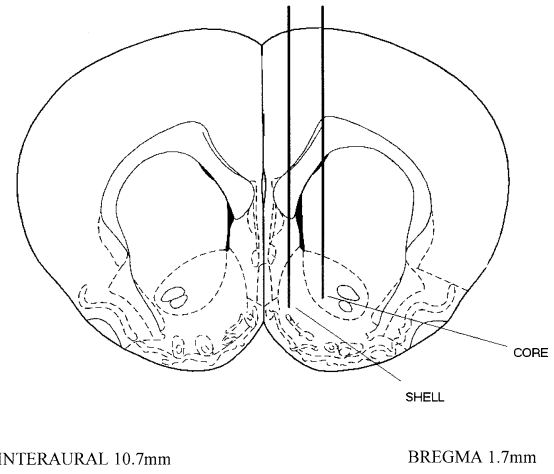

Fig. 1 A diagrammatic representation showing the position of the dialysis probes in the shell and core of the nucleus accumbens. The diagram was adapted from Paxinos and Watson (1996). The *stippled* portion at the tip of the probe illustrates the active dialysis membrane

Data analysis

The data were analysed using analysis of variance (ANOVA). The effects of strain on mean DA overflow were analysed using a two-way ANOVA, with rat strain and brain region as the independent factors. The influence of the drugs administered on the test day were analysed using an ANOVA for repeated measures, with pretreatment prior to the test day, time and the drug given on the test day as the independent factors. When appropriate, post-hoc analyses were performed using the Student's *t*-test (two groups in the experiment) or Duncan's test (more than two groups in the experiment).

Drugs

L-(–)-Nicotine hydrogen tartrate and D-amphetamine sulphate were purchased from Sigma Chemicals. The drugs for injection were dissolved in sterile saline such that the animals received the required dose in a volume of 0.1 ml/100 g. The nicotine solutions were titrated to pH 7.2 with NaOH prior to injection. All doses are expressed as the free base.

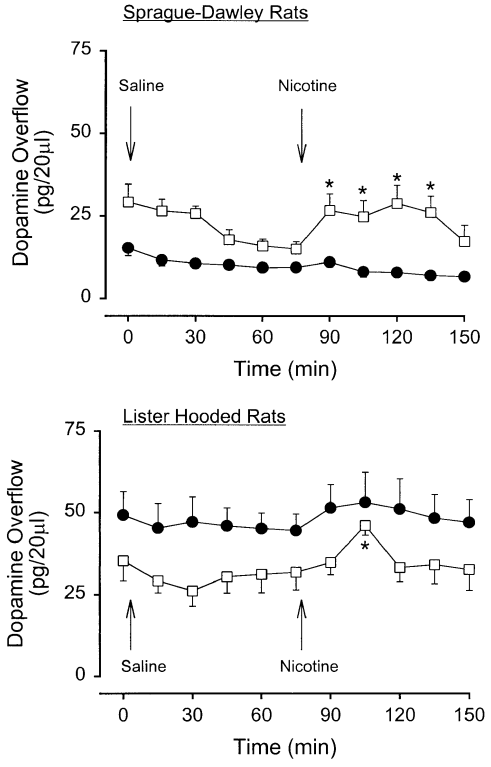

Fig. 2 The effects of nicotine on extracellular dopamine (DA) in the core (*filled circles*) and shell (*open squares*) of the nucleus accumbens of Sprague-Dawley and Lister hooded rats. The animals were challenged with subcutaneous injections of saline and nicotine (0.4 mg/kg) at the *points* indicated by the *arrows*. The results are expressed as mean±SEM of 4–6 observations. The basal extracellular concentrations of DA in the accumbal shell of Sprague-Dawley rats, measured in the first sample collected before the injection of saline, were significantly higher ($P<0.05$) than the concentration found in dialysates of the accumbal core of Sprague-Dawley rats. The mean concentration of DA in this sample, measured in dialysates taken from the core of Lister hooded rats, was significantly higher ($P<0.05$) than the concentration measured in dialysate samples taken from the core of Sprague-Dawley rats. *$P<0.05$ Significantly higher than sample immediately preceding the injection of nicotine

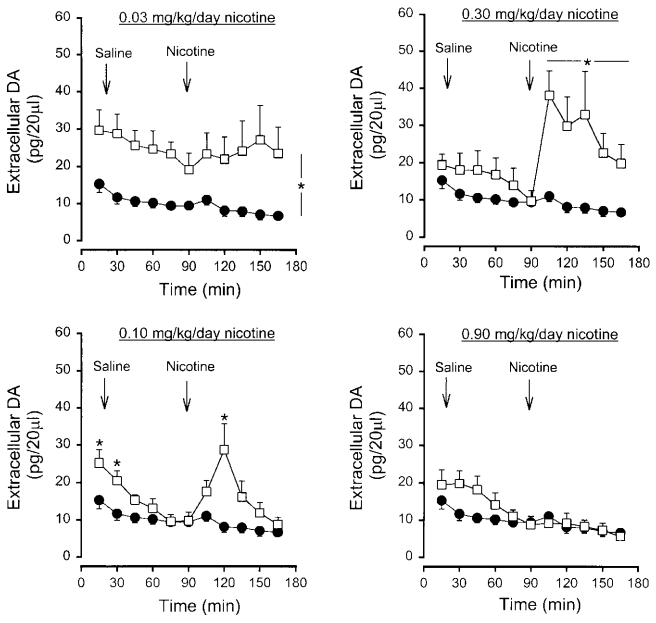

Fig. 3 The influence of nicotine pretreatment on the response to nicotine in the accumbal core of Sprague-Dawley rats. The animals were pretreated with nicotine for 7 days with daily injections of saline (*filled circles*) or nicotine (*open squares*) at the doses indicated at the *top* of each panel. On day 9, the animals were challenged with subcutaneous saline followed by nicotine (0.40 mg/kg) at the *points* indicated by the *arrows*. The results are expressed as mean±SEM of 6 observations. *$P<0.05$ significantly different from saline-pretreated rats

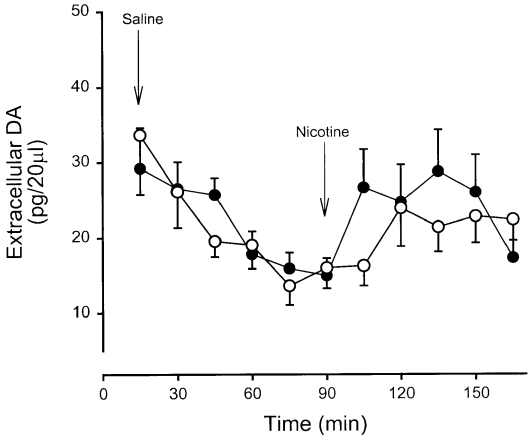

Fig. 4 Sprague-Dawley rats were pretreated for 7 days with daily injections of saline (*filled circles*) or nicotine (0.30 mg/kg/day; *open circles*). On the test day, they were challenged with saline followed by nicotine (0.40 mg/kg) at the *points* indicated by the *arrows*. The results are expressed as mean±SEM of 6 observations

Results

The concentration of DA, measured in dialysate samples of the accumbal shell of Sprague-Dawley rats, taken prior the control injection of saline, was higher ($P<0.05$) than the concentration measured in dialysates of the accumbal core (Fig. 2). The acute administration of nicotine to drug-naive Sprague-Dawley rats increased DA overflow in the shell (drug × time $F_{1,50}=5.14$, $P<0.01$) but not the core of the nucleus accumbens (Fig. 2). When compared with saline-pretreated rats, pretreatment with nicotine for 7 days increased ($F_{4,25}=3.35$, $P<0.05$) the basal overflow of DA in the core of the accumbens measured in the samples collected prior to the injection of nicotine (Fig. 3). Post-hoc analysis indicated that this effect was significant in the rats pretreated with 0.03 mg/kg ($F_{1,10}=13.47$, $P<0.01$) or 0.10 mg/kg (pretreatment × time $F_{4,40}=3.97$, $P<0.01$). The effect of pretreatment with 0.30 mg/kg nicotine approached significance ($F_{4,40}=2.30$, $P=0.075$). The administration of a nicotine injection on the test day stimulated DA overflow in the accumbal core (drug × pretreatment $F_{4,25}=5.24$, $P<0.01$). Post-hoc analysis indicated that pretreatment with nicotine caused sensitisation of the re-

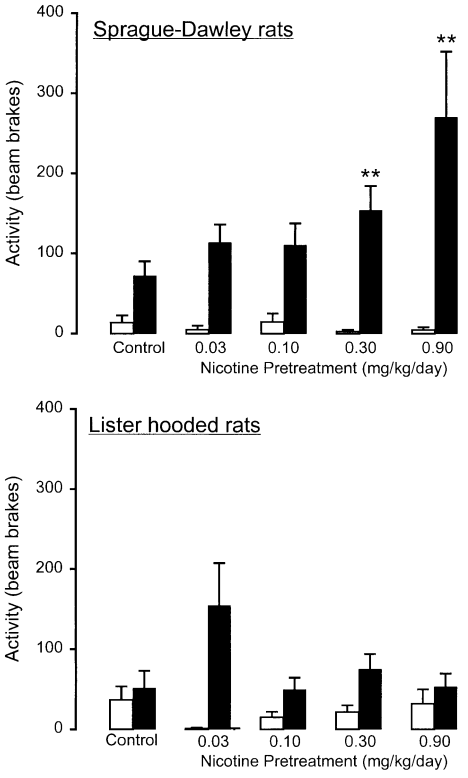

Fig. 5 The locomotor activity of Sprague-Dawley (*top panel*) and Lister hooded (*bottom panel*) rats was measured in the 20 min following an injection of saline (*open columns*) or nicotine (0.40 mg/kg; *filled columns*) in rats pretreated with daily injections of saline or nicotine. The results are presented as photobeam crossings and are expressed as mean±SEM of 4–6 observations. ***P*<0.01 significantly different from saline-pretreated rats

sponse to the drug that was significant for rats pretreated with 0.10 mg/kg/day (drug challenge × pretreatment × time $F_{4,40}$=3.38, P<0.05) or 0.30 mg/kg/day nicotine (drug challenge × pretreatment $F_{1,10}$=12.36, P<0.01) This response was not observed in the animals pretreated with nicotine at doses of 0.03 mg/kg/day or 0.90 mg/kg/day, although the increase in basal DA overflow, observed prior to the nicotine challenge in the rats pretreated with 0.03 mg/kg nicotine, was maintained after the nicotine injection on the test day. Pretreatment with nicotine (0.3 mg/kg per day for 7 days) had no significant effect on the basal extracellular DA concentration in the shell of the accumbens (Fig. 4). Pretreatment also had no significant effect on the response to a challenge dose of nicotine on the test day.

The administration of nicotine on the test day stimulated the locomotor activity of Sprague-Dawley rats when compared with the response to saline ($F_{1,24}$=58.54, P<0.001; Fig. 5). Pretreatment with nicotine resulted in sensitisation of the response (pretreatment × drug $F_{4,24}$=3.70, P<0.05). Unlike the DA response in the accumbal core, the greatest response was observed in the rats pretreated with the highest dose of nicotine (0.9 mg/kg/day) used in the pretreatment regimen.

Unlike the results for Sprague-Dawley rats, the extracellular DA concentration in dialysates of the accumbal shell of Lister hooded rats tended to be lower than the concentration in dialysates of the core, although this difference did not approach statistical significance. Thus, when compared with Sprague-Dawley rats, basal levels of extracellular DA were higher (P<0.01) in the core, but not the shell of the accumbens of the Lister hooded animals (strain × brain region $F_{1,26}$=4.86, P<0.05; Fig. 2). Acute injections of nicotine (0.4 mg/kg) to drug-naive Lister hooded rats also stimulated DA overflow in the shell ($F_{1,12}$=19.35, P<0.01), but not the core, of the nu-

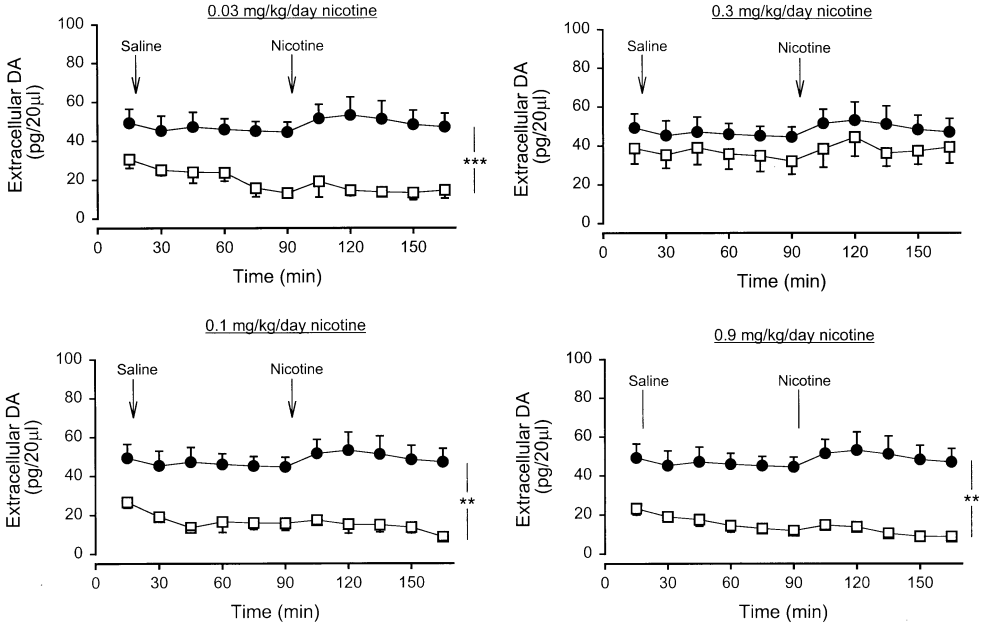

Fig. 6 The influence of nicotine pretreatment on the response to nicotine in the accumbal core of Lister hooded rats. The animals were pretreated with nicotine for 7 days with daily injections of saline (*filled circles*) or nicotine (*open squares*) at the doses indicated at the *top* of each panel. On day 9, the animals were challenged with subcutaneous saline followed by nicotine (0.40 mg/kg) at the *points* indicated by the *arrows*. The results are expressed as mean±SEM of 6 observations. ***P*<0.01, ****P*<0.001 significantly different from saline-pretreated rats

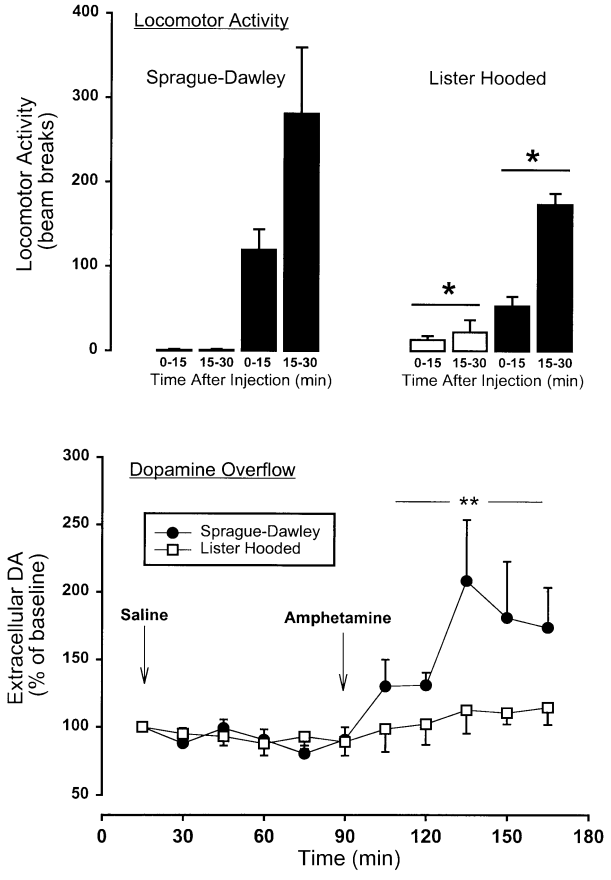

Fig. 7 The effects of D-amphetamine (0.5 mg/kg) on locomotor activity (*top panel*) and dopamine overflow in the accumbal core of Sprague-Dawley and Lister hooded rats. The results are expressed as the mean±SEM of 6 observations. The results in the *top panel* are presented as photobeam crossings for 2×15-min subtrials following a subcutaneous injection of saline (*open columns*) and D-amphetamine (*filled columns*). The results in the *bottom panel* show the changes in dopamine overflow, expressed as a percentage of the dialysate concentration measured immediately prior to the injection, in animals challenged with subcutaneous saline and D-amphetamine (0.50 mg/kg) at the points indicated by the *arrows*. The basal overflow values of DA in the sample prior to the saline injection was 24.4±8.1 pg/20 µl for Sprague Dawley rats and 30.4±8.5 pg/20 µl for Lister hooded rats. *P<0.05, **P<0.01 significantly different to the response in Sprague-Dawley rats

cleus accumbens, although the effect was less sustained than that measured in Sprague-Dawley rats treated in the same way (Fig. 2). When compared with Sprague-Dawley rats, the Lister hooded rats challenged with saline had higher basal levels of locomotor activity ($F_{1,41}$=5.83, P<0.05; Fig. 5). As with the Sprague-Dawley rats, a nicotine challenge on the test day increased ($F_{1,15}$=12.02, P<0.01) locomotor activity. This response, however, was not enhanced significantly by pretreatment with nicotine prior to the test day.

In marked contrast to the effects observed in the Sprague-Dawley rats, pretreatment with nicotine decreased ($F_{4,21}$=7.35, P<0.01) the basal extracellular levels of DA in the core of the nucleus accumbens (Fig. 6). Post-hoc analysis for the individual pretreatment doses showed that the effect was significant for rats pretreated with 0.03 ($F_{1,10}$=19.6, P<0.001), 0.10 ($F_{1,8}$=13.6, P<0.01) or 0.90 ($F_{1,8}$=16.4, P<0.01), but not 0.30 mg/kg/day nicotine. In all cases, the reduction was sustained throughout the period of the experiment and was not reversed by an injection of nicotine. Additionally, there was no evidence that pretreatment with nicotine, at any of the doses tested, resulted in sensitisation of its effects on DA overflow in the accumbal core of the Lister hooded rats.

The acute administration of D-amphetamine (0.5 mg/kg s.c.) increased the activity ($F_{1,8}$=87.23, P<0.001) of both strains of rats (Fig. 7). However, the response in Sprague-Dawley rats was significantly greater (drug × strain $F_{1,8}$=10.95, P<0.05) than that observed in the Lister hooded animals. The amphetamine injections also increased the overflow of DA in the nucleus accumbens core ($F_{1,8}$=28.50, P<0.001; Fig. 7). Again, however, the increment in DA overflow in the Sprague-Dawley rats was significantly greater (drug × strain $F_{1,8}$=11.78, P<0.01) than that observed in the Lister hooded animals.

Discussion

The results of the present study have confirmed the results of previous experiments in this laboratory (Benwell and Balfour 1992; Balfour et al. 1998; Birrell and Balfour 1998) which showed that prior treatment with daily injections of nicotine resulted in sensitisation of its stimulatory effects on DA overflow in the core of the nucleus accumbens. They have also confirmed the results of the recent study by Cadoni and Di Chiara (2000) which demonstrated that the sensitisation was restricted to the core of the structure and was not observed in the accumbal shell. This extends previous observations from this laboratory that suggested that sensitisation of the DA response to nicotine is also not seen in the dorsal striatum of nicotine-pretreated rats (Benwell and Balfour 1997). The study, however, has also revealed that the effects of nicotine pretreatment are complex and influenced by the dose of nicotine used during the pretreatment phase of the experiment and the strain of animals used for the investigation. In Sprague-Dawley rats, pretreatment with nicotine resulted in an increase in the basal extracellular levels of DA that was significant for the rats pretreated with the lower doses investigated. The mechanism underlying this effect remains to be determined, although previous studies in this laboratory suggest that, under similar test conditions, pretreatment with nicotine may diminish the control of the neurones, which project to the core of the accumbens, by inhibitory autoreceptors (Balfour et al. 1998). It seems reasonable to suggest that this may contribute to the mechanism underlying the response. Its putative psychopharmacological consequences have not been explored further in this study. It should be remembered, however, that the measurements were made in rats tested in a novel environ-

ment and may, therefore, reflect an effect of nicotine pretreatment on DA overflow in the accumbal core of rats exposed to a novel stimulus.

Sensitised DA responses were observed in Sprague-Dawley rats pretreated with nicotine at doses of 0.10 mg/kg/day or 0.30 mg/kg/day, but not in animals treated with 0.03 mg/kg/day or 0.90 mg/kg/day. In contrast, the peak locomotor response was observed in the rats pretreated with this high dose of nicotine. These data are consistent with the results of previous experiments in this laboratory which have revealed a dissociation between the expression of sensitised DA responses to nicotine in the core of the accumbens and the expression of sensitised locomotor responses to the drug that are often also observed in nicotine-pretreated rats (Shoaib et al. 1994; Balfour et al. 1996; Birrell and Balfour 1998). It seems reasonable to suggest, therefore, that the sensitised DA response may be implicated in the expression of other psychopharmacological properties of nicotine, including its potential to cause dependence (Balfour et al. 1998, 2000). This conclusion is consistent with recent evidence that repetitive administration of psychostimulant drugs of abuse, including nicotine, results in a selective sensitisation of the DA projections to the core of the accumbens (Cadoni and Di Chiara 2000). This effect has been implicated in development of classically conditioned 'habit responding' for the drugs that underlies the transition to dependence (Di Chiara 1999, 2000). Corrigall and Coen (1989) showed that the doses of nicotine that reinforce self-administration also exhibit a bell-shaped dose–response relationship and concluded that higher doses of the drug may not be reinforcing because its aversive properties become predominant at these doses. This conclusion is supported by results which show that higher doses of nicotine are anxiogenic (File et al. 1998; Ouagazzal et al. 1999). It may be relevant, therefore, that the doses of nicotine that elicit sensitisation are similar to those self-administered by rats during the first hour of access to nicotine (Shoaib and Stolerman 1999). Thus, the data are consistent with the possibility that sensitisation of DA overflow occurs in response to doses of nicotine at which its rewarding effects predominate but not in response to doses that are predominantly aversive.

This study has also revealed an interesting strain difference in the effects of repeated nicotine on DA overflow in the core of the accumbens. Lister hooded rats, exposed to the same pretreatment regime as the Sprague-Dawley rats, had reduced basal overflows of DA and did not exhibit a sensitised DA response to the drug. Additionally, the acute effects of nicotine on DA overflow in the accumbal shell of Lister hooded rats seemed to be blunted when compared with the response in the accumbal shell of Sprague-Dawley rats. There are a number of explanations for the differences observed. It is possible that the two strains metabolise nicotine at significantly different rates and, as a result, the dosing regimen employed did not result in similar plasma nicotine concentrations in the two strains. Preliminary, unpublished results from our laboratory suggest that this is unlikely to be the case. The results presented here showed that, in control animals, basal DA overflow in the core was significantly higher in Lister hooded rats and that their basal levels of locomotor activity were also higher. Additionally, Lister hooded rats also showed a blunted response to D-amphetamine when compared with Sprague-Dawley rats. Thus, it is possible that the differences in the responses to acute D-amphetamine and repeated nicotine reflect strain differences in the mesolimbic DA responses to these drugs that may be related to an increased intrinsic basal tone in the pathway.

The data presented reflect the results of a study in which the rats were tested in a novel environment following only 7 days of pretreatment. Therefore, the differences observed may simply reflect differences in the period of pretreatment required to elicit the sensitised responses. Nevertheless, the results suggest that the two strains used for the experiments respond differentially to the pretreatment regime employed for this study. Thus, they may provide a valuable resource for investigating the neurobiology underlying differences in susceptibility to nicotine dependence. Shoaib and colleagues (1997) have reported significant strain differences in the acquisition of nicotine self-administration and the effects of nicotine pretreatment on the rate at which animals acquire the response. In their study, nicotine pretreatment seemed to facilitate acquisition of nicotine self-administration in Sprague-Dawley rats. Lister hooded rats were not investigated, but in another hooded strain (Long Evans) nicotine pretreatment seemed to impair acquisition of the response although this was not significant. Future studies might usefully explore further the putative relationship between acquisition of responding for nicotine and the influence of repetitive nicotine on DA overflow in the accumbal core.

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