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Psychostimulant sensitization: differential changes in accumbal shell and core dopamine

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Abstract

The nucleus accumbens has been subdivided into a shell and a core compartment on the basis of histochemical and connectional differences. Recently, we reported that behavioral sensitization to morphine is associated with an increased dopamine transmission in the caudate-putamen and in the nucleus accumbens core as well as a decreased response in the nucleus accumbens shell following acute morphine challenge. We have now performed a similar study in rats sensitized to amphetamine and to cocaine. Behavioral sensitization was induced by daily administration of a single dose of 1 mg/kg s.c. of amphetamine for 10 days or of 10 mg/kg i.p. of cocaine twice a day for 14 days. Microdialysis was performed 10–14 days after the last injection of amphetamine and 7–10 days after the last injection of cocaine. Both schedules resulted in robust behavioral sensitization in response to challenge with 0.25 and 0.5 mg/kg of amphetamine and to 5 and 10 mg/kg of cocaine, respectively. Subjects pre-exposed to amphetamine showed a sensitization of dopamine transmission in the nucleus accumbens core but not in the nucleus accumbens shell. Subjects pre-exposed to cocaine showed sensitization of dopamine transmission in the core only to the lower dose of cocaine. In the shell no change was observed after the lower dose of cocaine while a significant reduction of the dopamine response was observed after the higher dose. These results suggest that behavioral sensitization might result from reciprocal changes in the response of nucleus accumbens dopamine in the shell and in the core to drug challenge.

Keywords: Psychostimulants sensitization; Cocaine; Amphetamine; Nucleus accumbens shell; Nucleus accumbens core

1. Introduction

Repeated response-contingent and non-contigent exposure to psychostimulants is known to induce a sensitization to their behavioral stimulant effects (Segal and Mandell, 1974; Post, 1980; De Wit and Stewart, 1981; Segal and Shuckit, 1983; Robinson and Becker, 1986; Kalivas and Stewart, 1991; Hooks et al., 1994) . Psychostimulants acutely increase extracellular dopamine in terminal dopamine fields by an action on the dopamine transporter and this action is thought to mediate the motor stimulant and reinforcing properties of those drugs (Kelley and Iversen, 1975; Koob et al., 1981; Bozarth, 1986; Wise and Bozarth, 1987; Koob, 1992). Given this, it is not surprising that the mechanism of behavioral sensitization has been primarily searched at the level of the dopamine system.

Interest into the mechanism of behavioral sensitization derives from the role that has been attributed to this phenomenon in the development of psychomotor stimulant-induced psychosis and in the mechanism of drug addiction and craving (Post and Contel, 1983; Segal and Shuckit, 1983, Robinson and Berridge, 1993; Stewart and Badiani, 1993). Thus evidence has been provided that behavioral sensitization to psychostimulants, as well as to opiates, is associated with presynaptic sensitization of dopamine transmission (Kalivas and Stewart, 1991). This notion, however, is debated mainly on the basis of lack of correlation between the time-course of changes in the responsiveness of dopamine transmission, as estimated from the extracellular dopamine concentration in the nucleus accumbens and in the caudate-putamen and behavioral sensitization (see Di Chiara, 1995 for discussion).

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Thus, for about 1 week following interruption of psychostimulant treatment, behavioral sensitization can take place in the absence of any presynaptic sensitization of dopamine transmission. Biochemical sensitization is therefore observed after one and more commonly after two weeks from drug treatment (Robinson et al., 1988; Akimoto et al., 1989, 1990; Kalivas and Stewart, 1991; Segal and Kuczensky, 1992a,b; Paulson and Robinson, 1995). Existing studies have focused mainly on dopamine transmission in the caudate-putamen and in the nucleus accumbens but few have examined the relation between behavioral sensitization and changes in dopamine transmission in the two subdivisions of the nucleus accumbens shell and core (Pierce and Kalivas, 1995). These subdivisions appear not only anatomically (Heimer et al., 1991a,b) but also functionally distinct as they show a different resposiveness to conventional rewards and to drugs of abuse (Pontieri et al., 1995, 1996; Bassareo and Di Chiara, 1999).

We have recently reported that behavioral sensitization to morphine is associated with an increase of dopamine transmission in response to morphine in the dorsal caudate-putamen and in the nucleus accumbens core but not in the shell where dopamine responsiveness is actually reduced (Cadoni and Di Chiara, 1999). In the present study we have investigated the changes of dopamine transmission in the shell and in the core of the rat nucleus accumbens associated with behavioral sensitization to amphetamine and cocaine. Protocols for inducing behavioral sensitization to amphetamine and to cocaine were taken from previous studies (Wolf et al., 1993; Henry and White, 1995). Dialysis probes, one aimed at the shell and the other at the core of the nucleus accumbens were implanted 10–14 days after amphetamine exposure and 7–10 days after cocaine exposure which correspond to one of the time at which it is observed the greatest behavioral sensitization, according to previous study (Henry and White, 1995). The effect of challenge with two different doses of amphetamine and cocaine on behavior and dialysate dopamine was investigated.

2. Materials and methods

2.1. Animals and treatment protocol

Male Sprague–Dawley rats (Charles River, Calco, Italy) of 125–150 g at the beginning of the treatment were housed in groups of three per cage, with food and water ad libitum, under an artificial 12 h light–dark cycle and standard conditions of temperature and umidity. After 3–4 days, rats were administered subcutaneously once a day for ten days (on days 1 to 5 and 8 to 12) with 1 mg/kg of amphetamine sulphate or administered intraperitoneally twice a day (10:00 and 18:00) for 14 days with 10 mg/kg of cocaine hydrochloride. Control rats for each group were injected with an equivalent volume of saline. Rats were taken from their home cages, injected and returned immediately to the cage.

All animal experimentations have been conducted in accordance with the guidelines for care and use of experimental animals of the European Communities Directive (86/609/EEC; D.L.: 27.01.1992, No. 116).

2.2. Surgery

After 10 to 14 days from the last injection of amphetamine and after 7 to 10 days from the last injection of cocaine the animals were implanted, under chloral hydrate anaesthesia (400 mg/kg i.p.) with vertical concentric dialysis probe, prepared essentially according to the method of Di Chiara et al. (1993) as modified by Tanda et al. (1996). The length of the dialysing area was of 1.5 mm. Each rat was implanted with two probes, one at the level of the nucleus accumbens shell (A = 2.2 L = 1.2 from bregma, V = 7.9 from dura), and the other at the level of the core (A = 1.6 L = 1.8 from bregma, V = 7.7 from dura) according to the atlas of Paxinos and Watson (1987).

2.3. Analytical procedure

On the day following surgery the rats, transferred from the day before in a hemispherical cage, were connected to an infusion pump and perfused with a Ringer's solution (NaCl 147 mM, KCl 4 mM, $CaCl_2$ 2.2 mM) at a constant flow rate of 1 μl/min. Dialysate samples (20 μl) were taken every 20 min and injected into an high performance liquid chromatograph (HPLC) equipped with a reverse phase ODS column (LC-18 DB, 15 cm, 5 μm particle size, Supelco, Bellefonte, PA, USA) and a coulometric detector (ESA, Coulochem II, Bedford, MA, USA) in order to quantitate DA. The first electrode of the detector was set at +75 mV (oxidation) and the second at −125 mV (reduction). The composition of the mobile phase was 50 mM NaH_2PO_4, 0.1 mM Na_2–EDTA, 0.5 mM *n*-octyl sodium sulfate and 15% methanol; pH was adjusted to 5.5. The sensitivity of the assay for DA was 2 fmol/sample.

2.4. Behavior

To analyse behavioral responses to drug treatments during the dialysis experiments and following the challenge with amphetamine and cocaine, the animals were videotaped and two behavioral categories were distinguished: a *non-stereotyped activity*, i.e., a pattern of normal exploratory behavior including forward locomotion, sniffing upward, grooming and rearing and a *stereotyped activity*, i.e., a behavioral pattern confined to a restricted area of the cage not directed to any specific goal including

confined gnawing, sniffing and licking. The behavior was evaluated by an observer unaware of the treatment the animals received. The percentage of time spent by the rat performing each behavior was recorded, throughout the test session, for 3 h following amphetamine challenge and for 2 h after cocaine.

2.5. Histology

At the end of the experiment, rats were transcardially perfused with 50 ml saline and 50 ml of a 10% formaldehyde solution. The probes were removed and brains were cut by Vibratome in serial coronal slices of 100 μm oriented according to the atlas of Paxinos and Watson (1987). In this manner the location of the probes was reconstructed and referred to the atlas of Paxinos and Watson. Fig. 1 shows the location of the probes in the nucleus accumbens shell and core of the animals sensitized to amphetamine and cocaine and of control animals.

2.6. Materials

Amphetamine sulphate (0.25 and 0.5 mg/kg calculated as salt, Sigma, Milan, Italy) and cocaine HCl (5 and 10 mg/kg i.p. calculated as salt, S.A.L.A.R.S., Italy) were dissolved in saline and injected, respectively subcutaneously in a volume of 1 ml/kg of body weight and intraperitoneally in a volume of 3 ml/kg of body weight.

2.7. Statistics

Difference in behavioral scores and in the levels of extracellular DA between groups were assessed by two way analysis of variance (ANOVA) for repeated measures. Results showing significant overall changes were subjected to post-hoc Tukey's test with significance for $P < 0.05$. Basal values were the means of three consecutive samples differing by no more than 10%. The data were expressed

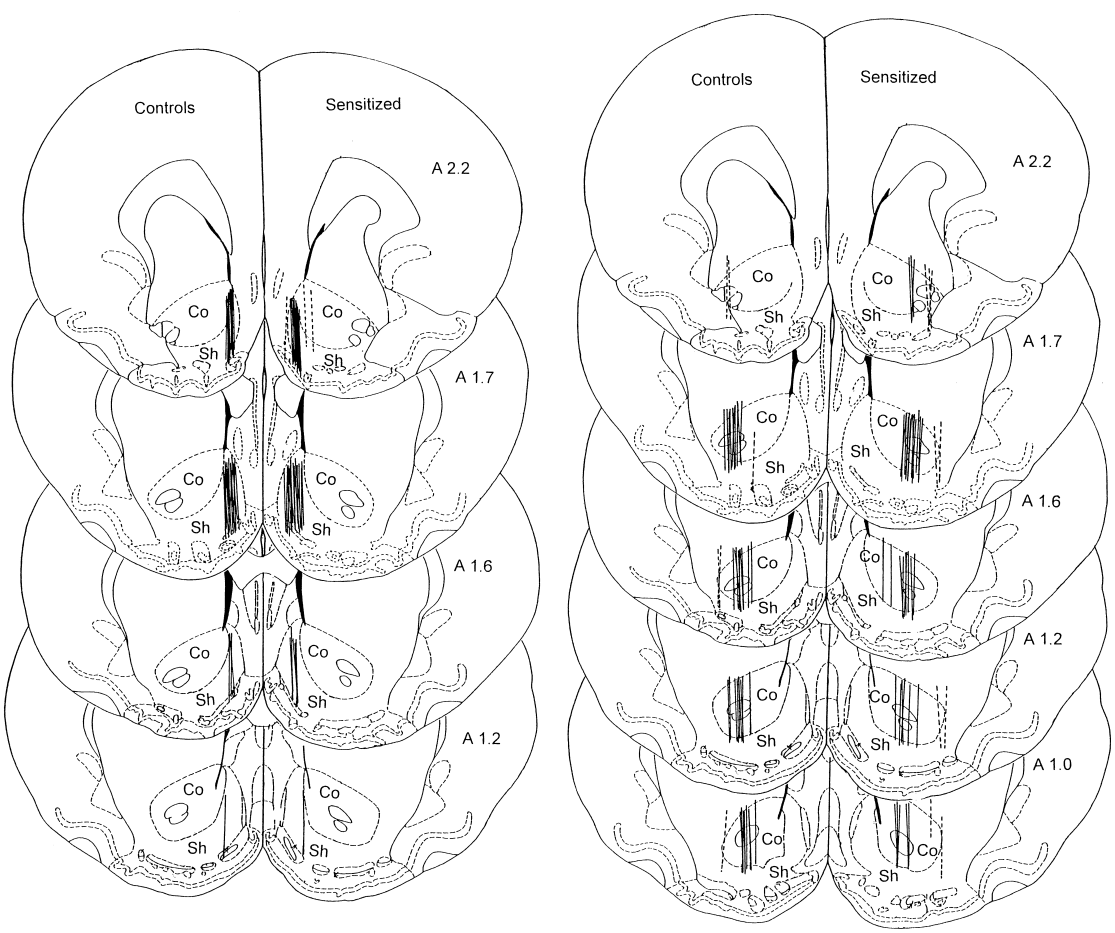

Fig. 1. Location of the dialysis probes (dialysing portion) within the nucleus accumbens shell (left drawings) and core (right drawings) of controls and sensitized animals utilized in the present study. Although the probes aimed to the shell where always implanted in both groups on the left side of the brain and the probes aimed to the core on the right side in this drawings the probes of the sensitized group are represented in the contralateral emisphere for clarity of comparison. The numbers in each forebrain section (redrawn from Paxinos and Watson, 1987) indicate millimeters anterior from bregma. Stippled lines refer to probes not correctly placed and therefore animals not included in the statistical analysis. Sh, Co shell and core of the nucleus accumbens.

as percentage of basal values. The data from animals with incorrect placement of the dialysis probes were excluded.

3. Results

3.1. Behavior

After 10 to 14 days from the last injection of amphetamine, challenge with 0.25 and 0.5 mg/kg of amphetamine produced a more pronounced behavioral stimulation in amphetamine-pretreated animals as compared to saline controls (Fig. 2). In control animals the dose of 0.25 mg/kg of amphetamine (Fig. 2A and B) induced a short lasting behavioral activation characterized mainly by exploratory behavior (sniffing upward and short lasting spells of locomotion). The same dose produced in amphetamine-pretreated rats a longer and more pronounced locomotor stimulation ($F(5,78) = 2.82$, $P < 0.05$) associated with spells of stereotyped activity (confined sniffing directed to the floor) ($F(5,78) = 4.29$, $P < 0.01$). A dose of 0.5 mg/kg of amphetamine potentiated non-stereotyped activity ($F(8,198) = 5.85$, $P < 0.001$) in amphetamine-pretreated animals and elicited a stereotyped activity otherwise absent in control animals ($F(5,132) = 6.15$, $P < 0.0001$), (Fig. 2C and D)).

Fig. 3 shows the effect of 5 and 10 mg/kg i.p. of cocaine 7–10 days after the last injection in control and cocaine-pretreated animals. The dose of 5 mg/kg of cocaine (Fig. 3A and B) produced in control rats only a short lasting arousal with sniffing upward while a marked hypermotility and rearing ($F(5,90) = 10.25$, $P < 0.0001$) interrupted by downward sniffing ($F(5,90) = 12.18$, $P < 0.0001$) was observed after the same dose in cocaine-pretreated rats. After the dose of 10 mg/kg of cocaine (Fig. 3C and D) behavioral activation was further increased in sensitized animals as compared to controls ($F(5,90) = 2.14$, $P < 0.05$) particularly in the form of confined sniffing ($F(5,90) = 5.03$, $P < 0.001$).

3.2. Microdialysis

Challenge with 0.25 and 0.5 mg/kg s.c of amphetamine produced a significant increase of dialysate dopamine from the shell and from the core of animal pretreated with amphetamine or saline (Fig. 4). While there was no significant difference in the increase of extracellular dopamine in nucleus accumbens shell (Fig. 4A and C) of the two groups (amphetamine 0.25 mg/kg: $F(9,117) = 0.64$, $P > 0.05$; amphetamine 0.5 mg/kg: $F(9,225) = 1.12$, $P > 0.05$) animals behaviorally sensitized to amphetamine showed a greater increase in the nucleus accumbens core (Fig. 4B and D) compared to controls (amphetamine 0.25 mg/kg: $F(9,117) = 4.71$, $P < 0.0001$; amphetamine 0.5 mg/kg: $F(9,243) = 4.10$, $P < 0.0001$). Post hoc comparisons revealed a significant difference at 20 and 40 min (Tukey's test $P < 0.05$).

Fig. 5 shows the effect of 5 and 10 mg/kg of cocaine on dialysates from the nucleus accumbens shell and core of control animals and of animals behaviorally sensitized to cocaine. Both doses of cocaine significantly increased the extracellular concentrations of dopamine in the shell and in the core of both groups. In the nucleus accumbens shell while at the dose of 5 mg/kg (Fig. 5A) there was no significant difference between groups ($F(6,133) = 0.13$,

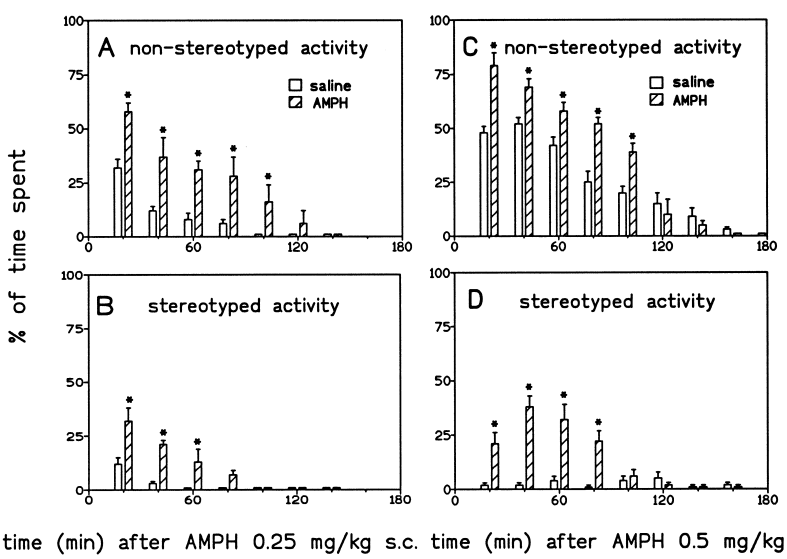

Fig. 2. Behavioral effects induced in control animals (unfilled bars) and in animals sensitized to amphetamine (AMPH) (hatched bars) by challenge with 0.25 mg/kg s.c. (A and B) and 0.5 mg/kg s.c. (C and D) of amphetamine (see Materials and Methods for details). The results are expressed as means ± S.E.M. of the percentage of time spent performing each behavioral item. $^*P < 0.05$ by Tukey's test versus the correspondent value of the control. The time points at which the sum of the percentage spent in the different behavioral items is not 100, the difference has to be referred to sedation or no activity.

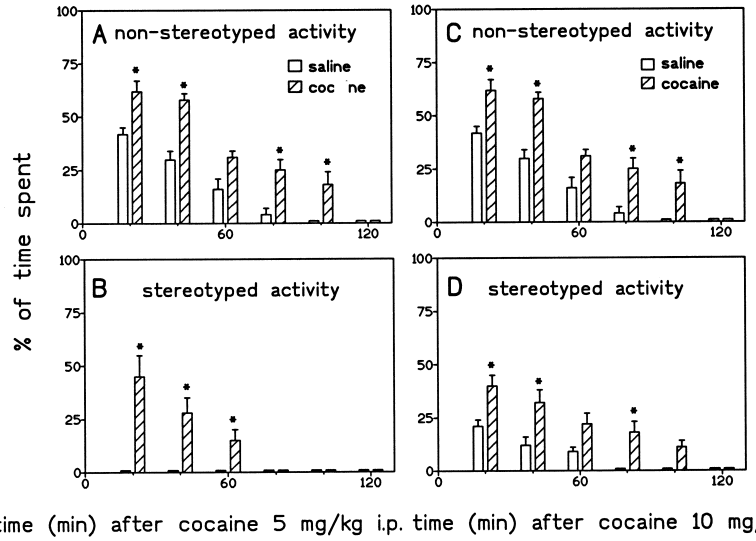

Fig. 3. Behavioral effects induced in control animals (unfilled bars) and in animals sensitized to cocaine (hatched bars) by challenge with 5 mg/kg i.p. (A and B) and 10 mg/kg i.p. (C and D) of cocaine (see Materials and Methods for details). The results are expressed as means ± S.E.M. of the percentage of time spent performing each behavioral item. * $P < 0.05$ by Tukey's test versus the correspondent value of the control. The time points at which the sum of the percentage spent in the different behavioral items is not 100, the difference has to be referred to sedation or no activity.

$P > 0.05$) at the dose of 10 mg/kg Fig. 5C a significant difference was observed ($F(6,111) = 2.19$, $P < 0.05$). Post hoc comparison of the data showed a significant decrease at 20 min (Tukey's test $P < 0.05$) in the sensitized group compared to controls. In the nucleus accumbens core a significant effect of group was obtained in response to 5 mg/kg of cocaine (Fig. 5B) ($F(1,131) = 11.36$, $P < 0.005$) but no significant timexgroup interaction ($F(6,119) = 0.74$,

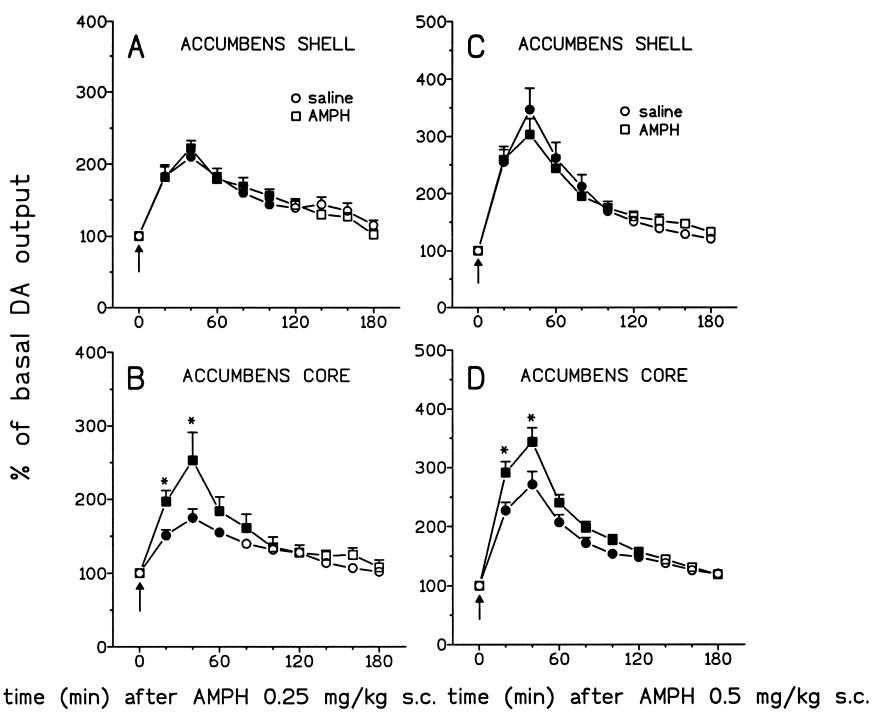

Fig. 4. Effect of challenge with 0.25 mg/kg s.c. and 0.5 mg/kg s.c. of amphetamine (AMPH) on basal DA output in dialysates from the nucleus accumbens shell (A and C) and core (B and D) of control animals (circles) and animals sensitized to amphetamine (squares). Basal values of controls ($n = 23$) and sensitized rats ($n = 21$) were, respectively: *shell* 100 ± 15 and 123 ± 13 fmoles/sample (no significant difference between groups $F(1,42) = 1.32$ $P > 0.05$); *core* 128 ± 11 and 137 ± 15 fmoles/sample (no significant difference between groups $F(1,42) = 0.24$ $P > 0.05$). The results (means ± S.E.M.) are expressed as percent of basal values. Filled symbols represent points significant different ($P < 0.05$) from respective basal values by two way ANOVA followed by Tukey's test. * $P < 0.05$ versus the corresponding time point of the control group by two way ANOVA followed by Tukey's test. For statistical analysis between groups see Results.

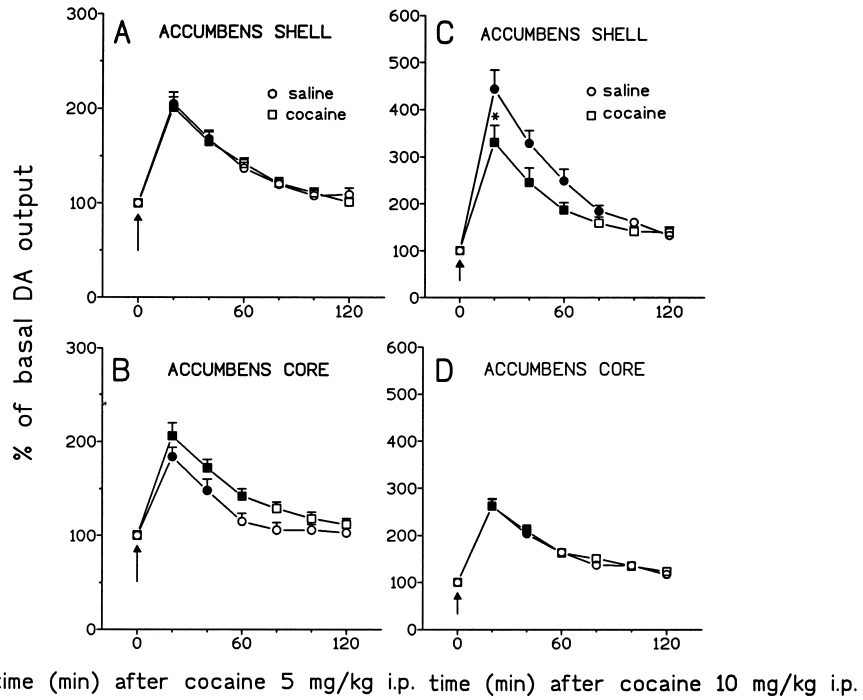

Fig. 5. Effect of challenge with 5 mg/kg i.p. and 10 mg/kg i.p. of cocaine on basal DA output in dialysates from the nucleus accumbens shell (A and C) and core (B and D) of control animals (circles) and animals sensitized to cocaine (squares). Basal values of controls ($n = 16$) and sensitized rats ($n = 23$) were respectively: *shell* 93 ± 11 and 104 ± 9 fmoles/sample (no significant difference between groups $F(1,37) = 0.60$, $P > 0.05$); *core* 152 ± 19 and 147 ± 12 fmoles/sample sample (no significant difference between groups $F(1,37) = 0.05$, $P > 0.05$). The results (means $\pm$ S.E.M.) are expressed as percent of basal values. Filled symbols represent points significant different ($P < 0.05$) from respective basal values by two way ANOVA followed by Tukey's test. $^{*}P < 0.05$ versus the corresponding time point of the control group by two way ANOVA followed by Tukey's test. For statistical analysis between groups see Results.

$P > 0.05$), while no significant effect of group ($F(1,117) = 0.50$, $P > 0.05$) and time $\times$ group interaction ($F(6,105) = 0.18$, $P > 0.05$) was obtained in response to 10 mg/kg of cocaine (Fig. 5D). Post hoc analysis of the data after challenge with 5 mg/kg of cocaine revealed a greater increase in extracellular dopamine in the nucleus accumbens core of animals sensitized to cocaine (Tukey's test $P < 0.05$).

4. Discussion

The present results show that the responsiveness of the nucleus accumbens dopamine undergoes reciprocal changes in the shell and in the core of rats behaviorally sensitized to amphetamine and cocaine. While dopamine responsiveness in the nucleus accumbens core was increased in rats sensitized to amphetamine, dopamine responsiveness in the shell was reduced in rats sensitized to cocaine. The observation of an increased response to the drug in the nucleus accumbens core of amphetamine sensitized rats is in agreement with previous studies (Robinson et al., 1988; Wolf et al., 1993; Paulson and Robinson, 1995) and is consistent with the location of the probes in the nucleus accumbens as deduced from direct examination of the drawings reported in these studies. One study, however, (Pierce and Kalivas, 1995) reports a preferential increase of dopamine in the shell compared to the core after amphetamine in rats sensitized to cocaine. However, in this study amphetamine was microinjected in the nucleus accumbens which makes it difficult to compare these results with ours obtained after systemic administrations of amphetamine. Sensitization of dopamine transmission in the nucleus accumbens core is consistent with our previous results obtained in a model of opiate sensitization (Cadoni and Di Chiara, 1999).

Behavioral sensitization to cocaine also appears to be associated with a sensitization of dopamine transmission in the core upon challenge with a dose of 5 mg/kg; however, upon challenge with 10 mg/kg of cocaine the response in the shell of the nucleus accumbens was reduced but no differences were obtained in the nucleus accumbens core. These results might account for the inconsistencies in the relationship between dopamine transmission in the nucleus accumbens and behavioral sensitization to cocaine reported in the literature (Segal and Kuczensky, 1992b; Kalivas and Duffy, 1993; Hooks et al., 1994; Meil et al., 1995; Heidbreder et al., 1996; Neisewander et al., 1996). Such inconsistencies might be in part related to the interval between the last exposure to cocaine and the testing of sensitization. Thus, studies reporting a sensitization of dopamine transmission to cocaine utilized long (more than 14 days) intervals (Kalivas and Duffy, 1993; Hooks et al., 1994; Heidbreder et al., 1996) while those who failed to observe it utilized an interval of 7 days or less. In our study we

utilized an interval of 7–10 days after the last injection of cocaine because this interval coincided with maximal behavioral sensitization (Henry and White, 1995 and personal observations). Failure to observe a sensitization to the presynaptic effects of cocaine on dopamine transmission is commonly interpreted in terms of a role of changes at the postsynaptic level (see Pierce and Kalivas, 1997 for review). However, another possibility is raised by the present and by our previous studies (Bassareo and Di Chiara, 1999) suggesting that behavioral sensitization is also related to a reduction of dopamine responsiveness in the nucleus accumbens shell. If this is the case one should assume that dopamine has opposite functions in the nucleus accumbens shell and core. Thus, stimulation of dopamine transmission in the nucleus accumbens shell might tend to counteract the stimulation of motor activity induced by stimulation of dopamine transmission in the nucleus accumbens core. If this hypothesis is correct, behavioral sensitization can be the result of either a sensitization of dopamine transmission in the nucleus accumbens core or to a reduction of dopamine responsiveness in the nucleus accumbens shell or both.

In conclusion, our results suggest that differential changes in the responsiveness of dopamine transmission in the nucleus accumbens shell and core are associated with amphetamine and cocaine-induced behavioral sensitization. While nucleus accumbens core dopamine undergoes sensitization no such change is observed in the nucleus accumbens shell where, eventually, a reduction of dopamine responsiveness is obtained in cocaine sensitized animals. These observations are consistent with the notion that the nucleus accumbens core is involved in motor function and with the possibility that an increase of dopamine responsiveness in this area might facilitate stimulus-response associations and the maintenance of high rates of instrumental responding in self-administration paradigms (Piazza and Le Moal, 1998). In turn, reduction of dopamine responsiveness in the shell might modulate the expression of dopamine activity in the nucleus accumbens core. According to this proposal, dopamine in the nucleus accumbens shell would modulate in an inhibitory fashion the expression of motor activation induced by activation of dopamine transmission in the nucleus accumbens core. A similar relation between nucleus accumbens shell and core has been proposed for the role of nucleus accumbens dopamine in latent inhibition (Weiner et al., 1996). Dopamine of the nucleus accumbens shell might play this role via its projections to the ventral pallidum and entopeduncolar nucleus which partially overlap with the correspondent projections from the nucleus accumbens core (Heimer et al., 1991b).

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