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Isolation rearing impairs the reinforcing efficacy of intravenous cocaine or intra-accumbens *d*-amphetamine: impaired response to intra-accumbens D1 and D2/D3 dopamine receptor antagonists

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Abstract. Male Lister hooded rats were raised from weaning either alone (isolation reared) or in groups of five (socially reared controls). At 5 months of age, bilateral guide cannulae were implanted within the nucleus accumbens, and experiments began. The effect of isolation rearing upon the reinforcing efficacy of the intravenous self-administration of cocaine (experiment 1), or the bilateral intra-accumbens self-administration of *d*-amphetamine (experiment 2) was assessed. Self-administration was made contingent upon the acquisition of a novel lever-pressing response. Two identical levers were available within each operant chamber. Responding on one lever resulted in the delivery of drug (experiment 1: cocaine, 1.5 mg/kg per infusion; experiment 2: *d*-amphetamine, 0.25 μg/side), responding on the second, control lever was recorded but had no programmed consequences. Animals were not "primed" with noncontingent infusions at any time. For experiment 1, animals received intra-accumbens infusions of the D1 dopamine receptor antagonist SCH-23390, or the D2 dopamine receptor antagonist sulpiride over two test sessions. Within each session, animals received a cumulative series of doses of each dopamine receptor antagonist. A validation group received doses of each antagonist according to more conventional methods (one dose per session). In either case, intra-accumbens infusions of SCH-23390 or sulpiride enhanced the rate of the self-administration of cocaine in socially reared controls. However, isolation rearing impaired this response to intra-accumbens infusions of the dopamine receptor antagonists. Experiment 2a examined the acquisition of the intra-accumbens self-administration of *d*-amphetamine. Socially reared controls acquired readily a selective response upon the drug lever. However, isolation reared animals acquired a selective response at a greatly retarded rate. In experiment 2b, a full *d*-amphetamine dose-response function was examined. Isolation rearing impaired the response to a range of doses of *d*-amphetamine. In experiment 2c, the infusate (1 μg *d*-amphetamine per infusion) was adulterated with either SCH-23390 or sulpiride. Adulteration with either dopamine receptor antagonist enhanced the rate of response by socially reared controls. Isolation rearing impaired this response to SCH-23390, and blocked the response to sulpiride. These data are discussed in relation to the functioning of cortico-limbic-striatal systems, with particular reference to the mesoaccumbens dopamine projection.

Key words: Isolation rearing – Intravenous self-administration – Intracranial self-administration – Cocaine – *d*-amphetamine – Dopamine – Nucleus accumbens – SCH-23390 – Sulpiride

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Introduction

Social isolation at an early age has been reported to enhance a wide range of spontaneous behaviours, including locomotor activity (Morgan 1973; Weinstock and Speiser 1973; Sahakian et al. 1975, Einon and Morgan 1978; Garzon et al. 1979; Guisado et al. 1980; Garzon and Del Rio 1981; Gentsch et al. 1981a,b; Jones et al. 1990; Phillips et al. 1993a), stereotypy (Kostowski and Czlondowski 1973; Sahakian et al. 1975; Einon and Sahakian 1979), food consumption (Morgan and Einon 1975; Fiala et al. 1977) and tail pinch-induced oral behaviours (Sahakian and Robbins 1977).

In particular, isolation has been suggested to enhance the propensity to self-administer drugs of abuse (e.g. Katz and Steinberg 1970; Kostowski et al. 1977; Alexander et al. 1978), and hence to possess important implications for the aetiology of human drug addiction. Thus, isolation rearing enhanced the ability of *d*-amphetamine to increase the control over behaviour exerted by a conditioned reinforcer (Jones et al. 1990), and enhanced the discriminability of a *d*-amphetamine cue (Fowler et al. 1993). Moreover, isolation rearing enhanced the rate of

the self-administration of some classes of drugs of abuse, including ethanol (Schenk et al. 1990) and opiates (Alexander et al. 1978, 1981; Hadaway et al. 1979; Marks-Kaufman and Lewis 1984; Bozarth et al. 1989). By contrast, isolation rearing has not produced consistent effects upon the self-administration of psychomotor stimulant drugs. Thus, isolation housing has been reported to have no effect upon both the self-administration of *d*-amphetamine (Schenk et al. 1988) or cocaine (Bozarth et al. 1989; Boyle et al. 1991), or to enhance the rate of self-administration of cocaine (Schenk et al. 1987).

A companion paper showed that isolation rearing impaired the acquisition of the intravenous self-administration of cocaine, and shifted a dose-response function for cocaine to the right (Phillips et al. 1994a). Since lesions of dopamine terminals within the nucleus accumbens using 6-hydroxydopamine are known to disrupt selectively the self-administration of cocaine (Roberts et al. 1977, 1980; Pettit et al. 1984), it was suggested that enhanced responsivity of the mesoaccumbens dopamine projection following isolation rearing (see Jones et al. 1992, and Discussion) may lead to dysfunction of systems within the nucleus accumbens postsynaptic to the dopamine projection. Thus, the present study examined the functional status of D1 and D2 dopamine receptors within the nucleus accumbens following isolation rearing during the self-administration of psychomotor stimulants.

Animals may compensate for a partial blockade of dopamine receptors following systemic neuroleptics by increasing the rate of intravenous self-administration of psychomotor stimulant drugs (de Wit and Wise 1977; Risner and Jones 1980; Ettenberg et al. 1982; Woolverton 1986; Koob et al. 1987; Roberts et al. 1987, 1989; Britton et al. 1991; Corrigall and Coen 1991; Hubner and Moreton 1991; Peltier and Schenk 1991). While such evidence successfully identifies the relevant receptors mediating reinforcing effects of stimulants, it cannot be used to localise these receptors at a neural level. However, a recent study demonstrated that intra-accumbens infusions of the D1 dopamine receptor antagonist SCH-23390 enhanced the rate of the self-administration of cocaine (Robledo et al. 1992). Accordingly, experiment 1 examined the effect of isolation rearing upon the functional efficacy of D1 and D2 dopamine receptors within the nucleus accumbens in the intravenous self-administration of cocaine. During test sessions for the self-administration of cocaine, animals were infused with ascending doses of the D1 dopamine receptor antagonist SCH-23390 ((*R*)-(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*–3-benzazepin-7-ol; Iorio et al. 1983) or the D2 dopamine receptor antagonist sulpiride ([–]-*N*-1-[ethylpyrrolidin-2-ylmethyl]-2-methoxy-5-sulphamoyl benzamide; Jenner and Marsden 1981; Creese et al. 1983). The effects of these infusions upon the rate of self-administration, and the effect of isolation rearing upon the response to these infusions were then examined.

Because of the intravenous mode of drug administration, concurrent drug effects upon distal neuroanatomical sites conceivably may confound assessment of the role of the nucleus accumbens in drug reinforcement. The direct intracerebral self-administration of reinforcing drugs may overcome these problems, and has been reported using a wide range of species, drugs and placements (e.g. Bozarth and Wise 1981; Goeders and Smith 1983; Hoebel et al. 1983; see Phillips et al. 1994b). Accordingly, experiment 2a examined the effect of isolation rearing upon the acquisition of the intra-accumbens self-administration of *d*-amphetamine, while experiment 2b determined dose-response functions for the reinforcing effect of *d*-amphetamine in isolates and socially reared rats. The use of *d*-amphetamine is determined partly by the reported lack of reinforcing efficacy of intra-accumbens cocaine (Goeders and Smith 1983), but allows the analysis to extend to another member of the psychomotor stimulant class of drugs with a somewhat different cellular site and mode of action (Kuczenski 1983). Finally, our recent work showing that the intra-accumbens self-administration of *d*-amphetamine was enhanced following adulteration of the infusate with either SCH-23390 or sulpiride (Phillips et al. 1994b) allowed a characterisation in experiment 2c of the effect of isolation rearing on possible differential effects of isolation rearing on responses to these dopamine receptor antagonists.

Materials and methods

Subjects

A total of 21 male Lister hooded rats was used (Olac, Bicester, UK), 13 in experiment 1, and 8 in experiment 2. Seventeen animals were obtained at 21 days of age, and immediately were divided into two groups (matched by body weight) and housed either in groups of four and five (Social condition, $n = 9$), or one (Isolation condition, $n = 8$). Socially reared animals were housed in cages $51 \times 32 \times 19$ cm high. Isolation reared animals were housed individually in cages $33 \times 21 \times 19$ cm high. Four socially reared animals were obtained as a validation group to experiment 1 at 2 months of age (see experiment 1 below). Housing conditions consisted of a 12 h:12 h reversed light:dark cycle (lights off 0900 hours) at a constant temperature of 22°C. Animals were aged 20 weeks at the start of experiments, and body weights ranged from 300 to 350 g. Experiments were carried out between 1300 and 1600 hours. Sufficient food to maintain body weight at 95% free feeding weight was made available at 1700 hours. Access to water was unrestricted.

Apparatus

Experiment 1 was carried out using four operant chambers ($28 \times 26 \times 28$ cm; Gerbrands, Arlington, Mass., USA), which were equipped as described previously (Phillips et al. 1994a). For experiment 2, one chamber was fitted in addition with a second infusion pump for the intra-accumbens delivery of infusates (Model 50–4928 with multiple microsyringe attachment: Harvard Apparatus, Edenbridge, UK). Intra-accumbens infusions were carried out through a dual-channel liquid swivel (Harvard Apparatus, Edenbridge, UK) with two-channel connector attachment (Plastics One, Roanoke, Va., USA). Depression of the left lever by the experimenter turned the houselight on, extended the levers and began the session. Subsequent depression of one lever (the drug lever) caused the houselight to extinguish, the lever light to turn on, and the levers to retract. After a period of 1 s, the infusion pump was activated. For experiment 1, the pump activation period was 4 s, and a 0.2-ml intravenous infusion of cocaine solution was deliv-

ered. After a further period of 16 s, the levers again were extended into the operant chamber (total retraction time: 20 s), the lever light was extinguished and the houselight turned on. For experiment 2 , the pump activation period was 5 s, and a 0.1-µl intra-accumbens infusion was delivered. After a further period of 55 s, the levers again were extended into the operant chamber (total retraction time: 60 s), the lever light was extinguished and the houselight turned on. Depression of the drug lever again would result in an infusion of drug, while depression of the second lever (the control lever) was recorded but had no programmed consequences at any time.

Drugs

Drugs used in these experiments were: cocaine hydrochloride (Rhone-Poulenc-Rorer, Dagenham, UK), *d*-amphetamine sulphate (Sigma, Poole, UK), (−)-sulpiride (Sigma, Poole, UK) and SCH-23390 maleate (Schering, Bloomfield, N.J., USA). Cocaine was dissolved in sterile 0.9% saline (Animalcare, Dunnington, UK). All other compounds were dissolved in sterile phosphate buffered saline immediately prior to use, which also served as vehicle. For experiment 1, doses of cocaine, SCH-23390 and sulpiride were calculated as the salt. For experiment 2, doses of *d*-amphetamine also were calculated as the salt. However, all doses of sulpiride and SCH-23390 were calculated with regard to *d*-amphetamine (see experiment 2c below).

Surgery

Rats were anaesthetised with an injection IP of a solution containing 2,2,2-tribromoethanol in sterile phosphate buffered saline (Avertin; volume injected: 10 ml/kg; for method of preparation, see Phillips et al. 1994c). When animals were anaesthetised, bilateral stainless steel guide cannulae (experiment 1: 22 gauge, Cooper's Needle Works, Birmingham, UK; experiment 2: 22 gauge double cannulae; Plastics One, Roanoke, Va., USA) were implanted to gain access to the postero-medial NAcc. The stereotaxic coordinates used were: AP + 3.4 mm from bregma, L ± 1.7 mm from the midline, V - 5.2 mm from the surface of dura (Pellegrino et al. 1979). After surgery, the implanted guide cannulae were closed by inserting stainless steel wire obturators (experiment 1: 29 gauge, Coopers Needle Works, Birmingham, UK; experiment 2: 28 gauge double dummy cannulae with dust caps, Plastics One, Roanoke, Va., USA), and the animals returned to their home cages. Animals in experiment 1 were prepared in addition with chronic jugular catheters according to standard procedures (e.g. Caine et al. 1992). In these animals, streptokinase (825 IU/day; Hoechst UK, Hounslow, UK) was used routinely to flush catheters and maintain patency.

Procedure

Experiment 1: intravenous self-administration of cocaine. Effect of isolation rearing upon the response to intra-accumbens infusions of SCH-23390 or sulpiride. The operant procedure was identical to that used previously (see Phillips et al. 1994a). Briefly, depression of the drug lever by the animal resulted in a delivery of 1.5 mg/kg cocaine. Depression of the control lever was recorded but had no programmed consequences. Non-contingent "priming" infusions of cocaine were not delivered at any time during these experiments. Before beginning intra-accumbens infusions of dopamine receptor antagonists, animals were exposed to at least 12 previous 3-h self-administration sessions. Acquisition was more rapid by socially reared controls, but the performance of both groups stabilised within five sessions of the start of training (see Phillips et al. 1994a). All animals tested acquired the self-administration response.

Animals received an intra-accumbens infusion of vehicle immediately before the start of two test sessions. When the control rate of infusion had stabilised (30 min), each animal was removed from the operant chamber at 30-min intervals and infused with ascending doses of SCH-23390 or sulpiride. The order in which the drugs were encountered was counterbalanced across subjects. The cumulative doses of drug infused were calculated to account for the total amount of drug infused earlier in the session. For example, at the time appropriate to assess the effects of 1 µg of each drug, it was known that a total of 0.25 µg had been administered previously. Thus, to assess the effects of 1 µg, 0.75 µg was infused at this time. Previous work had shown that the duration of action of both drugs well exceeded the total duration of the test sessions (see validation group below). The doses of SCH-23390 and sulpiride each animal was calculated to receive were: 0.03125, 0.0625, 0.25, 1, 4 and 8 µg.

A separate group of socially reared animals were utilised as a validation group for the cumulative dose procedure above. These animals received intra-accumbens infusions of vehicle, and two doses of SCH-23390 or sulpiride (1 µg and 8 µg in each case) immediately before the start of three 3-h test sessions.

Experiment 2a: intra-accumbens self-administration of d-amphetamine. Acquisition. Experiments began following surgery and a period of recovery of 1 week. The active drug lever (left or right) was fully counterbalanced across subjects. The effect of isolation rearing upon the acquisition of *d*-amphetamine self-administration was then assessed. Each animal was placed in the operant chamber and attached to the connector for the intra-accumbens delivery of *d*-amphetamine. The experimenter started the session by a single press upon the left lever. The operant chamber was then closed. Depression of the drug lever by the animal resulted in a delivery of 0.25µg *d*-amphetamine (see also Apparatus). Non-contingent "priming" infusions of *d*-amphetamine were not delivered at any time during these experiments. After 30 min or ten infusions, whichever occurred sooner, each animal was removed from the operant chamber and returned to the home cage. Hence, animals were permitted a maximum of ten 0.1-µl infusions, each containing 0.25 µg *d*-amphetamine during any one session. Sessions were conducted twice per week, each separated by at least 72 h. Five sessions were required for the two groups to achieve asymptotic levels of performance. All animals tested acquired a selective self-administration response after five sessions of acquisition training.

Experiment 2b: intra-accumbens self-administration of d-amphetamine. Dose-response function. After completing experiment 1, animals were exposed to a sixth session with *d*-amphetamine available at the acquisition dose of 0.25 µg/0.1 µl infusion. The two groups exhibited a similar rate of response. The dose of *d*-amphetamine subsequently was doubled repeatedly over the following three sessions. Thus, the doses of *d*-amphetamine available during experiment 3 were: 0.25, 0.5, 1 and 2 µg/infusion.

Experiment 2c: intra-accumbens self-administration of d-amphetamine. Adulteration of the d-amphetamine reinforcer with SCH-23390 and sulpiride. Following the completion of experiment 2b, the standard dose of the *d*-amphetamine reinforcer was increased to 1 µg/infusion. During subsequent sessions, the *d*-amphetamine reinforcer was then adulterated according to a Latin Square design with calculated doses of sulpiride and SCH-23390. The doses were calculated to represent free base molar proportions of the standard dose of *d*-amphetamine. Conditions and ratios of antagonists with respect to *d*-amphetamine were: *d*-amphetamine alone ("vehicle" condition), 0.125: 1 SCH-23390 (1.3 µg/µl), 0.25: 1 SCH-23390 (2.6 µg/µl), 0.5: 1 SCH-23390 (5.19 µg/µl), 0.125: 1 sulpiride (0.85 µg/µl), 0.25: 1 sulpiride (1.7 µg/µl), 0.5: 1 sulpiride (3.4 µg/µl).

Histology

At the conclusion of the experiments, animals were anaesthetised deeply (administration IP of 200 mg sodium pentobarbitone: Eu-

thatal, RMB Animal Health, Dagenham, UK) and perfused transcardially with 10% formal saline. Brains were blocked and sectioned at 100 µm on a freezing microtome. The sections were mounted on glass slides and stained with Cresyl violet. The accuracy of cannula placements, and the effects of intracerebral infusions upon brain tissue were then assessed.

Statistical analysis

Because only ten infusions were permitted during any one session for experiment 2 (intra-accumbens self-administration of *d*-amphetamine), these sessions were of variable length. Hence, to standardise the presentation of data, Local Responses/min are shown on figures. This measure excludes lever retraction time (1 min/infusion). Experiments were subjected to three-factor parametric analyses of variance [Factor 1, Group (Social, Isolate); Factor 2, Lever (Active, Control); Factor 3, experiment 1: Dose (SCH-23390 or sulpiride: 0, 0.03125, 0.0625, 0.25, 1, 4, 8 µg); experiment 2a: Day (1, 2, 3, 4, 5), experiment 2b: Dose (*d*-amphetamine: 0.25, 0.5, 1, 2µg), experiment 2c: Antagonist (0, 0.125: 1 SCH-23390, 0.25: 1 SCH-23390, 0.5: 1 SCH-23390, 0.125: 1 sulpiride, 0.25: 1 sulpiride, 0.5: 1 sulpiride]. The factor "Group" represents the sole nested factor in these experiments.

Statistically significant main effects ($P < 0.05$) were analysed further. Within-factor comparisons for factors containing two levels were made using simple main effects parametric analyses of variance (Winer 1971). Within-factor comparisons with baseline conditions (factors containing more than two levels) were also analysed initially using simple main effects analysis of variance, but then were completed post hoc using Dunnett's *t* test (D-*t*; Winer 1971).

Results

Histological examination verified that all infusion sites intended for the NAcc were within the posteromedial portion, just medial to the anterior commissure, and were well within 0.2 mm of each other in the rostro-caudal dimension (see Fig. 1A and 1B). Subjects showed only limited gliosis around the infusion site and no appreciable neuronal loss in the medial core and shell regions. Glial aggregation, when present, was found to be restricted to the immediate area of the infusion site (Fig. 1C).

Experiment 1: intravenous self-administration of cocaine. Effect of isolation rearing on the response to intra-accumbens infusions of SCH-23390 or sulpiride

Baseline behaviour. Under control conditions, both socially reared and isolation reared groups exhibited a preference for responding upon the drug lever by comparison with the control lever [Fig. 2; drug lever versus control lever: socially reared, SCH-23390 session: $F(1,4) = 60.1$, $P < 0.01$, sulpiride session: $F(1,4) = 14.5$, $P < 0.05$; isolation reared, SCH-23390 session: $F(1,3) = 10.6$, $P < 0.05$, sulpiride session: $F(1,3) = 16.3$, $P < 0.05$]. Moreover, the baseline rates of response upon the drug lever and control lever by the two groups were very comparable [socially reared versus isolation reared, drug lever, SCH-23390 session: $F(1,7) = 0.1$, NS, sulpiride session: $F(1,7) = 1.5$, NS; control lever, SCH-23390 session: $F(1,7) = 0.8$, NS, sulpiride session: $F(1,7) = 0.3$, NS].

Effects of intra-accumbens dopamine receptor antagonist challenge. The two groups demonstrated striking differences in response to dopamine receptor antagonist challenge. Thus, the socially reared group increased responding upon the drug lever markedly, and selectively in response to intra-accumbens infusions of either SCH-23390 or sulpiride [drug lever, simple main effects, SCH-23390: $F(4,16) = 11.4$, $P < 0.001$; sulpiride: $F(4,16) = 30.6$, $P < 0.001$; control lever, simple main effects: SCH-23390: $F(4,16) = 1.2$, NS; sulpiride: $F(4,16) = 0.6$, NS; lever × dose simple interaction effects, SCH-23390:

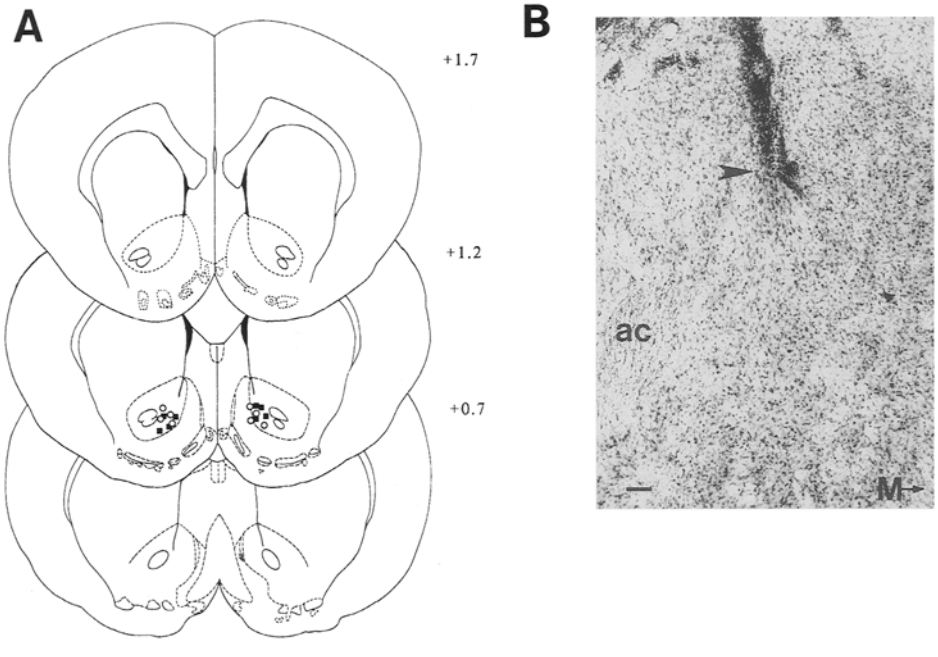

Fig. 1. A Coronal sections through the rat brain, showing cannulae placements within the postero-medial nucleus accumbens. To preserve clarity, four representative placements are shown from experiment 1 (*filled squares*), and four placements from experiment 2 (*open circles*). Numbers adjacent to each section indicate distance from Bregma (mm). Redrawn from the atlas of Paxinos and Watson (1986). **B** Photomicrographs of one half of the midbrain from one animal having received bilateral infusions within the nucleus accumbens. *Large arrow*, lower extremity of infusion site. *M with arrow*, medial area of brain; *bar* in lower right corner, 100 µm; *ac*, anterior commissure

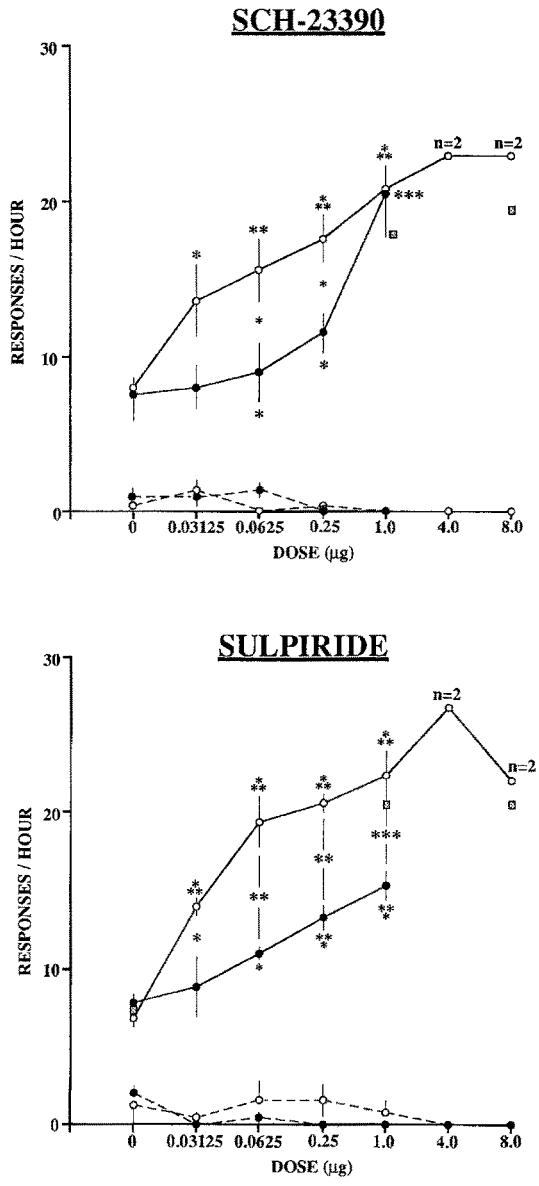

Fig. 2. The effect of isolation rearing upon the self-administration of cocaine (schedule: FR1; dose of cocaine: 1.5 mg/kg per infusion), following intra-accumbens infusions of the D1 dopamine receptor antagonist SCH-23390 or the D2 dopamine receptor antagonist sulpiride. *Dotted lines*, control lever, *solid lines*, drug lever. *Filled circles*, isolation reared animals, *open circles*, socially reared control animals. Unless indicated otherwise, *stars* represent statistical significance of comparisons with the respective vehicle condition; $*P < 0.05$; $**P < 0.01$; $***P < 0.001$. A validation group was infused with doses of 4 µg and 8 µg of each dopamine receptor antagonist, immediately before the start of 3-h sessions. These data, which show the rate of response by these animals over 3 h have been included for illustrative purposes *(gray squares)*, but were not included in statistical analyses

$F(4,16) = 10.1$, $P < 0.001$; sulpiride: $F(4,16) = 24.3$, $P < 0.001$]. Furthermore, while the isolation reared group also increased the rate of response upon the drug lever in response to intra-accumbens infusions of either SCH-23900 or sulpiride [SCH-23390: $F(4,12) = 15.2$, $P < 0.001$; sulpiride: $F(4,12) = 15.9$, $P < 0.001$], in general they did so to a far lesser degree than did the socially reared animals [group × dose interactions, SCH-23390: $F(4,28) = 2.9$, $P < 0.05$; sulpiride: $F(4,28) = 7.0$, $P < 0.001$]. In contrast to the reduced response of isolation reared animals to intra-accumbens infusions of relatively low doses of SCH-23390, the highest dose of SCH-23390 (1 µg) did increase the rate of response by this group to a degree comparable with socially reared animals [1 µg SCH-23390, isolation reared versus socially reared: $F(1,7) = 0.0$, NS]. Thus, the dose -response function for SCH-23390 exhibited by isolation reared animals was shifted to the right of the socially reared group. The response by the isolation reared group to sulpiride at no time matched that of socially reared animals (Fig. 2, lower panel). Thus, the response by isolation reared animals to either D1 or D2 dopamine receptor antagonist challenge was impaired by comparison with socially reared controls.

A validation group received intra-accumbens infusions of either SCH-23390 or sulpiride immediately prior to 3-h sessions. Increased rates of response by this group were at all times comparable with rates observed using the cumulative dose procedure reported above (see Fig. 2). Thus, the cumulative dose procedure represents a valid, and true representation of the effects of SCH-23390 and sulpiride upon the rates of response maintained by cocaine reinforcement.

Experiment 2a: intra-accumbens self-administration of d-amphetamine. Acquisition

Socially reared controls acquired the *d*-amphetamine self-administration response more rapidly than did isolation reared animals [Fig. 3, top right panel; drug lever, socially reared versus isolation reared: $F(1,6) = 6.6$, $P < 0.05$]. This was most evident during the first three days of acquisition: by day 5 the rates of response upon the drug lever by the two groups were very comparable [day 5, drug lever, socially reared versus isolation reared: $F(1,6) = 0.6$, NS]. Rates of response upon the control lever increased across days in both groups before declining by day 5 (Fig. 3, bottom right panel). Moreover, the rates of response upon the two levers by the isolation reared animals did not differ until very late in training (Fig. 3, bottom left panel). Socially reared animals demonstrated a strong preference for responding upon the drug lever even on the first day of training (Fig. 3, top left panel). Thus, isolation reared animals acquired a selective response upon the drug lever less readily than socially reared controls.

Experiment 2b: intra-accumbens self-administration of d-amphetamine: dose-response function

Increasing the dose of *d*-amphetamine available in the infusate enhanced selectively the rate of response exhibited upon the drug lever by both groups [Fig. 4; lever × dose simple interaction effects, socially reared: $F(3,9) =$

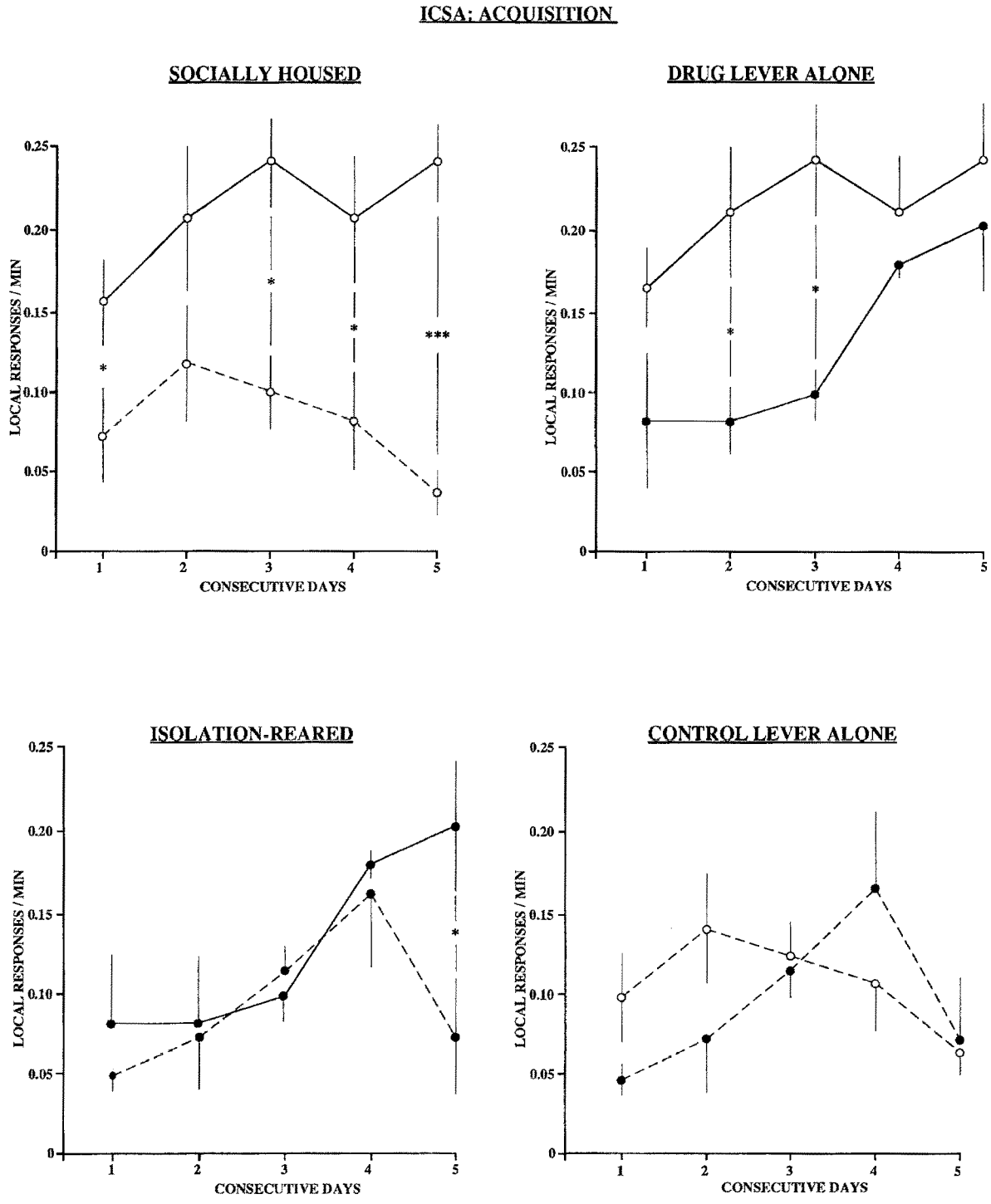

Fig. 3. Effect of isolation rearing upon the acquisition of bilateral intra-accumbens self-administration of *d*-amphetamine (schedule: FR1; dose: 0.25 µg/0.1 µl infusion). Biweekly sessions were terminated after 30 min or after ten infusions had been received, whichever occurred sooner. *Solid lines*, drug lever; *dotted lines*, control lever. *Filled circles*, isolation reared animals; *open circles*, socially reared control animals. Drug lever and control lever responses for socially reared and isolation reared animals are presented in the *upper* and *lower left* graphs, respectively. For comparison, drug lever presses by the two groups are also presented in the *upper right* graph, and control lever presses in the *lower right* graph. Values represent means ± 1 SEM. Stars represent statistical significance of comparisons indicated; $*P < 0.05$; $***P < 0.001$

5.4, $P < 0.05$; isolation reared: $F(3,9) = 5.1$, $P < 0.05$]. However, the socially reared animals showed a far greater response to increases in the dose of the *d*-amphetamine reinforcer [group × dose simple interaction effect: $F(3,18) = 3.62$, $P < 0.05$]. Hence, the isolation reared animals were less reactive to changes in the value of the intra-accumbens *d*-amphetamine reinforcer than socially reared controls.

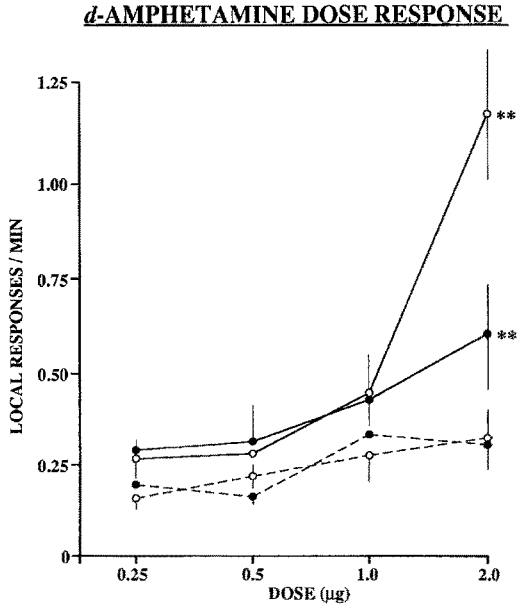

Fig. 4. Effect of isolation rearing upon the bilateral intra-accumbens *d*-amphetamine dose-response function (schedule: FR1; baseline dose: 0.25 µg/0.1 µl infusion). Biweekly sessions were terminated after 30 min or after ten infusions had been received, whichever occurred sooner. *Solid lines*, drug lever; *dotted lines*, control lever. *Filled circles*, isolation reared animals; *open circles*, socially reared control animals. Values represent means ± 1 SEM. *Stars* represent statistical significance of comparisons with the respective baseline condition; $^{**}P < 0.001$

Experiment 2c: intra-accumbens self-administration of d-amphetamine. Adulteration of the d-amphetamine reinforcer with SCH-23390 and sulpiride

Under baseline conditions, both groups showed a marked preference for responding upon the drug lever, by comparison with relatively low rates of response upon the control lever [Fig. 5; vehicle condition, drug lever versus control lever, socially reared: $F(1,3) = 19.2$, $P < 0.05$; isolation reared: $F(1,3) = 11.4$, $P < 0.05$]. Furthermore, the rates of response upon the control lever by either group were unaffected by dopamine receptor antagonist adulteration of the *d*-amphetamine reinforcer [control lever, simple main effect, socially reared: $F(6,18) = 0.8$, NS; isolation reared: $F(6,18) = 2.3$, NS]. Thus, the effects of adulteration, when present, were selective for the drug lever alone. In socially reared animals, the D1 dopamine receptor antagonist SCH-23390 increased the rate of response upon the drug lever at the lowest level of adulteration tested (Fig. 4, top panel; drug lever, vehicle versus 0.125: 1 SCH-23390:*d*-amphetamine, D-*t*: $P < 0.01$). Higher levels of adulteration with SCH-23390 did not affect the rate of response emitted by the socially reared group. In contrast, isolation reared animals were unaffected by the lowest level of SCH-23390 adulteration (vehicle versus 0.125: 1 SCH-23390:*d*-amphetamine: D-*t*: NS), but did increase the rate of response following adulteration with twice this proportion of SCH-23390 to *d*-amphetamine (vehicle versus 0.25: 1 SCH-23390:*d*-amphetamine, D-*t*: $P < 0.001$). In common with socially reared controls, the response rate exhibited by

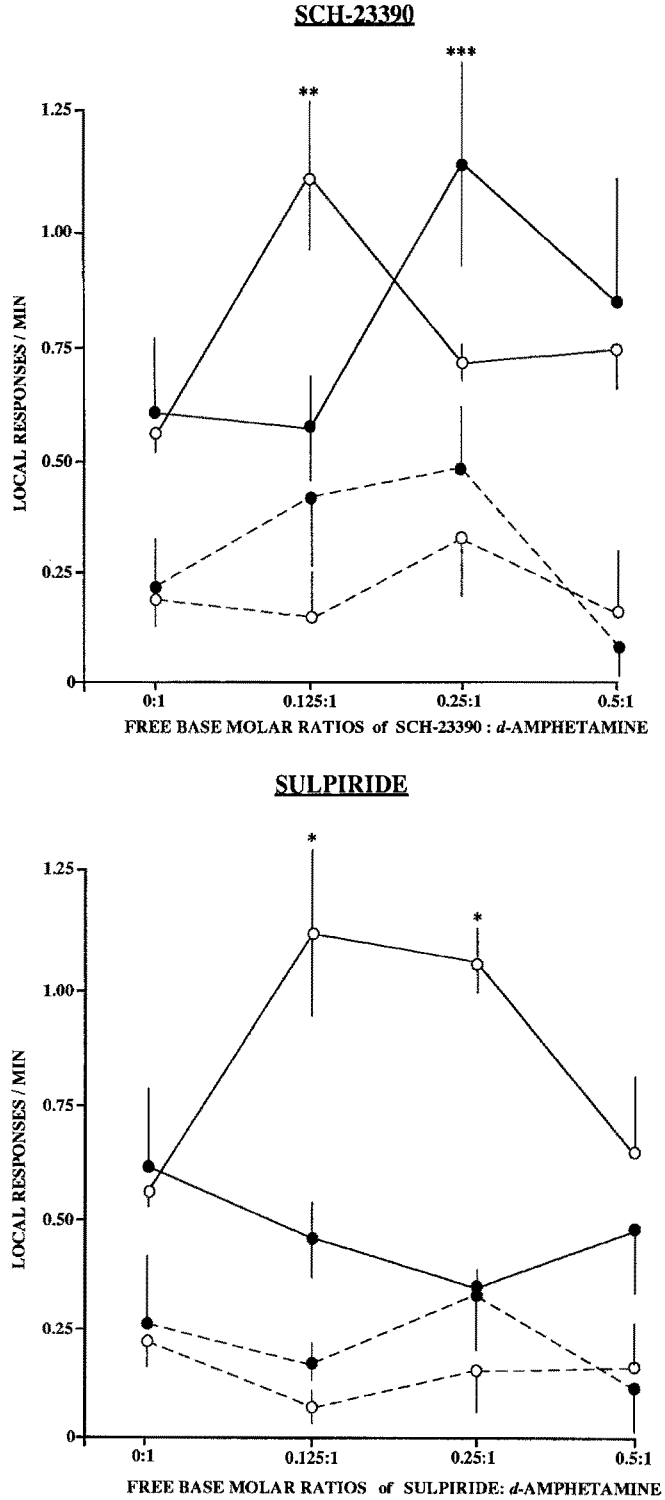

Fig. 5. Effect of isolation rearing upon the bilateral intra-accumbens *d*-amphetamine dose-response function (schedule: FR1; baseline dose: 1 µg/0.1 µl infusion). Biweekly sessions were terminated after 30 min or after ten infusions had been received, whichever occurred sooner. *Solid lines*, drug lever; *dotted lines*, control lever. *Filled circles*, isolation reared animals; *open circles*, socially reared control animals. The *d*-amphetamine reinforcer was adulterated with calculated proportions of the D1 dopamine receptor antagonist SCH-23390 and the D2 dopamine receptor antagonist sulpiride. Values represent means ± 1 SEM. *Stars* represent statistical significance of comparisons with the baseline condition; $^{*}P < 0.05$; $^{**}P < 0.01$; $^{***}P < 0.001$

SCH-23390. However, the dose-response function for SCH-23390 exhibited by the isolation reared animals was shifted to the right of the socially reared controls.

This pattern of results was emphasised following adulteration of the infusate with the D2 dopamine receptor antagonist sulpiride. Low-to-moderate levels of sulpiride adulteration increased the rate of response emitted by the socially reared group (vehicle versus 0.125: 1 sulpiride:*d*-amphetamine D-*t*: $P < 0.05$; vehicle versus 0.25: 1 sulpiride:*d*-amphetamine, D-*t*: $P < 0.05$), but no level of sulpiride adulteration affected the rate of response exhibited by the isolate-reared animals (drug lever, isolation reared, all doses: D-*t*: NS). However, a ratio of sulpiride:*d*-amphetamine of 0.25: 1 impaired the control over behaviour exerted by the drug lever (drug lever versus control lever: $F(1,3) = 0.8$, NS). Hence, socially reared animals increased the rate of response following adulteration of the infusate with sulpiride, but isolation reared animals were not affected in a consistent manner.

Discussion

Intra-accumbens infusions with either the D1 dopamine receptor antagonist SCH-23390 or the D2 dopamine receptor antagonist sulpiride enhanced the rates of the self-administration of intravenous cocaine. Similarly, adulteration of the *d*-amphetamine reinforcer with SCH-23390 or sulpiride enhanced the bilateral intra-accumbens self-administration of *d*-amphetamine. Isolation rearing impaired this response to the dopamine receptor antagonists in both the intravenous and intra-accumbens self-administration procedures. Isolation rearing also impaired the acquisition of the intra-accumbens self-administration of *d*-amphetamine, and shifted a dose-response function for *d*-amphetamine to the right. These results add to those reported recently (Phillips et al. 1994a), in which isolation rearing impaired the acquisition of the intravenous self-administration of cocaine, and shifted to the right a cocaine dose-response function. These data suggested that cocaine is a less effective reinforcer in isolates, but the present work extends the conclusions to *d*-amphetamine, another drug of the psychomotor stimulant class. Further, data reported recently confirmed the presence of the cardinal trait of the isolation syndrome (enhanced locomotor response to a novel environment) in the same cohort of animals which exhibited an impaired response to the reinforcing properties of intravenous cocaine (Phillips et al. 1994a). These findings were noted to contrast with those of Piazza and co-workers (Piazza et al. 1989, 1990), in which an enhanced locomotor response to a novel environment was observed to correlate with a more rapid rate of acquisition of the intravenous self-administration of *d*-amphetamine. However, manipulations utilised by the latter group, and that of isolation rearing were noted to be of uncertain equivalence (see Phillips et al. 1994a).

The contingent availability of intra-accumbens infusions of *d*-amphetamine supported readily the acquisition of a novel lever-pressing response in socially reared animals which was shown previously to be dependent specifically upon the presence of the *d*-amphetamine moiety within the infusate (Phillips et al. 1994b). All animals tested acquired the response. The intravenous cocaine self-administration response was also acquired by all animals. In our laboratory, all animals readily acquire the intravenous self-administration of cocaine, a 100% record to date which appears to contrast with that of other laboratories. There are three main possibilities which may account for this. Firstly, to date we have made use of a relatively high training dose of 1.5 mg/kg per infusion (with no toxicity-related losses), which would be expected to be more reinforcing than lower doses. Secondly, we do not administer noncontingent "priming" infusions at the start of sessions, a procedure which may be counterproductive in some animals. Thirdly, the Lister hooded rat is not generally used by other workers on self-administration, but may possess a greater propensity to acquire this form of response than other strains of rat. Requirements for the intra-accumbens self-administration of *d*-amphetamine were particularly stringent for this mode of self-administration. To control for any nonspecific activational properties of *d*-amphetamine, two identical levers were present within the operant chamber. Depression of one lever resulted in the intra-accumbens delivery of *d*-amphetamine, while responses on the second, control lever were recorded but had no programmed consequences. Socially reared animals readily acquired the new response selectively for the drug lever. Hence, this behaviour did not arise through any nonspecific locomotor activating properties of *d*-amphetamine. However, isolation rearing retarded the selective acquisition of responding on the drug lever. Only by the fifth training session did the isolation reared animals acquire a lever-pressing response that was selective for the drug lever. A companion paper reported a similar impairment by isolation reared animals in the control over behaviour exerted by low doses of the intravenous self-administration of cocaine (Phillips et al. 1994a). These results thus emphasise the reductions in reinforcing efficacy of psychomotor stimulants in socially isolated rats, regardless of the route of drug self-administration or the precise drug employed. It is possible that the enhanced rate of acquisition of the intra-accumbens self-administration response by socially reared controls represents an impaired response to *d*-amphetamine, as in this case more drug would be required to achieve the same level of reinforcing efficacy. However, in this field an enhanced rate of acquisition is interpreted to indicate an enhanced response to the reinforcing properties of the drug in question (e.g. Schenk et al. 1987; Piazza et al. 1989, 1990). Succeeding experiments in this paper (see below), together with the effects of isolation rearing upon the intravenous self-administration of cocaine (Phillips et al. 1993a) lend support for this interpretation. The independence of the effects on the peripheral or central routes of self-administration of the drugs strongly suggests that the differences between isolated and socially reared rats do not arise through the altered peripheral metabolism of the stimulants. In addition, the extension of the earlier results with cocaine to *d*-amphetamine has possible implications for the nature of the presynaptic changes that might underlie the altered responses in isolated rats.

Thus, the effects of *d*-amphetamine are known to be mediated, through binding to the synaptic vesicle amine transporter, by the impulse-independent release of presynaptic stores of dopamine as well as by release of newly synthesised dopamine and a re-uptake blocking action for the monoamine neurotransmitters (Kuczenski 1983; Zetterström et al. 1986), whereas cocaine mainly affects monoamine re-uptake in an impulse-dependent manner through its binding to the dopamine, noradrenaline and serotonin transporters (Ritz et al. 1987; Reith 1988; Richfield 1991), and the inhibition of reuptake (Izenwasser and Cox 1990; Izenwasser et al. 1990). The common response to these two psychomotor stimulants following isolation rearing suggests important differences in presynaptic regulation of the mesoaccumbens dopamine system, perhaps related to altered regulation of their transporters.

Impairments in the acquisition of the intra-accumbens self-administration of *d*-amphetamine by isolation reared animals could not be accounted for by a cytotoxic action of the drug at the site of infusion. Despite the receipt of at least 160 infusions, histological examination did not reveal any gross neuronal loss in the nucleus accumbens, and only minor gliosis along the track of implanted infusion cannulae. This may be accounted for by the restrictions placed upon the availability of *d*-amphetamine. A maximum of 20 μg *d*-amphetamine was permitted in any one week, in a total volume of 2 μl (100 nl per infusion). In addition, sterile procedures were adhered to rigorously throughout the experiments, and the infusion apparatus delivered accurate, and reproducible volumes of infusate (see Phillips et al. 1993b for detailed discussion). Thus, impairments in the acquisition of a selective lever-pressing response by isolation reared animals cannot be explained through nonspecific, or uncontrolled consequences of the intra-accumbens self-administration procedure itself.

The present results have added to a recent literature on the effects of intra-accumbens infusions of dopamine receptor antagonists during the course of psychomotor stimulant self-administration. Previously, intra-accumbens infusions of the D1 receptor antagonist SCH-23390 have been shown to increase the rate of the self-administration of intravenous cocaine (Robledo et al. 1992) and intra-accumbens *d*-amphetamine (Phillips et al. 1994b). This effect of SCH-23390 was most evident at a single ratio of SCH-23390:*d*-amphetamine – the same ratio as was found to be most effective in the present study. Presumably, higher quantities of SCH-23390 either impaired the reinforcing properties of *d*-amphetamine to a degree beyond that which it was possible to compensate for by increasing the rate of response, or it induced a significant degree of motor impairment. The latter study also showed that intra-accumbens administration of the D2 receptor antagonist, sulpiride, increased rates of self-administration of intra-accumbens *d*-amphetamine. In conjunction with the novel results of the present study of the effects of intra-accumbens sulpiride upon the intravenous self-administration of cocaine, these data suggest that both D1 and D2 dopamine receptors within the nucleus accumbens of socially reared rats mediate to an important degree the reinforcing properties of both psychomotor stimulant drugs. However, the D3 and the D2 receptors are closely related, while the D3 receptor is located preferentially within so-called limbic regions including the nucleus accumbens (Sokoloff et al. 1990). Hence, a possible interaction of sulpiride with the dopamine D3 receptor must be considered in the interpretation of the effects of the dopamine receptor antagonist on self-administration, even though sulpiride has five times more affinity for the D2 receptor than the D3 receptor (Sokoloff et al. 1990). Given the marked efficacy of intra-accumbens infusions of this drug upon the rate of intravenous self-administration of cocaine, and the clear effects upon the intra-accumbens self-administration of *d*-amphetamine, it is possible that the effects of sulpiride reflected predominantly a blockade of the D2 dopamine receptor subtype. Recently, however, Caine et al (1993) have shown that the D3 receptor agonist 7-OHDPAT, given systemically, can effectively reduce the intravenous self-administration of cocaine, suggesting that D3 receptors may also mediate its reinforcing efficacy. The development of more selective D3 receptor antagonists and antagonists will help to clarify the separate or related roles of these dopamine receptors in the nucleus accumbens.

The important findings of the present study were that isolation rearing impaired the response both to intra-accumbens SCH-23390 and sulpiride, and hence the functional efficacy of D1 and D2 dopamine receptors within the nucleus accumbens. This may have come about through the presence of abnormalities in the functioning of the mesolimbic dopamine system, since isolation rearing has been shown to enhance the ability of *d*-amphetamine to release dopamine within the nucleus accumbens (Jones et al. 1992). Isolation rearing severely shifted to the right the intra-accumbens sulpiride dose-response function maintained by the intravenous self-administration of cocaine, but blocked completely the enhanced rates of response following sulpiride adulteration of the intra-accumbens self-administration of *d*-amphetamine. Sulpiride also appeared to impair the control over behaviour by isolation reared animals, at a ratio of sulpiride:*d*-amphetamine of 0.25: 1. The reasons for this minor discrepancy are not entirely clear, but may relate to the mode of administration of the reinforcing drugs. Hence, the intravenous mode of delivery of cocaine would entail the recruitment of a number of brain areas other than the nucleus accumbens, which in turn may provide afferent input to the nucleus accumbens not provided by the direct intra-accumbens method of delivery of *d*-amphetamine. Nonetheless, both procedures revealed a severe dysfunction of D2 dopamine receptors within the nucleus accumbens.

A number of closely related procedures also enhance the responsivity of the dopamine system afferent to the nucleus accumbens, including repeated systemic administration of psychomotor stimulants (Robinson et al. 1988) and intra-ventral tegmental area administration of opiate receptor agonists (Kalivas and Duffy 1990; see also Kalivas and Duffy 1987; Vezina et al. 1987), or repeated exposure to stressful stimuli (Stamford et al.

1991). These manipulations impaired the functional efficacy of both primary (Katz 1982; Rosellini et al. 1982; Zacharko et al. 1983, 1990; Willner et al. 1991) and conditioned reinforcers (Phillips et al. 1994c). This impaired responsivity to reinforcement has been linked to dysfunctional D2 dopamine receptors within the nucleus accumbens (Phillips et al. 1994c; Willner et al. 1991). Indeed, isolation-induced impairments have been reported recently in the ability of D2 dopamine receptors within the nucleus accumbens to inhibit the production of D1 dopamine receptor-stimulated cAMP (Wilkinson et al. 1993). Thus, manipulations of the mesoaccumbens projection of the mesolimbic dopamine system which enhance the responsivity of this pathway have been suggested to initiate a cascade of events, originating within the VTA before being "transferred" to the NAcc (Wolf et al. 1993; see also Kalivas and Duffy 1993a,b).

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