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Differences in the Liability to Self-Administer Intravenous Cocaine Between C57BL/6 × SJL and BALB/cByJ Mice

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DEROCHE, V., S. B. CAINE, C. J. HEYSER, I. POLIS, G. F. KOOB AND L. H. GOLD. *Differences in the liability to self-administer intravenous cocaine between C57BL/6 × SJL and BALB/cByJ mice.* PHARMACOL BIOCHEM BEHAV **57**(3) 429–440, 1997.—Application of animal models of psychostimulant abuse for experimentation in mice is becoming increasingly important for studying the contribution of genetic differences, as well as the roles of selected (targeted) genes, in specific behaviors. The purpose of this study was to investigate strain differences in cocaine self-administration behavior between C57BL/6 × SJL hybrid mice and BALB/cByJ mice. These two strains were chosen because BALB/cByJ mice have a well-developed behavioral pharmacological profile, and hybrid strains on a C57BL/6 background are commonly used for generating transgenic expressing and knockout mutant mice. C57BL/6 × SJL mice dose-dependently acquired cocaine self-administration (1.0 mg/kg/injection but not 0.25 mg/kg/injection) by responding selectively in the active nose-poke hole and maintaining stable levels of daily drug intake; they also exhibited a characteristic inverted-U-shaped cocaine dose–effect function. BALB/cByJ mice failed to acquire cocaine self-administration at either dose under the same test conditions. The strain differences observed in self-administration did not seem to be attributed to other behavioral differences because the two strains exhibited similar amounts of spontaneous nose-poking in the absence of reinforcers, and BALB/cByJ mice responded more than C57BL/6 × SJL mice in a food-reinforced nose-poke operant task. Importantly, the dose–effect function for the motor stimulating effects of cocaine (3.8–30 mg/kg intraperitoneally) suggests enhanced sensitivity but reduced efficacy of cocaine in stimulating motor activity in BALB/cByJ mice relative to the C57BL/6 × SJL hybrid mice. These results indicate that the decreased liability of BALB/cByJ mice to acquire cocaine self-administration is not the result of differences in spontaneous activity or performance, but may reflect different sensitivities to the reinforcing, or rate-disrupting, properties of cocaine. The data support an influence of genetic background in the liability to self-administer cocaine. Thus, a hypothesis is proposed that the decreased liability of BALB/cByJ mice to acquire cocaine self-administration is related to differences in brain monoamine systems linked to the high "emotionality" profile of BALB/c mice in novel or fearful situations, including perhaps cocaine administration. © 1997 Elsevier Science Inc.

Cocaine Inbred strains Motor activity Psychostimulant Reinforcement Self-administration

CONSIDERABLE individual differences are apparent in the liability to abuse drugs in clinical populations. Although a large number of people have tried drugs at least once, only a fraction of those individuals persist in drug-taking behavior (48). Genetic background profoundly influences the responses to drugs of abuse (16,23,55) and may therefore influence the predisposition to abuse drugs, a hypothesis supported by clinical observations (66).

Nevertheless, information about the genetic determinants of cocaine abuse have been hampered by the slow development of intravenous self-administration techniques in mice, despite the well-characterized murine genetics. Intravenous self-administration, which is well established in rats (47,54,67), was first implemented in restrained mice following repeated cannulation of the tail vein (17,32). More recently, chronic cannulation of the jugular vein has been employed for self-administration in freely moving mice (10), leading to a sophisticated characterization of cocaine self-administration in C57BL/6 mice (25). Use of the intravenous self-administration technique for mice has the same advantages that have made it such a powerful animal model in other species. Animals intravenously self-administer almost exclusively compounds abused by

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humans, and the specific pattern of intake for each drug is quite comparable (70).

The use of mice in intravenous self-administration experiments offers enormous advantages for studying the genetic determinants as well as the molecular mechanisms underlying drug abuse behavior. The availability of inbred strains and recombinant inbred strains, together with powerful analytical tools such as genetic correlations and quantitative trait loci analyses, may permit identification of genetic determinants for the liability to abuse drugs (16,23,35). Equally important is the utility of applying gene-targeting techniques, such as transgenic expression and knockout mutations, to the study of the molecular mechanisms underlying drug abuse and dependence (9,14,53,68).

The purpose of this study was to characterize the reinforcing effects of cocaine in one inbred, BALB/cByJ, and one hybrid, C57BL/6 × SJL, mouse strain using the intravenous self-administration technique. The selection of strains to be compared was based on several considerations. First, BALB/c mice have been studied extensively and have been shown to have markedly different behavioral and/or neurochemical profiles compared with other mouse strains, including C57BL/6, in tests such as exploratory activity, avoidance and maze learning, emotionality (fearfulness), responses to stressful stimuli, intracranial self-stimulation and responses to psychostimulant and opiate drugs. Second, because C57BL/6 is a common parental background strain used for generating knockout (e.g., C57BL/6 × 129) and transgenic (e.g., C57BL/6 × SJL) mice, characterization of the hybrid would contribute to an emerging database of the behavioral traits of these hybrid strains. Finally, this study sought to contribute to the literature on genetic differences in intravenous cocaine self-administration behavior by extending observations beyond those already demonstrated for the C57BL/6J and DBA/2J mouse strains (10,24). To examine whether strain differences observed in self-administration might be attributable to other behavioral differences, groups of naive mice were also tested for: a) spontaneous nose-poke activity in the absence of reinforcers, b) acquisition of a food-reinforced task identical to that used for self-administration, and c) the unconditioned motor response to cocaine.

METHODS

Subjects

Adult male mice from one inbred strain (BALB/cByJ, n = 89) and one F1 hybrid cross (C57BL/6 × SJL, n = 70), obtained from The Scripps Research Institute breeding colony, were housed 2–10 mice/cage in Plexiglas cages (28 × 17 × 11.5 cm or 44 × 23 × 19.5 cm) with sawdust bedding changed weekly. Colony temperature was maintained at 24°C. Subjects for motor activity and food-reinforced operant studies were maintained under conditions of a regular light/dark cycle (lights on 0600 h, lights off 1800 h), whereas those for self-administration and spontaneous nose-poke responding studies were maintained under conditions of a reverse light/dark cycle (lights on 2200 h, lights off 1000 h). Subjects were provided food and water ad lib, except for subjects in food-reinforced operant studies, which were maintained under conditions of food restriction at 85% of their initial body weight. Animals tested for food-reinforced operant responding were weighed prior to each daily training session (conducted Monday through Friday) and were given food for a 3-h period following completion of each training session and for a 3-h period daily on the weekends.

Drugs

Cocaine hydrochloride (NIDA, Rockville, MD, USA), Brevital Sodium (methohexital sodium; Eli Lilly, Indianapolis, IN, USA), Streptase (streptokinase; Astra Pharmaceutical Products, Westborough, MA, USA), and Timentin (ticarcillin disodium and clavulanate potassium; SmithKline Beecham, Philadelphia, PA, USA) were dissolved in saline (0.9%).

Apparatus

Operant chambers. The same six small Plexiglas chambers (14.9 × 15.2 × 18.3 cm) were used for studies examining drug-reinforced, food-reinforced, and nonreinforced nose-poke responding. These small chambers were located within larger exterior boxes (Coleman coolers) equipped with exhaust fans that also functioned to mask background noise. Each chamber contained one wall with two small holes (0.9 cm diameter, 4.2 cm apart, 1.5 cm from the floor) equipped with photobeams to detect nose-poke responses. When the photocell in the hole defined as active was triggered by a nose-poke, the infusion pump or pellet dispenser was activated to deliver one reinforcer (one injection or one food pellet). Following reinforcer delivery, a timeout period was initiated during which further nose-pokes were recorded but did not result in additional reinforcers. A nose-poke in the other hole, defined as inactive, was without scheduled consequences at any time. The interior of the experimental chambers was dark during all operant testing. The chambers were fully removed and disassembled periodically for cleaning and disinfecting to ensure the health and welfare of the animals.

For intravenous self-administration, a small Plexiglas divider (5.4 × 6.4 × 0.3 cm) separated the two nose-poke holes. Thus, the animal was required to walk around, or climb over, the divider to go from one hole to the other. Nose-poke responses in the hole defined as active produced an infusion (50 μl/2 s) from a 10-ml syringe containing the cocaine solution attached to a Razel® syringe pump (mounted outside the exterior box) equipped with a 5-rpm motor. The syringe was connected via Tygon tubing to a swivel, constructed in the laboratory according to Brown et al. (5), mounted on a balance arm above the Plexiglas chamber. A small length of Tygon tubing attached to the exit of the swivel entered the chamber from above and was connected to the external cannula of the intravenous catheter in the mouse.

For food-reinforced operant responding, the Plexiglas divider was removed and replaced by a metal food trough. Nose-poke responses in the active hole triggered a pellet dispenser mounted outside the Plexiglas chamber (Ralph Gerbrands Co., Arlington, MA, USA) to deliver food pellets (20 mg; P. J. Noyes Co. Inc., Lancaster, NH, USA) into the trough.

Motor activity. Motor activity was measured in large Plexiglas cages placed into frames (29.2 × 50.5 cm) mounted with photocell beams (San Diego Instruments, San Diego, CA, USA). The horizontal locomotion frames consist of a 4 × 8 array of beams. A second tier frame (7 cm in height) consisting of eight beams equally spaced along the long axis was used to record vertical activity (rearing). The numbers of total beam breaks (horizontal plus vertical) were evaluated.

General procedures

Catheter construction, implantation surgery, and maintenance. The chronic intravenous catheter for mice was similar to that described previously for use in rats (8), with minor modifications in sizing (1) and materials (19). Briefly, one end

of a 6-cm length of soft Silastic tubing (i.d. 0.30 mm, o.d. 0.64 mm) was immersed in Hemo-de (solvent) to expand the tip for fitting to a 22-ga steel cannula with a plastic screw-threaded pedestal (collar) and bent at a right angle. The cannula was then encased in dental cement with a piece of durable mesh secured to the bottom, and a small dab of silicone-based adhesive was placed 1.2 cm from the open tip of the Silastic tubing. The catheters were immersed in 70% ethanol for 20 min prior to surgical implantation. After implantation, the exposed tip of the external cannula was secured with a stopper consisting of a small piece of removable Tygon tubing closed at one end with monofilament.

Catheter implantation surgery. The mouse was anesthetized with a halothane/oxygen vapor mixture and maintained at approximately 1.5% halothane delivered via a miniature nosecone with tubes for vapor entry and exhaust to a ventilation system. Throughout the procedure, the animal was supported by a heating pad to prevent hypothermia. After shaving and application of 70% alcohol and iodine preparatory solution, incisions were made in the midscapular region as well as anteromedial to the forearm above the external right or left jugular vein. A catheter was passed subcutaneously from the dorsal incision to the ventral incision. Following isolation of the jugular vein, a 22-ga needle was inserted into the vein 0.5 cm above the pectoral muscle, to facilitate insertion of an 18-ga modified needle that had been filed to be used as a guide for the Silastic tubing. Once the tubing was inserted approximately 0.6 cm into the vein, the modified needle was removed and the tubing was further inserted to the level of the small dab of silicone-based adhesive. The catheter was then tied gently to the vein with two sutures (surgical silk 4-0; Ethicon), one suture above and one suture below the small dab of silicone. Approximately 50 μl of physiological saline mixed with Timentin (100 mg/1.5 ml) and Streptase (1.3 mg/ml) was flushed through the catheter to prevent infection and sustain catheter patency, and the catheter was then capped with a Tygon stopper. Animals were allowed a minimum of 4 days recovery before the beginning of self-administration testing.

Catheter evaluation, maintenance, and repair. Methohexital sodium is an ultra-short-acting barbiturate that when flushed through the catheter produces overt signs of sedation within seconds. The methohexital test was performed once prior to the first self-administration session and once after every five self-administration sessions thereafter. At least 4 h after a cocaine self-administration session, and at least 12 h prior to the next session, approximately 25–50 μl of aqueous 1% methohexital sodium was flushed through the catheter. Animals that showed no signs of sedation were removed from the experiment or were recatheterized in the left jugular vein. The catheters were routinely maintained for the first 3 days following surgery by flushing daily with 50 μl of saline mixed with Timentin and Streptase. Thereafter, the catheters were flushed with 50 μl of saline mixed with heparin (30 units/ml) prior to a self-administration session and the same solution but including Streptase (1.3 mg/ml) following the self-administration session. The maintenance procedures for the catheters were modified from Emmett-Oglesby and Lane (19).

Intravenous self-administration. Self-administration sessions (one per day, 2 h each, 7 days/week) were conducted between 1200 and 1800 h. Cocaine was available under a fixed-ratio 1 (FR 1) schedule throughout the experiment. Acquisition of cocaine self-administration was tested at a dose of 0.25 mg/kg/injection with a 4-s timeout period or a dose of 1.0 mg/kg/injection with a 20-s timeout period (n = 20 BALB/cByJ and n = 16 C57BL/6 × SJL). The longer timeout period was used for the higher cocaine dose to minimize the risk of accidental overdose during initial exposures to the drug, whereas a shorter timeout period was used for the lower dose in an attempt to facilitate self-administration. Acquisition was tested for a minimum of five, and a maximum of seven, consecutive sessions. Stable responding, termed "baseline," was defined as at least three consecutive self-administration sessions in which the total number of reinforcers (total cocaine intake) remained constant within 20% deviation of the mean of these sessions and, in addition, required greater than 70% active-specific responses (active nose-pokes/total nose-pokes) over two consecutive self-administration sessions. Following acquisition at 1.0 mg/kg/injection, a dose–response study was performed in which the dose of cocaine was varied such that a new dose was introduced and presented for 3 consecutive days before changing the dose again. The doses (0.13, 0.25, 0.5, 1.0, 2.0, and 4.0 mg/kg/injection) were randomized according to a Latin square design to compare order effects; saline substitution for cocaine was given last to minimize the influence of extinction.

Spontaneous nose-poke responding in naive mice. Groups of naive noncatheterized C57BL/6 × SJL and BALB/cByJ mice (n = 6/strain) were placed in the self-administration chambers under conditions similar to those applied for a self-administration session (2 h) except that scheduled reinforcement was not available. The number of nose-pokes in both holes was recorded.

Food-reinforced operant responding. Training sessions (one per day, 15 min each, 5 days/week) were conducted between 0800 and 1100 h for 5 consecutive days. Access to food pellets was on an FR 1 schedule. One group of animals (n = 8/strain) was trained with no timeout period, and a second group (n = 8/strain) was trained using a 4-s timeout period in an effort to more accurately mimic the drug self-administration procedure.

Motor activity. Motor activity testing was performed during the light portion of the light/dark cycle under ambient overhead lighting conditions. Mice were brought into the motor activity testing room 1 h prior to the start of testing. After a 2-h period of habituation to the motor activity cages, mice were injected with saline and their motor response was recorded for an additional 2 h. Two days later, the same procedure was applied to the same groups of mice, but instead of saline, animals were injected with cocaine. In both strains, four doses of cocaine were tested (3.8, 7.5, 15, or 30 mg/kg) using a between-subjects design (n = 47 BALB/cByJ, n = 32 C57BL/6 × SJL). All injections were administered intraperitoneally (IP) in a volume of 1 ml/100 g body weight.

Data Analysis

Given that similar dependent variables were involved in the two operant paradigms (acquisition of a nose-poke response using food or cocaine as a reinforcer), these data were analyzed in similar fashion. The total number of responses and a discrimination index were used as the dependent measures in the analyses of the acquisition of these operant tasks. The number of responses was analyzed by a three-way repeated measures ANOVA, with strain (BALB/cByJ vs. C57BL/6 × SJL) as a between-subjects factor and hole (active vs. inactive) and day (each daily session) as within-subjects factors. The discrimination index was calculated at the end of each session for each animal (active responses/total responding). Discrimination indexes were analyzed by a two-way repeated measures ANOVA, with strain as a between-subjects factor and day as a within-subjects factor. In addition, for the

dose–effect experiment, the number of reinforcers was analyzed by a three-way repeated measures ANOVA, with strain as a between-subjects factor and hole and dose of cocaine as within-subjects factors. For motor activity studies, the total number of beam breaks following saline and cocaine challenge was analyzed by a two-way repeated measures ANOVA, with dose of cocaine as a between-subjects factor and treatment (saline vs. cocaine) as a within-subjects factor. Newman–Keuls, Duncan's, and simple main effects analyses were used to determine the locus of significant main effects and interactions. A significance level of $p < 0.05$ was used for all statistical analyses.

RESULTS

Cocaine Intravenous Self-Administration

Acquisition study. BALB/cByJ and C57BL/6 × SJL mice differed in the acquisition of intravenous cocaine self-administration under the conditions tested. Although neither strain of mice acquired stable self-administration at 0.25 mg/kg/injection, C57BL/6 × SJL mice achieved baseline criteria at 1.0 mg/kg/injection. Thus, at 0.25 mg/kg/injection, for both strains, the number of active responses did not differ from the number of inactive responses and animals did not stabilize drug intake (Fig. 1A, C). However, total overall responding [$F(1, 10) = 29.3$, $p < 0.0005$] was significantly higher in C57BL/6 × SJL mice ($n = 5$) as compared with the BALB/cByJ mice ($n = 7$).

At 1.0 mg/kg/injection, BALB/cByJ and C57BL/6 × SJL mice ($n = 7$/strain) differed in the number of nose-poke responses in both holes over the 5 days of testing [strain × hole × day interaction, $F(4, 48) = 4.28$, $p < 0.005$]. C57BL/6 × SJL mice exhibited consistent responding in the hole resulting in cocaine delivery but a gradual and sustained decrease in responding in the inactive hole [hole × day interaction, $F(4, 24) = 4.61$, $p < 0.01$] (Fig. 1B). This pattern of responding resulted in a progressive increase of the discrimination index (active responses divided by total responses) [$F(4, 24) = 9.5$, $p < 0.0001$] (Fig. 2B). The value for inactive responses on day 2 for one mouse was greater than 2 standard deviations from the inclusive group mean and therefore was replaced by the group mean value. In BALB/cByJ mice, the number of nose-poke

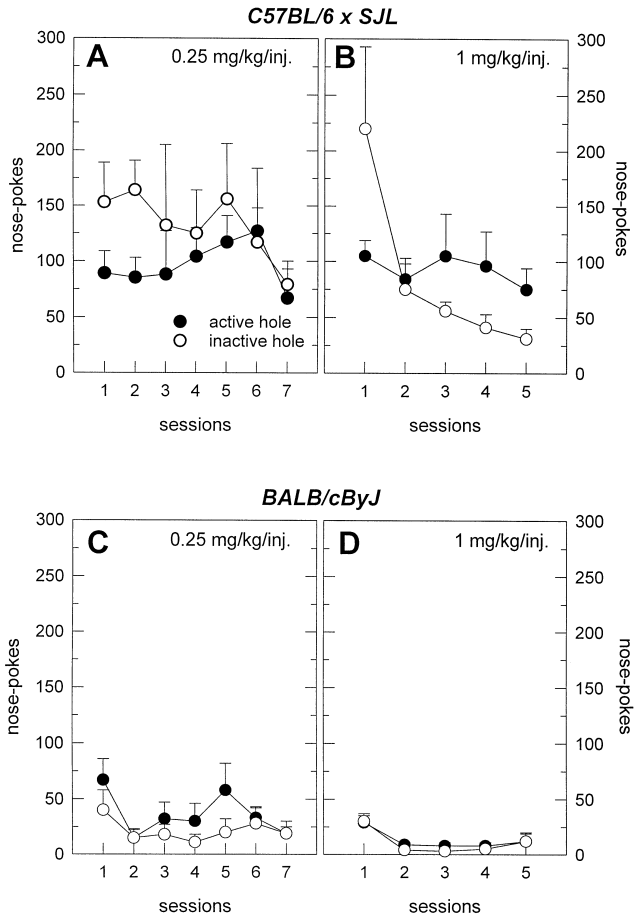

FIG. 1. Intravenous cocaine self-administration in C57BL/6 × SJL (upper panel) and BALB/cByJ (lower panel) mice. Acquisition was studied at 0.25 mg/kg/injection (A, $n = 5$; C, $n = 7$) or 1.0 mg/kg/injection (B, $n = 7$; D, $n = 7$) for seven or five training sessions, respectively. Values represent mean ± SEM number of active (filled circles) and inactive (open circles) nose-poke responses for each 2-h session.

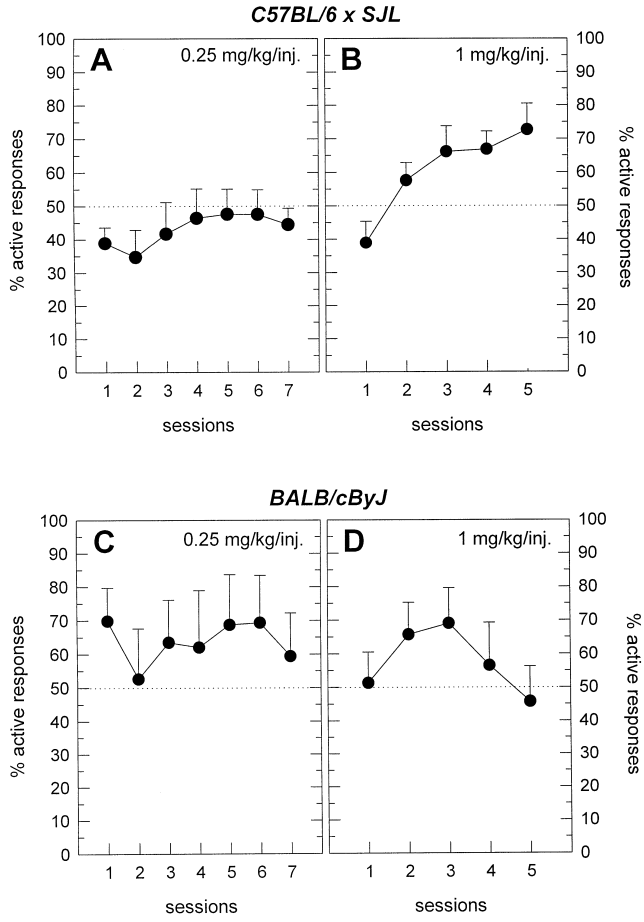

FIG. 2. Intravenous cocaine self-administration in C57BL/6 × SJL (upper panel) and BALB/cByJ (lower panel) mice. Acquisition was studied at 0.25 mg/kg/injection (A, C) or 1.0 mg/kg/injection (B, D) for seven or five training sessions, respectively. Data are portrayed as mean ± SEM percent active responses (discrimination index). Chance performance (active/total responses = 50%) is indicated by dotted lines.

responses in both holes was similar, resulting in a lack of discrimination (<70%) after 5 days of testing (Fig. 2D). At 1.0 mg/kg/injection, as for the lower dose, total nose-poke activity was significantly lower in the BALB/cByJ as compared with the C57BL/6 × SJL mice [$F(1, 12) = 24.25, p < 0.0005$].

Overall, of mice that started self-administration training, there was a 30% (6/20) failure rate for catheters in the BALB/cByJ mice and a 12.5% (2/16) failure rate in C57BL/6 × SJL mice. All catheter failures occurred during the acquisition phase, and data from these animals were not included in the results.

Dose–effect study. Results are presented for a group of C57BL/6 × SJL mice ($n = 6$) that met baseline criteria for intravenous cocaine self-administration (1.0 mg/kg/injection). In these mice, substitution of different doses of cocaine resulted in dose-dependent changes in the number of reinforcers obtained [ANOVA, dose effect, $F(6, 30) = 8.08$, $p < 0.0001$] (Fig. 3A). Further analysis revealed that responding for the two lowest doses of cocaine was significantly higher than responding for saline. Higher doses of cocaine produced a characteristic pattern of dose-dependent decreases in responding as a result of increases in the interval between injections (see Fig. 4). The discrimination of the active nose-poke was also dose-dependent [ANOVA, dose effect, $F(6, 30) = 7.7$, $p < 0.0001$], with the discrimination index decreasing for lower doses of cocaine (Figs. 3B, 4). The response profile for a representative C57BL/6 × SJL mouse is shown in Fig. 4. Loss of the discrimination between active and inactive nose-poke responses at lower cocaine unit doses, contrasted with increases in the interinjection interval and enhanced discrimination at higher doses, is supportive of self-administration behavior based on a response–reinforcer contingency.

Nonreinforced exploratory behavior in the self-administration chamber. There was no inherent response bias to either nose-poke hole, as indicated by the absence of preference for one hole [ANOVA, hole effect, $F(1, 10) = 0.0108$, $p = 0.75$] in both strains [ANOVA, strain × hole interaction, $F(1, 10) = 0.047$, $p = 0.83$]. In contrast to the tests for acquisition of cocaine self-administration, there was no difference in total nonreinforced nose-pokes between the BALB/cByJ mice (mean ± SEM = 654.1 ± 102.1) and C57BL/6 × SJL mice (533.3 ± 134) [ANOVA, strain effect, $F(1, 10) = 1.29$, $p = 0.28$].

Food-reinforced operant responding. Both strains acquired operant responding for food under an FR 1 schedule (Fig. 5A). Each strain of mice exhibited increased responding in the hole resulting in food delivery, along with a gradual and sustained decrease in responding in the inactive hole [hole × day interaction, $F(4, 28) = 34.55$, $p < 0.0001$ for BALB/cByJ, $F(4, 28) = 6.81$, $p < 0.001$ for C57BL/6 × SJL]. The number of active responses became significantly greater than the number of inactive responses on day 3. However, BALB/cByJ and C57BL/6 × SJL mice differed in total number of responses for food [ANOVA, strain × day × hole interaction, $F(4, 56) = 4.57$, $p < 0.01$]. BALB/cByJ mice made significantly more reinforced responses than hybrid mice during the last 3 days of testing, while the two strains did not differ significantly for inactive nose-pokes. The discrimination index increased across sessions [ANOVA, day effect, $F(4, 56) = 35.75$, $p < 0.0001$] to a level above chance performance (>50% active/total responses) from day 3 to the end of training (Fig. 5B). However, percent active responding did not differ between strains [ANOVA, strain × day interaction, $F(4, 56) = 1.462$, $p = 0.22$].

Relative to the schedule with no timeout period, when a 4-s timeout period was employed, BALB/cByJ [ANOVA, day × hole interaction, $F(4, 28) = 17.4$, $p < 0.0001$] and C57BL/6 × SJL mice [ANOVA, day × hole interaction, $F(4, 28) = 9.83$, $p < 0.0001$] acquired the operant task but acquisition was delayed (Fig. 5C). Under these conditions, the number of active responses became significantly greater than the number of inactive responses on day 4. As when trained with no timeout, BALB/cByJ and C57BL/6 × SJL mice differed in the total number of responses [ANOVA, strain × day × hole interaction, $F(4, 56) = 3.519$, $p < 0.01$]. BALB/cByJ mice made more active responses than C57BL/6 × SJL mice on days 4 and 5, while the two strains did not differ for inactive responses at any time. The discrimination index increased across sessions [ANOVA, day effect, $F(4, 56) = 25.28$, $p < 0.0001$] to a level above chance performance on days 4 and 5 (Fig. 5D). However, percent active responding did not differ between strains [strain × day interaction, $F(4, 56) = 0.747$, $p = 0.5644$].

Cocaine-induced motor activity. Due to the short duration of action of cocaine, only the data collected during the first 60 min of all motor activity sessions were analyzed and represented graphically. Data for the total amount of activity for saline and cocaine tests are presented for each dose group for both the BALB/cByJ strain and the C57BL/6 × SJL strain. All doses reflect $n = 8$ mice/group, except 7.5- and 15-mg/kg

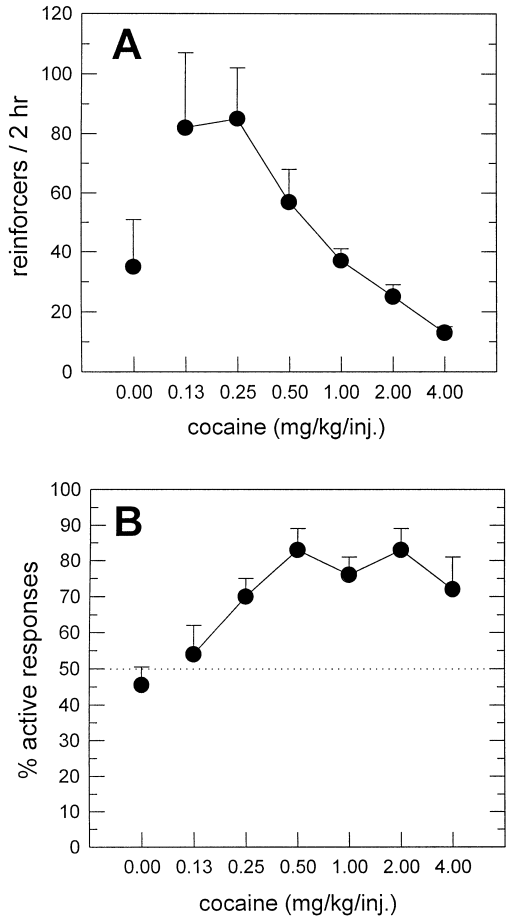

FIG. 3. Dose–effect curves for cocaine self-administration in C57BL/6 × SJL mice ($n = 6$). Number of reinforcers (A) and % active responses (discrimination index; B) are shown as a function of varying cocaine unit dose. Values represent the mean ± SEM of the 3-day substitution with each dose. Chance performance (active/total responses = 50%) is indicated by the dotted line (B).

doses for the BALB/cByJ mice, which represent 15–16 mice/group. An additional group of BALB/cByJ mice was tested at each of these doses because there was considerable variability in the response at the 7.5-mg/kg dose in the original group tested. In both strains, cocaine produced a significant increase in motor activity as compared with saline levels [treatment effect, $F(1, 43) = 24.83$, $p < 0.001$ for BALB/cByJ mice, $F(1, 28) = 43.9$, $p < 0.0001$ for C57BL/6 × SJL; Fig. 6, upper panel]. However, all doses of cocaine produced motor stimulation of a similar magnitude in the BALB/cByJ mice, whereas the C57BL/6 × SJL hybrid mice exhibited a dose-related elevation [dose × treatment interaction, $F(3, 28) = 13.65$, $p < 0.001$], increases being significant only at the two highest doses, 15 mg/kg ($p < 0.0001$) and 30 mg/kg ($p < 0.0001$). A between-strains analysis of total motor activity following cocaine administration indicated that there was a significant difference in the dose–effect curves [group × dose interaction $F(3, 71) = 7.4$, $p < 0.001$] accounted for by differences in the response to the two highest doses of cocaine (15 and 30 mg/kg). Furthermore, a comparison of the motor activity following cocaine 30 mg/kg with saline for each strain using a 2-factor repeated measures ANOVA revealed that the maximal stimulation produced by cocaine in this study was higher in the C57BL/6 × SJL than in the BALB/cByJ mice [$F(1, 14) = 6.2$, $p < 0.05$]. The 60-min time course of motor activity portrayed in 10-min intervals is shown in Fig. 6, lower panel. Because there were no significant differences among saline treatments within strains, the saline tests that preceded each cocaine dose were pooled for graphical presentation of the time course effects.

DISCUSSION

In this study, C57BL/6 × SJL mice dose-dependently and rapidly acquired cocaine self-administration. By the fifth day of testing, these mice responded selectively in the active nose-poke hole and maintained stable levels of daily drug intake. The acquisition of cocaine self-administration observed here in C57BL/6 × SJL mice was remarkably similar to that recently reported for the C57BL/6 parental strain (25). Following the acquisition phase, the C57BL/6 × SJL mice exhibited a characteristic inverted-U-shaped dose–effect function when different doses of cocaine were substituted for cocaine self-administration. In contrast to C57BL/6 × SJL mice, when tested under identical test conditions, BALB/cByJ mice failed to acquire self-administration of either dose of cocaine as determined by the criteria established in this study.

It should be noted that only two doses of cocaine were systematically tested in the acquisition studies presented here. Therefore, it is possible that lower, or higher, doses than those examined might have supported self-administration in BALB/cByJ mice under these conditions. However, in other studies in this laboratory, doses of cocaine even lower (0.10 and 0.20

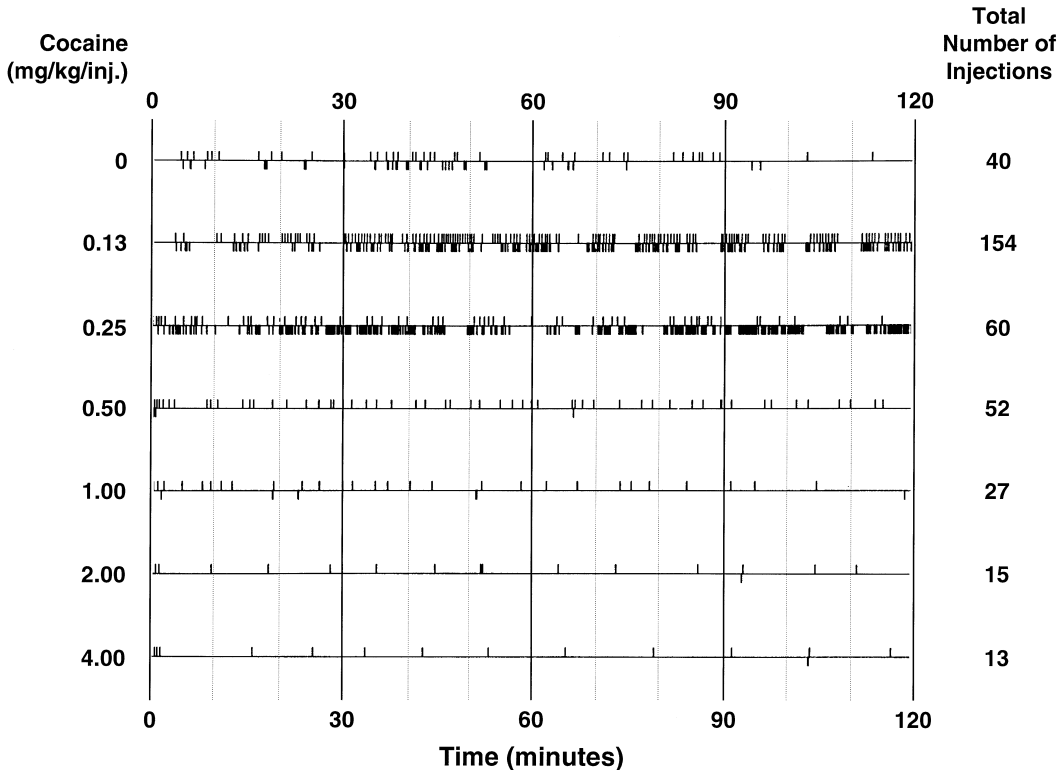

FIG. 4. Event record of nose-poke responding for a representative C57BL/6 × SJL mouse self-administering various doses of cocaine. The last day of each 3-day dose substitution is shown, with the exception of 1.0 mg/kg/injection, which represents the final day of acquisition. Time is depicted along the horizontal axis. Each upward deflection denotes nose-pokes resulting in delivery of a single injection (active nose-poke), and each downward deflection indicates nose-pokes with no programmed consequence (inactive nose-pokes). Doses of cocaine are shown to the left of each record, and the total number of injections/session to the right.

mg/kg/injection IV) than the lowest dose tested here failed to maintain stable responding in naive BALB/cByJ mice (50). Finally, different results may have been obtained if the training period had been extended for the BALB/cByJ mice, as has recently been shown for DBA/2J mice (24).

The decreased ability of BALB/cByJ mice to acquire cocaine self-administration under conditions identical to those that were found to support self-administration in C57BL/6 × SJL mice was unlikely to be the result of performance or learning deficits. First, equivalent amounts of nose-poking activity were observed in the two strains of mice in the absence of reinforcers. More importantly, the BALB/cByJ mice performed comparably to the C57BL/6 × SJL mice in a similar task in which food pellets functioned as the reinforcer. These findings are consistent with previous reports that BALB/c mice perform better than C57BL/6 mice in tests of avoidance conditioning and maze learning (4) and in operant tasks for reinforcers other than cocaine (11).

It is possible that differences in pharmacokinetics could account for differences in the behavioral effects of cocaine between BALB/cByJ and C57BL/6 × SJL mice. However, Ruth and colleagues (52) have demonstrated similar brain concentrations of cocaine in BALB/c and C57BL/6 mice following systemic injections of cocaine (5 mg/kg IP). Clearly such measurements need to be performed across a wide variety of mouse strains.

Although the behavior of the C57BL/6 × SJL hybrids is likely to be influenced by both parental lines, the discussion of our results will focus on previous comparisons of BALB/c mice (various substrains have been utilized historically) with C57BL/6 mice. To date, there has been little behavioral pharmacological characterization of the SJL background [but see (34) for nicotine responsivity] and virtually no studies describing the behavioral traits of this hybrid cross. Interestingly, a comparison of strains in a food-reinforced operant task identical to that described here has shown that C57BL/6, SJL, and C57BL/6 × SJL hybrids exhibit similar performance. In addition, the rate-disruptive effects of cocaine on operant responding were virtually identical between the C57BL/6 and hybrid mice (27).

Because the BALB/cByJ mice appeared more sensitive than C57BL/6 × SJL mice to the motor stimulant properties of low doses of cocaine, it may be postulated that the doses of cocaine presented for self-administration produced motor effects typically seen in rodents after treatment with high doses of psychostimulants, such as stereotyped behaviors, that may have interfered with the ability of BALB/cByJ mice to respond to cocaine as a reinforcer. Although stereotyped behavior was not systematically rated in this study, observation of BALB/cByJ mice during the self-administration sessions suggested that cocaine more often produced an immobility in the BALB/cByJ mice (see below), rather than repetitive local movements suggestive of stereotyped behavior. Others have shown that BALB/c mice, as compared with C57BL/6 mice, are not particularly sensitive to dopaminergic agonist-induced stereotyped behavior (7,11,56,60). However, Cazala (11) has described interesting qualitative differences between BALB/c mice relative to C57BL/6 mice following high, behavior-disrupting doses of *d*- or *l*-amphetamine in that while the BALB/c manifested immobility, the C57BL/6 exhibited stereotyped movements like those observed in the rat.

Studies of psychostimulant-induced activity have generally reported a reduced stimulant effect in BALB/c mice relative to C57BL/6 mice, or an absence of hyperactivity in BALB/c mice, following challenges with amphetamine (37,41), cocaine (18,49,52,59), or apomorphine (7,60). In many cases, however, only a single dose of the stimulant was tested (37,49,59,60), thus making conclusions about the direction of differences in sensitivity to the drug problematic. Some studies reported qualitative differences in responses to stimulants between the different strains, such as opposite effects of amphetamine (0.5–2.0 mg/kg IP), which dose-dependently increased activity in C57BL/6 but decreased activity in BALB/c mice, and scopolamine (2.0–6.0 mg/kg IP), which dose-dependently increased activity in BALB/c but decreased activity in C57BL/6 mice (41). Cocaine dose-dependently increased Y-maze crossing activity in C57BL/6 mice, but only decreased rearing in BALB/c mice (52). Taken together, these various studies may be consistent with our findings of enhanced sensitivity but reduced efficacy of cocaine in stimulating motor activity in BALB/cByJ mice relative to the C57BL/6 × SJL hybrid mice. Given that acute cocaine administration produces anxiogenic

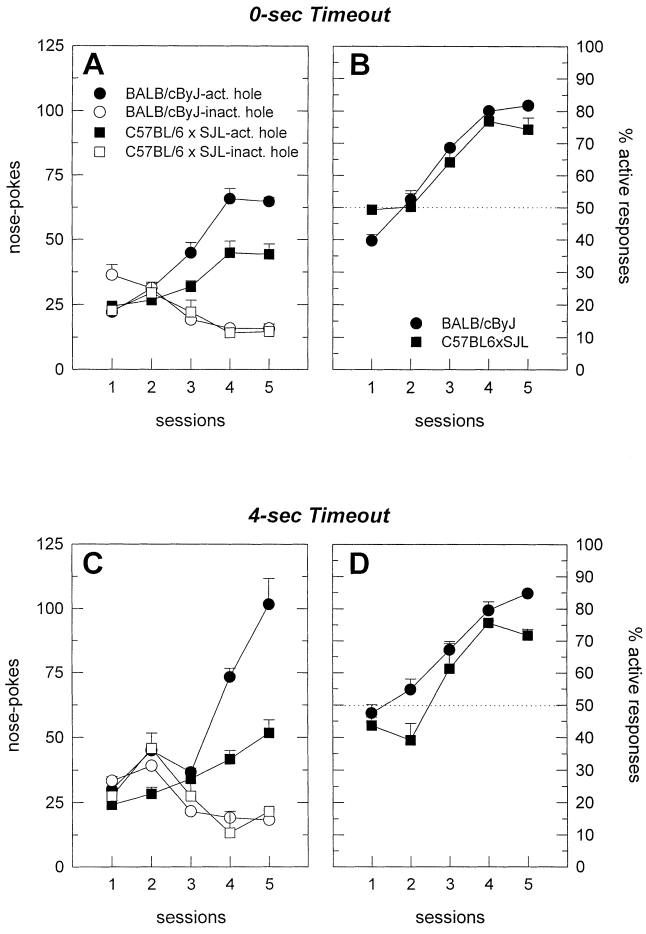

FIG. 5. Food-reinforced operant responding in BALB/cByJ and C57BL/6 ± SJL mice under an FR 1 schedule with no timeout (upper panel) or an FR 1 schedule with 4-s timeout (lower panel) for five training sessions. In panels A and C, values represent mean ± SEM number of active (filled circles) and inactive (open circles) nose-poke responses for each 15-min session. In panels B and D, data are expressed as mean ± SEM percent active responses (discrimination index). Chance performance (active/total responses = 50%) is indicated by dotted lines (B, D). n = 8 mice/strain under each schedule.

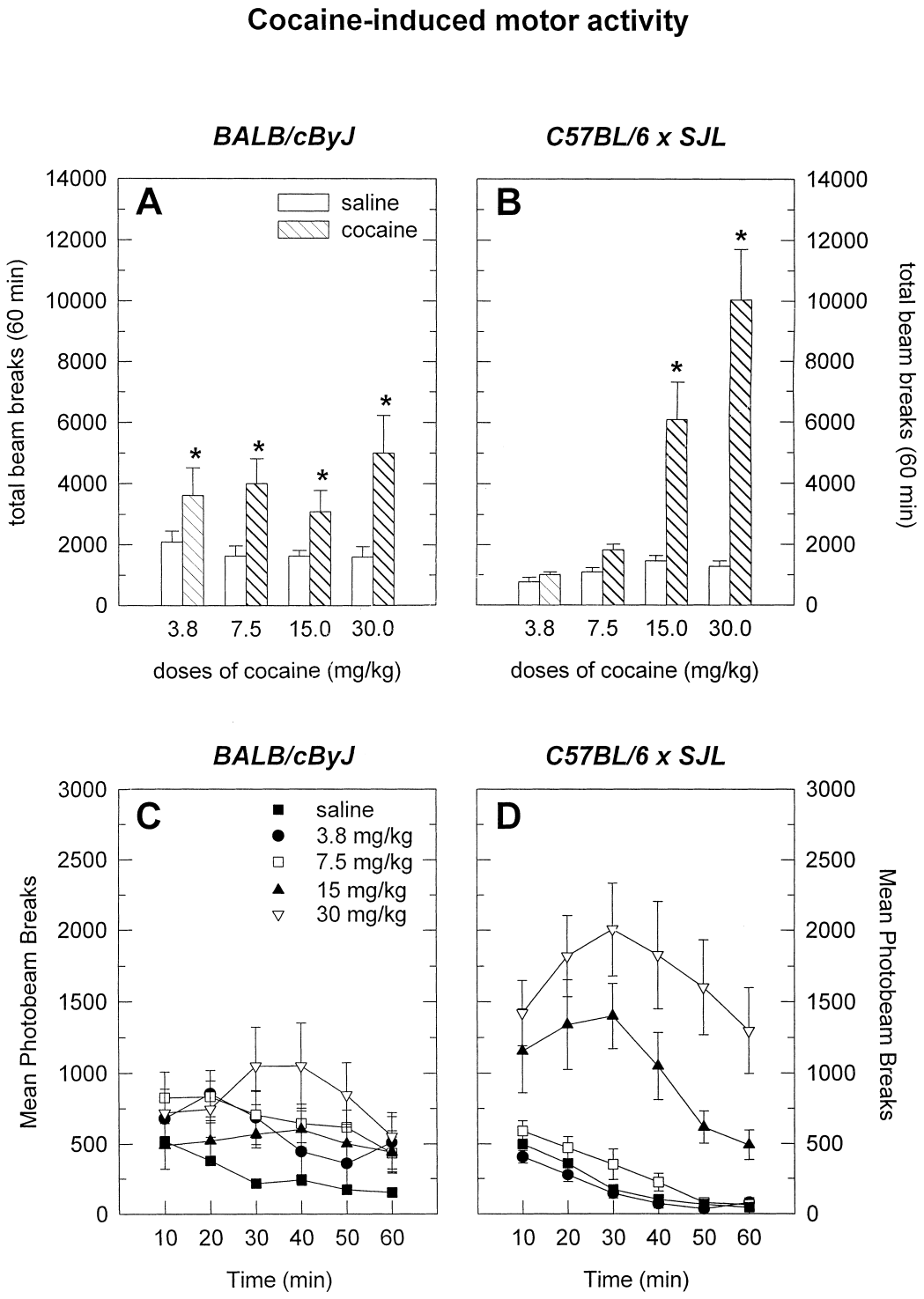

FIG. 6. Dose–effect function of cocaine-induced motor activity in BALB/cByJ (A, C) and C57BL/6 × SJL mice (B, D). In panels A and B, values represent mean ± SEM total photocell beam interruptions for 60 min following IP injections of cocaine (3.8–30 mg/kg) or saline. In panels C and D, the time course of motor activity is portrayed using 10-min means ± SEM with all saline data pooled for graphical presentation. All doses reflect $n = 8$ mice/group, except the 7.5- and 15-mg/kg doses for the BALB/c mice, which represent 15 or 16 mice/group. *$p < 0.05$ as compared with saline.

effects in rodents (22,58,69) including mice (15), such an influence may oppose the psychostimulant effects of cocaine, particularly in BALB/c mice. Because self-administered cocaine also produces anxiogenic effects in rodents (20,21), it is tempting to speculate that a dominance of anxiogenic effects of cocaine over other effects of cocaine in BALB/cByJ mice is related to the reduced liability of this strain to self-administer cocaine observed in the present study.

Compared with C57BL/6 mice, BALB/c mice have higher brain levels of serotonin (33,61), lower brain levels of norepinephrine (2,56,61), and up to twice the brain concentration of tyrosine hydroxylase (12). However, BALB/c mice are not different from C57BL/6 mice in striatal dopamine concentrations (56), basal dopamine metabolism (38,60), dopamine uptake sites, or inhibition of dopamine reuptake induced by cocaine (3,49). There are conflicting reports in the literature in relation to quantitative differences in D-2 dopaminergic elements and associated behavioral responses in these mouse strains. Some have reported striatal D-2 dopamine receptor binding to be twofold higher in BALB/c mice relative to C57BL/6, but no difference in haloperidol-induced catalepsy or apomorphine-induced stereotypy (56), whereas others have reported a decreased number of D-2 receptors in the striatum and substantia nigra associated with an increased sensitivity to haloperidol-induced catalepsy in BALB/c mice (31).

Of greater relevance perhaps is a small but intriguing literature demonstrating quantitative differences in dopaminergic responses in particular brain regions in response to stress, including novelty, between BALB/c and C57BL/6 mice (6,26,62). Thus, foot shock-induced stress increased the activity of mesocortical dopamine neurons, measured by changes in dopamine metabolism, by 380% and 200% of control values in BALB/c and C57BL/6 mice, respectively (26). More importantly, the introduction of the mice into a novel open field increased dopamine metabolism in the frontal cortex of BALB/c mice by an average 97%, but had no significant effect in C57BL/6 mice. These different neurochemical responses were inversely proportional to the motor activity of the two strains in the open field, and indeed the authors proposed that, relative to the C57BL/6 mice, the BALB/c mice exhibited high emotionality and reduced exploration, with increased sensitivity to stress, associated with an increased mesocortico-frontal dopaminergic response (62). Others confirmed the lack of changes in frontal cortical dopaminergic metabolism in C57BL/6 mice compared with another strain of mice (DBA), in response to immobilization stress (6). Importantly, cocaine administration can produce mesocortical dopaminergic activation similar to that produced by foot shock-induced stress in rats (30).

Such enhanced neurochemical and behavioral sensitivities to stress seem also to be apparent in the neuroendocrine axis in BALB/c mice. Thus, BALB/c mice show a marked sensitivity to CRF-induced decreases in locomotor activity and, conversely, an increased sensitivity to the anxiolytic effects of CRF receptor antagonists (13). In addition, compared with five other strains including C57BL/6, BALB/c mice exhibit the highest stress-induced corticosterone secretion (57). Taken together, these studies suggest that the BALB/c genotype may determine enhanced behavioral, neuroendocrine, and mesocortico-frontal dopaminergic responses to stress, including novelty-induced stress.

A large number of studies have analyzed individual differences in the liability of outbred rats to develop psychostimulant self-administration. These investigations suggest that animals predisposed to develop psychostimulant self-administration differ from more resistant subjects in a number of behavioral, neurochemical, and endocrinological features. Compared with resistant subjects, vulnerable subjects exhibit: a) increased locomotor activity in response to a novel environment (42) and to the injection of psychostimulants (29,42), b) decreased mesocortical and increased mesolimbic dopaminergic activity (28,29,46,51), paralleled by lower levels of tyrosine hydroxylase in the ventral tegmental area (39), and c) longer stress-induced corticosterone secretion (45) and hypersensitivity to both behavioral (43) and neural effects of corticosterone (44). Furthermore, positive correlations have been found between the rate of amphetamine self-administration during the acquisition phase and both the locomotor response to novelty and the plasma levels of corticosterone 2 h after stress.

If genotype contributes to these different behavioral and biochemical phenotypes associated with individual differences in the vulnerability for self-administering psychostimulants in outbred rats, then such individual differences might be manifested as group differences in inbred strains of mice with different genetic backgrounds. The data from the present study together with the literature on C57BL/6 and BALB/cByJ mice are consistent with, at least in part, the observations made in outbred rats. Thus, similar to resistant versus vulnerable rats, relative to C57BL/6, BALB/c mice exhibit: a) lower locomotor response to novelty (36,37,40,41,60–62,64,65), b) increased brain tyrosine hydroxylase (12), and c) enhanced mesocortical dopaminergic activation in response to stress, including novelty (26,62). However, contradictory to the prediction based on the rat models of individual vulnerability for psychostimulant self-administration, BALB/c mice exhibit: a) a greater stress-induced corticosterone response than C57BL/6J mice (57) and b) greater sensitivity to the motor stimulant properties of cocaine than C57BL/6J × SJL mice, but c) less liablity to self-administer cocaine under the present conditions than C57BL/6J × SJL mice.

This result prompts a closer examination of aspects of the BALB/cByJ behavioral and neurochemical phenotype that may resemble features so convincingly related to vulnerability for psychostimulant self-administration in rats. First, corticosterone secretion is also higher in Fisher than in Lewis rats, although Lewis rats seem to be more predisposed to acquire self-administration of a large variety of drugs (23). To explain this discrepancy it has been proposed (44) that the differences in stress-induced corticosterone secretion observed in outbred rats are environmentally determined, whereas the differences in their sensitivity to corticosterone are more influenced by genotype. Second, while cocaine stimulates motor activity at lower doses in the BALB/cByJ mice relative to the C57BL/6 × SJL mice, it seems less efficacious. Although the BALB/cByJ are very sensitive to low doses of cocaine, some behavioral effect of cocaine, perhaps an anxiogenic effect, may oppose or mask the motor stimulant properties of medium to higher doses of cocaine in BALB/cByJ mice. Given the medium dose of amphetamine (1.5 mg/kg) typically used to predict vulnerability for psychostimulant self-administration in rats (42), the BALB/c mice might therefore exhibit a "low responder" motor profile after amphetamine challenge. Moreover, a plethora of studies showed reduced exploratory activity of BALB/c mice, relative to other mouse strains, in novel environments that are particularly sensitive indicators of "emotionality" (fearfulness). Reduced exploration in response to novelty is in fact consistent with the behavioral phenotype of animals resistant to psychostimulant self-administration in the rat model of individual differences (42). This reduced exploration could result from either a hyporesponsiveness or a hyperresponsiveness

to novelty. The function relating arousal to performance is an inverted-U-shaped curve, and it may well be that BALB/c mice rest on the descending limb of this function.

BALB/c mice are shown to be mesocortically hypersensitive in their dopaminergic response to novelty in comparison with other mouse strains. Given the inverse relationship between frontal cortical and ventral striatal dopaminergic activation (63), it is tempting to hypothesize that the hypersensitivity of the mesocortical dopaminergic pathway in BALB/c mice in response to novelty-induced stress predicts a simultaneous hyposensitivity in the meso-accumbens pathway. Thus, if BALB/c mice are more sensitive to the anxiogenic properties of cocaine, they may be simultaneously less sensitive to the reinforcing effects of the cocaine, according to the presumed differential involvement of dopaminergic pathways in these different effects of the drug. Indeed, such an inverse relationship between mesocortical and mesolimbic dopaminergic activation, with a bias toward mesolimbic activation, has been demonstrated in rats predisposed to self-administer amphetamine (46), supporting the hypothesis that hyperactivation of the mesocortical dopamine pathway in BALB/c mice may contribute to their decreased liability to self-administer cocaine.

SUMMARY

In conclusion, the results presented here suggest that C57BL/6 × SJL hybrid mice are more likely to self-administer cocaine than are BALB/cByJ mice tested under identical conditions. The genetic determinants of this difference are unlikely to be related to differences in learning or performance because the BALB/cByJ mice performed comparably to C57BL/6 × SJL mice in a similar task reinforced with food pellets, and they have been shown to perform at least as well as C57BL/6 mice in other tests of learning (avoidance conditioning and maze learning) and motivation (intracranial self-stimulation). The differences in cocaine self-administration are more likely related to an increased responsiveness of BALB/c mice to novelty, including increased fearfulness and immobility and enhanced mesocortical dopaminergic activation, as well as increased endocrine (corticosterone) and central (CRF) responses to stress. Future studies may determine whether: a) BALB/cByJ mice exhibit a greater anxiogenic response to cocaine than other mice, b) BALB/cByJ mice exhibit a preferential mesocortical (relative to meso-limbic) dopaminergic response to cocaine, c) systemically administered anxiolytics (e.g., benzodiazepines) or centrally administered anxiolytics (e.g., CRF antagonists) increase the liability of BALB/cByJ mice to self-administer cocaine (20), and d) BALB/cByJ mice are liable to intravenously self-administer drugs of abuse with a lesser anxiogenic profile than cocaine (21).

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