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ORIGINAL INVESTIGATION

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Differential sensitivity to acute administration of cocaine, GBR 12909, and fluoxetine in mice selectively bred for hyperactive wheel-running behavior

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Abstract *Rationale:* To study the neural basis of genetic hyperactivity, we measured acute drug responses of mice (*Mus domesticus*) from four replicate lines that had been selectively bred (23–24 generations) for increased running-wheel activity. *Objectives*: We tested the hypothesis that the high-running lines would respond differently to cocaine, GBR 12909, and fluoxetine (Prozac) compared with four replicate, random-bred, control lines. We also tested the hypothesis that the high-running lines would display hyperactivity in cages without wheels. *Methods*: Drug trials were conducted at night, during peak activity, after animals were habituated (3 weeks) to their cages with attached wheels. Revolutions on wheels 10–40 min post-injection were used to quantify drug responses. In a separate study, total photobeam breaks (produced on the first and second 24-h period of exposure) were used to quantify basal activity in animals deprived of wheels. *Results:* Cocaine and GBR 12909 decreased wheel running in selected lines by reducing the average speed but not the duration of running, but these drugs had little effect in control lines. Fluoxetine reduced running speed and duration in both selected and control animals, and the magnitude of the reduction was proportional to baseline activity. Basal activity in animals deprived of wheels (quantified using photobeam breaks) was significantly higher in selected than control lines on the second day of testing. *Conclusions:* These results suggest an association between genetically determined hyperactive wheel-running behavior and dysfunction in the dopaminergic neuromodulatory system. Our selected lines may prove to be a useful genetic model for attention deficit hyperactivity disorder.

Keywords ADHD · Dopamine · Genetic selection · Hyperactivity · Locomotor activity · Wheel running

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Introduction

Understanding the genetic basis of behavior is one major goal of neuroscience. Although genetic engineering contributes toward such an understanding (Xu et al. 1994; Baik et al. 1995; Giros et al. 1996), this approach has limitations. For example, if behavior is controlled by many genes working in concert, then the proportion of behavior explained by single-gene manipulations will be small relative to the proportion explained by manipulations that affect many genes (Smolen et al. 2000). Furthermore, if the behavioral effects of a single gene depend on the genetic background, then genetically engineered mice from inbred-strain progenitors may not adequately represent similarly engineered mice from non-inbred populations (Crusio and Gerlai 1999; Cabib et al. 2000).

Artificial selection is a complementary tool to genetic engineering studies of behavior, and it is well suited to the study of complex traits controlled by many genes (Garland and Carter 1994; Gibbs 1999). Selective-breeding experiments have a long history in biology (Robertson 1980; Hill and Caballero 1992; Falconer and Mackay 1996) and have been successfully employed in neuroscience research (McClearn et al. 1978; Hausheer-Zarmakupi et al. 1996; Marley et al. 1998). We used selective breeding to increase voluntary wheel-running behavior in four replicate lines derived from the same heterogeneous, outbred base population of mice (*Mus domesticus*) (Swallow et al. 1998; Koteja et al. 1999; Carter et al. 2000; Rhodes et al. 2000; Bronikowski et al. 2001). Ge-

netic variation in the original base population (Hsd:ICR) is similar to variation among individuals in wild populations of *Mus domesticus* (Rice and O'Brien 1980; Carter et al. 1999; and references therein).

After 17 generations of selective breeding, females (which we have chosen to study here) from our selected lines displayed a 2.5-fold increase in the total number of revolutions run per day (Rhodes et al. 2000). Females from the selected lines have primarily increased their average running speed rather than the amount of time spent running (Swallow et al. 1998; Koteja et al. 1999; Rhodes et al. 2000; Koteja and Garland 2001). The selected-line females run in short bursts with short inter-bout pauses (Girard et al. 2001). As shown in this paper, the high-running female mice also exhibit 24-h hyperactivity in their cages (using photobeams to quantify activity) when they are deprived of wheels. Our selected lines of mice may therefore represent a novel murine model to study the genetic basis of generalized 24-h hyperactivity, such as that exhibited in human attention deficit hyperactivity disorder (ADHD, Porrino et al. 1983).

Many workers have argued that genetic hyperactivity in humans (and in the spontaneously hypertensive rat model of ADHD) is caused by impaired dopaminergic function (Carey et al. 1998; Sagvolden and Sergeant 1998; Papa et al. 2000; Russell 2000; Grace 2001; Solanto et al. 2001), although ADHD has also been associated with impaired noradrenergic function (Solanto 1998; Arnsten 2000, 2001). Hence, one plausible mechanistic explanation for the increased activity in our selected lines of mice is an alteration in dopaminergic function. Pharmacological intervention can provide valuable insight as to whether a particular neurochemical system has been altered (Fink and Reis 1981; Cabib and Puglisi-Allegra 1985; Jones et al. 1991; Castner et al. 1993; Giros et al. 1996; Giorgi et al. 1997; Henricks et al. 1997; Gainetdinov et al. 1999). For example, in the present study, if hyperactive (selectively bred) animals responded differently to drugs that affect dopaminergic function, compared with control (unselected) animals, then it could be inferred that some aspect of the dopaminergic system has been altered in the hyperactive animals.

We were interested in testing the effects of dopamine reuptake inhibitors not only because dopamine has been implicated in ADHD, but also because of the possible roles that dopamine plays in motivation (Berridge and Robinson 1998), reward (Di Chiara et al. 1993), and reinforcement (Damsma et al. 1992). Rodents are believed to perceive a reward from wheel running because it is not a goal-oriented behavior and because they run voluntarily (Sherwin 1998). Therefore, we hypothesized that animals that exhibit increased wheel running may perceive altered incentive (Berridge and Robinson 1998) for the wheel-running reward.

Dopaminergic function has also been associated with running speed (Freed and Yamamoto 1985) and locomotion in general (Vallone et al. 2000). In particular, recent "knockout" studies implicate the dopamine reuptake transporter (DAT) in mediating hyperactivity (Giros et al. 1996; Gainetdinov et al. 1999). Psychostimulant drugs, such as cocaine and amphetamine, ameliorated hyperactivity in the DAT knockouts, similar to their actions in ADHD subjects (Gainetdinov et al. 1999). Cocaine primarily blocks DAT, but may secondarily block other amine reuptake transporters, such as SERT, the serotonin transporter (Womer et al. 1994). Gainetdinov et al. (1999) suggested that cocaine attenuated the hyperactivity exhibited by the DAT knockout mice through its action on SERT, because the knockouts lacked DAT and fluoxetine (selective SERT inhibitor) caused a similar reduction in hyperactivity as did cocaine.

We wished to test the acute effects of cocaine on hyperactivity in our selected lines of mice and to determine whether cocaine acted primarily through its actions on SERT versus DAT. Therefore, after the cocaine trial, we conducted additional trials to measure the acute effects of fluoxetine and GBR 12909 (selective DAT inhibitor) to evaluate the respective contributions of these neuromodulatory systems.

Methods

Animals

Mice from generations 23 and 24 of an artificial selection experiment for high voluntary wheel-running behavior were studied (see Swallow et al. 1998 for details). The original progenitors were outbred, genetically variable (Rice and O'Brien 1980; Carter et al. 1999) laboratory house mice (*Mus domesticus*) of the Hsd:ICR strain, purchased from Harlan Sprague Dawley in 1993. After two generations of random mating, mice were randomly paired and assigned to eight closed lines (ten pairs in each). In each subsequent generation, when the offspring of these pairs were 6- to 8-weeks old, they were housed individually with access to a running wheel for 6 days, and a computer recorded wheel revolutions in 1-min intervals [Wahman-type activity wheels (1.12-m circumference, stainless steel and Plexiglas construction, Lafayette Instruments, Lafayette, Ind.) were attached to standard clear plastic housing cages via a stainless-steel tube inserted into a hole in the wall of the cage]. In four "selected" lines, the highest-running (quantified as total number of revolutions run on day 5 and day 6 of the 6-day test) male and female from each family were chosen as breeders to propagate the lines to the next generation. In the four "control" lines, a male and a female were randomly chosen from each family. Within all lines, the chosen breeders were randomly paired except that sibling matings were not allowed.

The purpose of having four replicate selected and four replicate control lines is to account for random genetic changes, such as founder effects and genetic drift, which can cause lines to diverge even in the absence of selection. Any particular genetic or phenotypic difference between a given selected line and a given random-bred control line may or may not be causally related to the phenotype that was actually under selection. For example, in the present study, if we were to compare the drug responses of only one hyperactive line with one control line, then we would have no way of determining whether any differences were the result of random genetic processes or the result of the selection for hyperactivity per se. Inferences about the causal factors underlying phenotypic changes in a selected line are greatly strengthened if replicate lines are maintained (Henderson 1989, 1997).

The Principles of Laboratory Animal Care (NIH publication no. 85–23, revised 1985) was followed, and all experiments were approved by the University of Wisconsin Animal Care Committee. Throughout the selection experiment and during this study, water

and food [Harlan Teklad Laboratory Rodent Diet (8604); after generation 23, breeding females were given Harlan Teklad Mouse Breeder Diet (7004)] were available ad libitum. Rooms were controlled for temperature (~22°C) and photoperiod 12-h/12-h light/dark (lights on at 0700 hours, central standard time).

To simplify analyses, only females were used in the present study. Different groups of mice were used for each of the drug trials that were conducted. For the cocaine trial, generation-23 animals that were not among those chosen as breeders to propagate lines to the 24th generation were used. Because exclusion of the top runners would have caused samples from the selected lines to be biased downward with respect to wheel running, the lowest-running animals in selected-line families were also excluded. Of the remaining mice, 48 were randomly chosen to participate (six per line, each from a different family).

To supply animals for the GBR 12909 and fluoxetine (Prozac) trials, generation-22 parents (that were not sacrificed for routine measurements) were allowed to produce a second litter. Six animals per line (from six separate families) were assigned to each of the GBR 12909 and fluoxetine trials. However, in line 1 (a random-bred control line), only four litters were successfully weaned, so only four animals were available for each trial. Similarly, in line 8 (selected), only five animals were used in each trial. Thus, the experimental design for the fluoxetine and GBR trials was slightly unbalanced.

Drug protocols

The animals used for the cocaine trial were placed in cages with access to running wheels in random order when they were approximately 68±1.4 days old (mean±SD). After 3 weeks of acclimation, mice were injected with either vehicle (0.9% saline) or cocaine – 20 mg/kg or 40 mg/kg cocaine in a volume adjusted to the body mass of the animal (0.01 ml/g). Animals were injected every other day for a total of three injection days, so that each individual received all three types of injections (vehicle, medium, and high dose) over the course of the three injection days. Each mouse per line received the three injections in a different order (one of the six permutations of the three doses), randomized across lines, such that possible effects of injection order did not need to be considered in statistical analyses.

Mice were injected in random sequence, but the same sequence was used on each of the injection days. This was done so that a mouse always received its injection at approximately the same time of day. It usually took less than 2 min to capture, inject, and return a mouse to its home cage. Injections began 2 h after lights off, during peak activity (unpublished data).

Animals for the GBR 12909 and fluoxetine trials were placed in cages with access to running wheels when they were approximately 38±2.4 days old. Even though animals in the GBR 12909 and fluoxetine trials were younger than the mice in the cocaine group, their running profiles were similar at the time they were given injections (see Results). Thus, we believe it is appropriate to compare results across all three drug trials. Otherwise, the GBR 12909 and fluoxetine trials proceeded similarly to that for cocaine. Fluoxetine was administered at 10 mg/kg and 20 mg/kg, as was GBR 12909. Doses were chosen after consulting the literature (for cocaine, Iijima 1995; Giros et al. 1996; Marley et al. 1998; Gainetdinov et al. 1999; for GBR 12909, Womer et al. 1994; Irifune et al. 1995; for fluoxetine, Possidente et al. 1992; Griebel et al. 1995; Gainetdinov et al. 1999). In most of these studies, however, drugs were administered during the day and wheel running was not used to measure drug responses (but see Iijima 1995). Therefore, we also conducted preliminary studies to determine behaviorally equivalent doses of the three uptake blockers.

Wheel rotations were monitored via computer in 1-min intervals throughout each trial. We compared acute responses of selected and control animals (Womer et al. 1994; Marley et al. 1998; Gainetdinov et al. 1999), which we defined to be wheel running produced in the 10- to 40-min period post-injection. The first 10 min was not included because wheel running was significantly suppressed by the vehicle injection during this period (see Fig. 1 for an example). Within this 10- to 40-min period, total wheel revolutions, total number of minutes that the wheel showed at least one revolution, and average speed of rotations (total number of wheel rotations divided by number of minutes with any wheel revolutions) were analyzed.

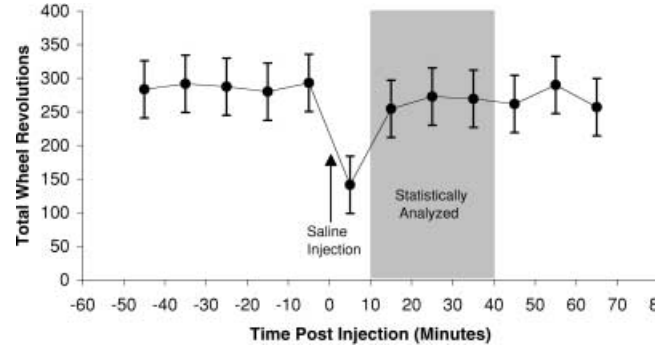

Fig. 1 The response of selected-line animals to the vehicle injection during the cocaine trial. *Data points* represent least-square adjusted means ±SEM from a repeated-measures analysis of total wheel revolutions in 10-min increments. During the first 10-min period after injection, wheel running was substantially reduced. For this reason, we omitted the first 10 min in statistical analyses, and analyzed minutes 10–40

Photobeam activity protocol

To determine whether the high wheel-running mice are also hyperactive when housed in cages without wheels, a separate group of 32 female mice (4 per line) from generation 24 were used. Animals (not chosen as breeders; low-running individuals excluded by family, as described above for cocaine trials) were placed in the photobeam cages when they were approximately 57±2-days old. Individual beam breaks (fine movements) and consecutive beam breaks (coarse movements or ambulations) were recorded continuously for 48 h using San Diego Instruments (San Diego, Calif.) software. Pine bedding, food, and water were available on the floor of the cages. Rat-sized photobeam activity cages were used (dimensions 48×25×20 cm), and there was slight variation in the distance of the photobeams from the floor of the cages. These distances were measured and entered as covariates in the statistical analyses, along with body mass, because both these quantities could affect the probability of photobeam breaks and consequently obscure the actual relationship between cage activity and line type (control versus selected lines).

Statistics

SAS (SAS Institute Inc.) PROC MIXED (which employs restricted maximum likelihood) was used to analyze the data. Line was always entered as a random effect nested within the fixed effect line type (selected or control). The lines were separately propagated for 24 generations; thus, individuals in a given generation do not represent independent data points and must be nested within the populations they arose from (Henderson 1989, 1997). Body mass and wheel freeness (total number of revolutions produced by the wheel after being accelerated to constant velocity, an inverse measurement of how resistant the wheel is to continued rotation) were included as covariates in all the analyses of wheel-running variables (except in those where wheel running variables were regressed on each other). Stage of the estrus cycle was not measured and hence was not entered as a cofactor in any analyses.

Baseline wheel running was compared between selected and control lines by considering mean total revolutions during the

2 days preceding injections for all three drug trials combined. Data were analyzed using a two-way analysis of covariance (ANCOVA), including line type, drug trial, and the interaction between drug trial and line type as cofactors.

To determine whether selected and control animals differentially responded to the drugs, both the absolute and proportional responses were analyzed, because baseline wheel running differed between the selected and control lines (see Results). For the absolute response, the wheel-running variables (total revolutions, minutes with any revolutions, or average speed 10–40 min post-injection) were analyzed using repeated-measures two-factor ANCOVA to test for an interaction between dose and line type (repeated measures was needed to account for the fact that the three doses were applied to the same individual on three separate days). Absolute responses were also analyzed separately for selected and control lines to determine the effects of the drugs in each line type. For the separate analyses, a one-factor, repeated-measures ANCOVA was used to determine the effect of dose on the wheel-running variables. To improve normality of residuals, minutes with any wheel rotations were always power transformed (see Y-axis legend of Fig. 3).

For the proportional response, a one-factor ANCOVA was used to test for a line type effect on the ratio of the wheel-running response after the high-dose injection to the response after the vehicle injection. To improve normality of residuals, the proportional responses were always rank transformed (data were highly positively skewed otherwise).

To test for rate dependency of drug effects, linear regression was used to determine the relationship between response to the high dose injection and baseline response to the vehicle injection. No covariates were entered in these analyses, because values for each individual were regressed against each other.

For the cage activity data, a one-factor ANCOVA was used to test for a line type effect on the total activity scores of the animals. Separate analyses were conducted for the first (novel) and second 24 h of activity. Body mass and the distances of the photobeams to the floor of the cages were always included as covariates.

Results

Baseline wheel running

Selective breeding for increased wheel running behavior has resulted in substantial divergence between the 4 selected and 4 control lines in total number of revolutions run per day (Fig. 2A). At generation 24 (see also Koteja and Garland 2001), female mice from selected lines (n=221) ran an average of 14,458 revolutions (16.2 km) per day (on day 5 and day 6 of the standard 6-day test), representing a 2.78-fold increase over females from control lines (n=79), which ran an average of 5205 revolutions (5.8 km) per day (Fig. 2A). The increase in wheel running was accomplished primarily by increased average running speed (2.37-fold increase), because there was only a 1.19-fold increase in the total number of minutes with any revolutions (Fig. 2B).

As expected, the selected-line individuals used in the three drug trials ran significantly more total revolutions than the control-line individuals. For example, considering the mean total revolutions run on the 2 days preceding injections, animals from selected lines ran 17,739±1032 versus 6946±1031 for control-line animals (least-square adjusted means and standard errors from a nested two-way ANCOVA, wheel freeness used as a covariate, drug trial and drug trial by line type interaction entered as cofactors, animals from all three drug trials were considered simultaneously, n=137). Baseline level of wheel running was similar for each drug trial (P value for the effect of drug trial on mean revolutions 2 days preceding injections = 0.63; P value for the interaction between drug trial and line type = 0.61).

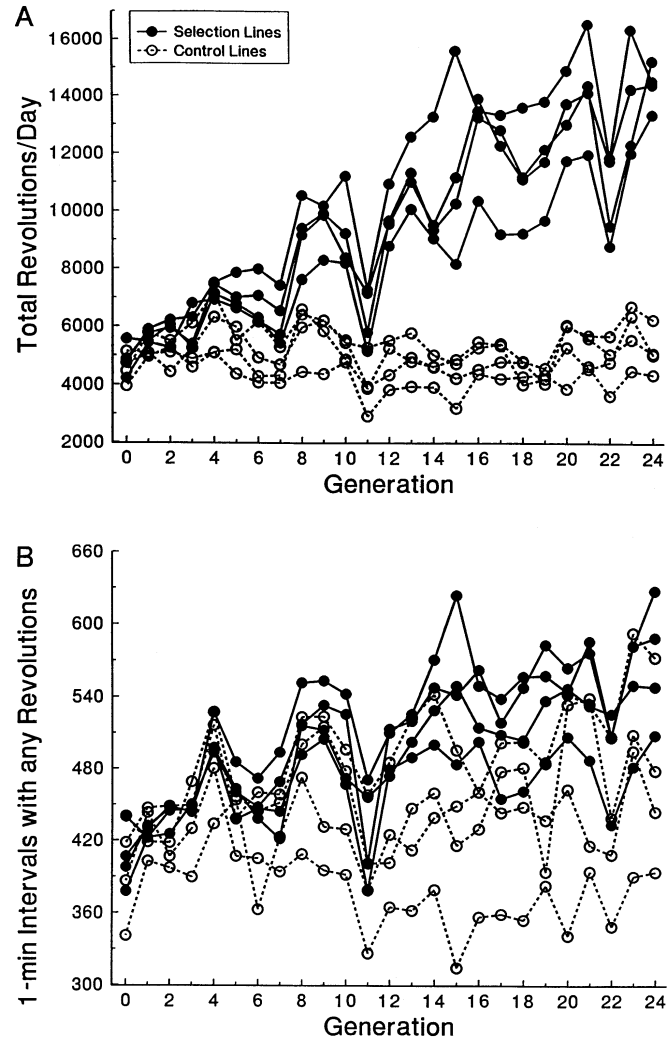

Fig. 2 **A** Mean wheel running (represented as total revolutions per day on day 5 and day 6 of a 6-day test; circumference of wheel = 1.12 m) of female mice from four replicate selected lines and four replicate control lines across generations. Wheel running increased in each of the selected lines, but showed little change in the control lines. **B** Mean number of minutes spent running (number of 1-min intervals during which any revolutions were recorded) for the same mice as in **A**. The time spent running did not diverge substantially between selected and control lines. Female mice in the selected lines accomplished more total revolutions per day mainly by increasing their average running speed, rather than the amount of time spent running

Drug responses

Dose–response profiles for cocaine and GBR 12909 were strikingly similar (Fig. 3), suggesting that cocaine

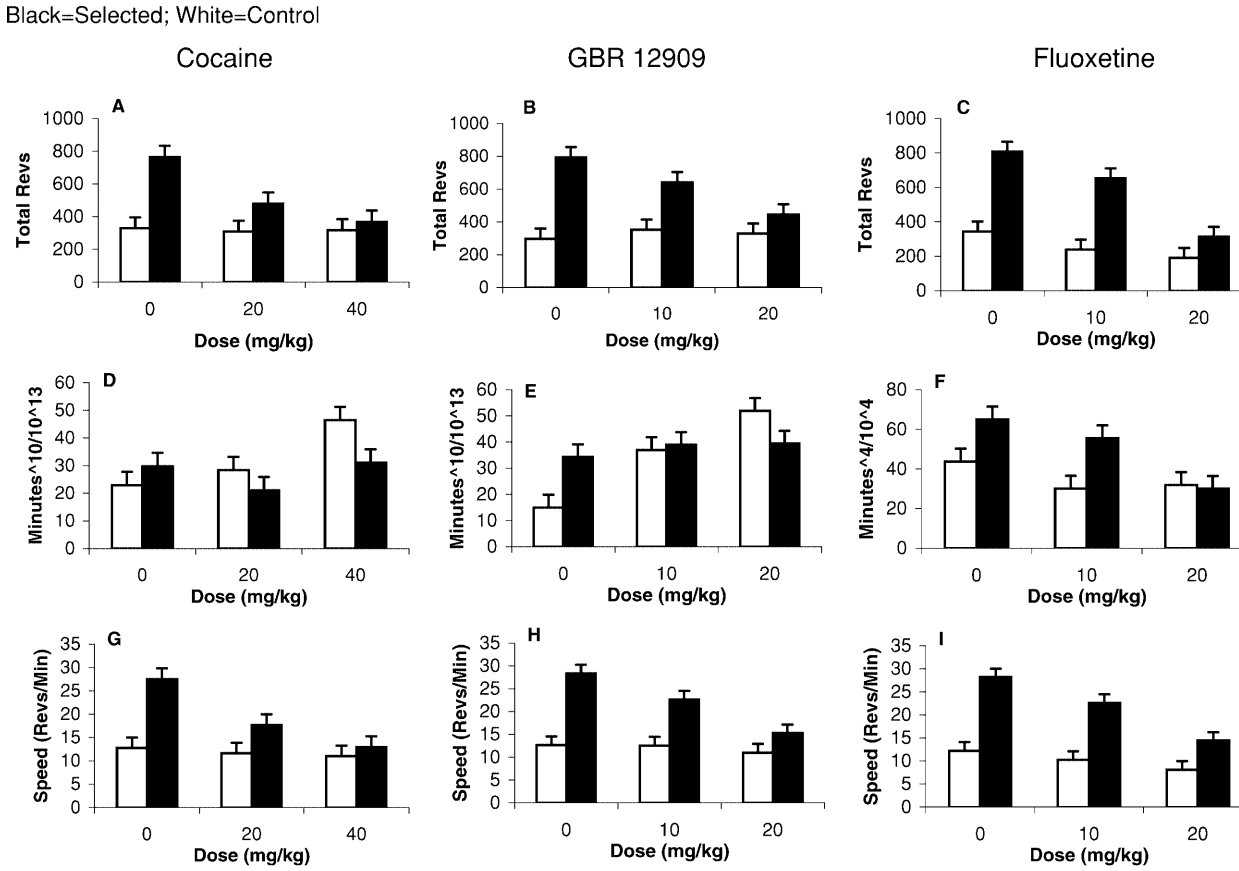

Fig. 3A–I The wheel-running response to i.p. administration of cocaine (*left column*), GBR 12909 (*middle column*), and fluoxetine (*right column*) in mice from selected and control lines. *Top row* shows the total revolutions produced during the 10- to 40-min post-injection period. *Middle row* shows the number of minutes (power transformed to reflect the statistical analysis conducted) with any wheel revolutions over the same time interval (10–40 min post-injection). *Bottom row* shows the average speed of running over the 10- to 40-min post-injection period. Dose–response profiles are similar for GBR 12909 and cocaine, but different for fluoxetine. Cocaine and GBR 12909 attenuated the total revolutions by reducing the speed, not the number of active minutes in mice from selected lines. Total revolutions for control animals remained the same because the number of minutes spent running increased, whereas speed slightly decreased. Fluoxetine, in contrast, reduced the total, speed, and minutes of revolutions in both selected and control animals. *Least-square adjusted means* and *standard error bars* are shown. *P* values for interactions between dose and line type using a two-way repeated-measures analysis of variance are reported in Table 1

acted by blocking DAT. Selected and control animals responded differently to cocaine whether or not the response was measured on an absolute scale or as a proportion of the baseline response to the vehicle injection (Table 1). Statistical results were similar for GBR 12909, although the effect of line type on proportional responses was marginally insignificant (Table 1).

Cocaine and GBR 12909 dose dependently decreased total revolutions run during the 10- to 40-min period post-injection in selected-line animals but had little effect in control-line animals (Fig. 3A, B). In a one-factor ANCOVA using data for selection-line animals only, dose was a significant predictor of total revolutions 10–40 min post-injection ($P<0.0001$ for cocaine; $P=0.001$ for GBR 12909). However, dose was not a significant predictor of total revolutions for control-line animals ($P=0.8203$ for cocaine; $P=0.2404$ for GBR 12909).

The dose-dependent decrease in total revolutions observed in selected animals in response to the DAT inhibitors was caused by a decrease in the speed of running, not by a decrease in the number of minutes active in the wheel (Fig. 3D, E, G, H). Dose did not affect the number of minutes spent running 10–40 minutes post-injection in selection animals ($P=0.22$ for cocaine, and $P=0.67$ for GBR 12909, one-way ANCOVA). The minutes variable was negatively skewed and was raised to the tenth power so that residuals were approximately normally distributed. Figure 3 reports the least-square means for the transformed minutes variable to reflect the statistical analyses that were conducted. The untransformed means for minutes of wheel running in selected-line animals were 24.7, 22.3, and 23.6 for cocaine doses 0, 20, and 40 mg/kg, and 26.9, 27.5, and 26.9 for GBR 12909 doses 0, 10, and 20 mg/kg, respectively.

Total revolutions in control animals did not change in response to injection of cocaine or GBR 12909 (Fig. 3A, B), because speed slightly decreased while number of minutes increased (Fig. 3D, E, G, H). Dose was a significant predictor of minutes of wheel running in control-line animals ($P=0.0003$ for cocaine, $P<0.0001$ for GBR

Table 1 Analysis of variance (ANOVA) table for statistical analyses of the drug response data. The *P* values in the left-hand column indicate differences in absolute responses to the drugs [least-square (LS) means for these analyses are displayed graphically in Fig. 3]. The *P* values in the right-hand column indicate differences in proportional responses to the drugs. The proportional response was quantified as the response after the high-dose injection divided by the response after the vehicle injection. Proportional responses were rank transformed and LS adjusted means ± SEM of the ranks are shown for control and selected lines. Higher rank indicates reduced sensitivity to the drug. Numerator degrees of freedom (NDF), denominator degrees of freedom (DDF), and *F* statistics are also presented. *P* values less than 0.05 are in *bold*. Body mass and wheel freeness (an inverse measure of wheel resistance) were included as covariates in all analyses and were occasionally significant. Sample size = 45–48 individuals for each analysis

Drug	Dependent variable	Repeated-measures test for dose–line type interaction				One-factor analysis of covariance for line type effect on rank-transformed proportional response					
		NDF	DDF	*F* statistic	*P* value	NDF	DDF	*F* statistic	*P* value	LS means of rank ±SEM	
										Control	Selected
Cocaine	Total revs	2	87	15.78	**<0.0001**	1	6	8.08	**0.0295**	30.5±2.77	18.5±2.77
	Minutes	2	91	3.67	**0.0292**	1	6	3.53	0.1094	28.6±2.88	20.4±2.88
	Speed	2	87	20.33	**<0.0001**	1	6	8.78	**0.0252**	30.8±2.81	18.2±2.81
GBR12909	Total revs	2	85	8.22	**0.0005**	1	6	5.99	0.0500	28.9±3.37	17.1±3.33
	Minutes	2	85	7.04	**0.0015**	1	6	5.74	0.0536	28.4±3.12	17.7±3.07
	Speed	2	85	8.01	**0.0007**	1	6	5.02	0.0663	27.4±2.67	18.8±2.61
Fluoxetine	Total revs	2	84	9.62	**0.0002**	1	6	0.71	0.4309	24.5±3.04	20.5±3.04
	Minutes	2	84	4.71	**0.0115**	1	6	0.13	0.7261	23.4±3.05	21.6±3.05
	Speed	2	82	9.92	**<0.0001**	1	6	1.08	0.3385	24.9±3.03	20.1±3.03

12909, one-factor ANCOVA). The untransformed means for minutes of wheel-running activity in control-line animals were 22.9, 25.9, and 28.4 for cocaine doses 0, 20, and 40 mg/kg, and 21.9, 27, and 29.5 for GBR 12909 doses 0, 10, and 20 mg/kg.

The fact that the DAT inhibitors did not increase minutes of running in selected animals (but did in controls) is not a consequence of a ceiling effect, but rather is evidence that the selected and control animals responded differently to these drugs. The number of minutes spent running during the 10- to 40-min period after the vehicle injection was similar in selected and control animals for mice used in the cocaine and GBR 12909 trials (one-way ANCOVA effect of line type on the vehicle response: P=0.48 for cocaine and P=0.11 for GBR 12909). Further, the greatest number of minutes of running occurred in control-line animals given the high doses of DAT inhibitors (see raw values above or Fig. 3 for transformed values).

In contrast to results for GBR 12909 and cocaine, fluoxetine decreased total revolutions, speed, and time spent running in both selected and control animals (Fig. 3F, I). Dose was a significant predictor of total revolutions, speed, and minutes of wheel running in control-line animals (P=0.004 for total, P<0.002 for speed, P=0.05 for minutes, one-factor ANCOVA) and in selected-line animals (P<0.0001 for total, P<0.0001 for minutes, P<0.0001 for speed). The untransformed means for minutes of wheel running were 23, 17.9, and 16.2 for control-line animals given fluoxetine doses 0, 10, and 20 mg/kg, respectively, and 28.4, 26.1, and 19.3 for selected-line animals. The absolute decrease in total revolutions, time running, and average speed was greater in magnitude for selected-line animals than controls, and the interaction between dose and line type in the two-factor ANCOVA was statistically significant (Table 1). However, the proportional decrease in wheel running after fluoxetine administration was similar for mice from selected and control lines (Table 1).

In each of the drug trials, individual response to the vehicle injection was a significant linear predictor of response to the high dose injection (Fig. 4, P value for the slope of the linear regression <0.0001 for cocaine, P=0.007 for GBR 12909, and P=0.0003 for fluoxetine; line was entered as a random effect, but line type and the interaction between line type and vehicle injection were not significant and, hence, were removed from the model; no covariates were entered). The slope was positive but less than unity in each case (Fig. 4). The intercept was significantly positive for cocaine (P=0.0031) and GBR 12909 (P=0.0041) but was not significantly different from 0 for fluoxetine (P=0.25). Thus, it appears that the DAT inhibitors increased wheel running in individuals with low baseline levels and decreased wheel running in individuals with relatively high baseline levels. In the previous analyses, we did not detect an effect of the DAT inhibitors on mean total revolutions among control-line animals because approximately half the control-line animals were stimulated and half were suppressed by the drugs (Fig. 4).

Wheel freeness and body mass were only occasionally significant predictors of wheel-running responses. When they were significant, wheel freeness was positively related to wheel running, and body mass was negatively related to wheel running. The random effect of line nested within line type was not significant in any analyses, indicating that genetic drift or founding effects had not significantly altered the traits that were measured here. As expected (for example, see Swallow et al. 1999), control-line animals were significantly heavier in body mass in all data sets except that for GBR 12909.

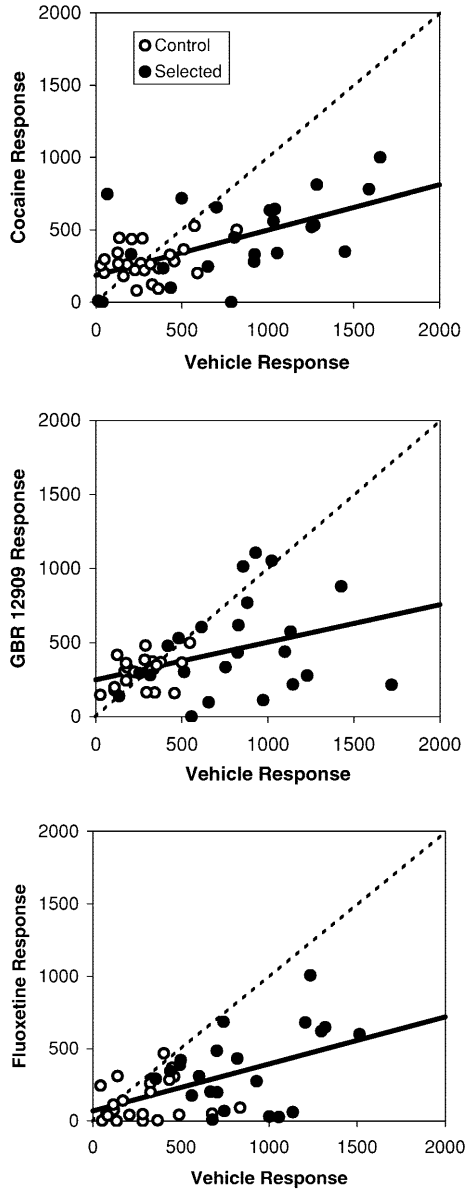

Fig. 4 Individual responses (total revolutions 10–40 min post-injection) after the high-dose injection plotted against responses following vehicle injection for cocaine (*top*), GBR 12909 (*middle*), and fluoxetine (*bottom*). The line of unity (*dashed*) is drawn to show the extent and direction of drug effects for each individual mouse. Also drawn are the regression lines (*solid*) to show the average response predicted by baseline rates of activity. Cocaine and GBR 12909 tended to stimulate wheel running in individuals with low baseline rates, but depressed activity in individuals with high baseline rates (intercept of the regression line was significantly positive). In contrast, fluoxetine depressed wheel running irrespective of baseline response (intercept of the regression line was not significantly different from zero)

Photobeam activity

Mice from selected lines exhibited higher numbers of both fine movements (counts of individual photobeam breaks; nested ANCOVA P=0.048) and coarse movements (counts of consecutive beam breaks, also termed ambulation; P=0.0004; Fig. 5) during the second 24-h period of testing. However, there were no significant differences on the first day of testing (P=0.26 for fine movements and P=0.07 for coarse movements; Fig. 5). On the first day, both selected and control animals exhibited relatively high levels of spontaneous activity (Fig. 5). By the second day, control animals displayed lower levels of activity, while selected animals continued to display high levels. In addition to the line type effects, both the distance of the photobeams from the floor of the cage and body mass were significant predictors of cage activity, as measured by the photobeam breaks. Distance was negatively related to photobeam counts, and body mass was positively related.

Discussion

Summary

We have developed a new animal model to study genetic hyperactivity: lines of mice artificially selected for increased voluntary wheel-running behavior (Swallow et al. 1998, 1999; Koteja et al. 1999; Carter et al. 2000; Rhodes et al. 2000; Koteja and Garland 2001; Bronikowski et al. 2001). In this study, we found that our high-running mice are also hyperactive in their cages when deprived of wheels, as demonstrated using photobeams to measure activity (Fig. 5). We also found that control and selected animals responded differently to drugs that inhibit the dopamine transporter protein. Cocaine and GBR 12909 reduced wheel running in hyperactive animals, but these same drugs had no average effect in control-line animals. The ability to partition total wheel revolutions into minutes of revolutions and average speed enabled us to show that the reduction in total wheel revolutions (by cocaine and GBR 12909) in selected lines was caused by a reduction in the average speed of running, not the number of minutes spent running. This result is particularly important because it shows that cocaine and GBR 12909 ameliorated the hyperactivity as it is normally expressed by our selected-line females, which is mainly by increased speed of wheel running (see Fig. 2 and above references).

Consideration of pharmacodynamics

The simplest neurochemical explanation of our results is that dopaminergic function is altered in the selection lines. We reached this conclusion because the DAT inhibitors elicited a proportionately greater response in selected than control lines. However, a more complicated interpretation is also possible. In theory, an alteration in any neurochemical system pre- or post-synaptically associated with dopaminergic neurons could have influenced the response to the DAT inhibitors. Clearly, further research is needed to fully characterize the neurochemical alterations in the selectively bred, hyperactive lines of mice. However, the present results are important because

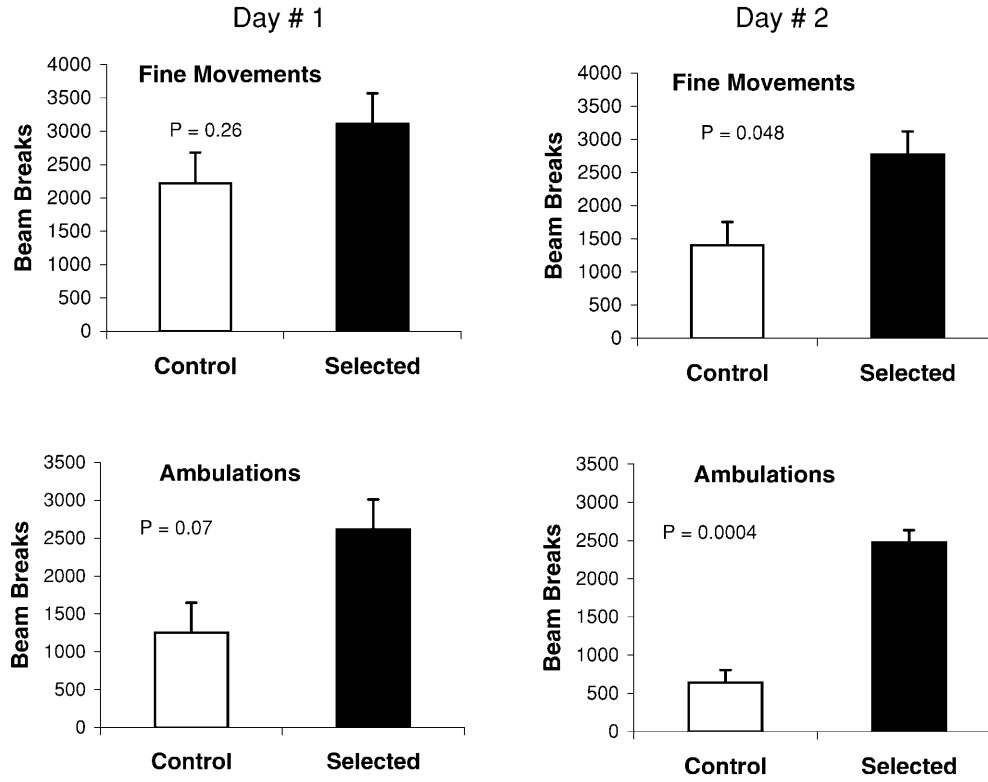

Fig. 5 Activity of mice from selected and control lines as recorded with photobeams over a 48-h period using rat-size cages (dimensions 48×25×20 cm). The *left column* represents the first 24 h; *right column* the second 24 h. The *top row* shows fine movements; *bottom row* coarse movements or "ambulations". *P* values are from nested analysis of covariance models, with line nested within line type, and such covariates as body mass. During the initial 24-h period, no significant differences were observed for fine or coarse movements; but, during the second day, mice from selected lines exhibited many more ambulations or coarse movements than controls, and moderately more fine movements. *Least-square adjusted means* and *standard error bars* are shown

they provide an a priori hypothesis to test: reduced dopaminergic function is associated with genetic hyperactivity in our mice. Recent evidence suggests that dopaminergic systems modulate incentive to acquire a reward, not the hedonic impact of the reward itself (see Berridge and Robinson 1998 for a review of the incentive salience hypothesis for the role of dopamine in reward). Therefore, an alteration in dopaminergic function is a reasonable mechanism for the hyperactive running, presuming that the mice perceive a reward from wheel running (Sherwin 1998).

Drug mechanisms

Genetic hyperactivity in humans is believed to result from abnormally low tonic dopaminergic activity within the nucleus accumbens, leading to abnormally highphasic dopamine responses (Grace 2001; ADHD has also been associated with altered noradrenergic function, Solanto 1998, 2001; Arnsten 2000, 2001). Results of our drug trials are consistent with this dopamine hypothesis, if one assumes that cocaine and GBR 12909 ameliorated the hyperactivity in our selected lines as a consequence of drug-induced increases in dopamine concentrations in extrasynaptic spaces within the nucleus accumbens. Increased dopamine in extrasynaptic spaces would increase stimulation of autoreceptors, which would downregulate the spike-dependent phasic component of dopamine release (Grace 2001). Cocaine is known preferentially to increase dopamine concentrations in the accumbens (Di Chiara and Imperato 1988). However, before diffusing to extrasynaptic spaces, dopamine would stimulate postsynaptic receptors, and the time course for diffusion to extrasynaptic spaces is unknown, and probably dose dependent.

In this study, we utilized acute rather than chronic drug administration to investigate the involvement of dopamine and serotonin in the hyperactive wheel running. Therapeutic efficacy of DAT inhibitors occurs immediately (within 2 h of oral administration, Solanto 1998) and is not thought to involve long-term adaptive responses (Solanto et al. 2001). However, SERT inhibitors often require chronic administration over days or even weeks. The mechanisms responsible for behavioral alteration after chronic exposure are complicated by such processes as receptor downregulation, induction of neurotrophins, and even neurogenesis (Jacobs et al. 2000; Stamford et al. 2000). To avoid these unintended complications, we felt it was essential to restrict our initial investigations to acute effects.

Rate-dependent effects

Rate-dependent effects of drugs occur when the drug effect is related to the control rate of response (Robbins and Sahakian 1979). An inverse relationship between control rate and drug effect is generally found after treatment with DAT inhibitors (Sanger and Blackman 1976; Robbins and Sahakian 1979). Our results are consistent with an inverse rate-dependent effect for cocaine and GBR 12909, because individuals with low basal activity

scores tended to be aroused by the drugs, whereas individuals with high basal scores were depressed (Fig. 4). This does not contradict the result that average total revolutions in control-line animals did not change in response to the DAT inhibitors because approximately half the control-line animals were stimulated and half were suppressed by the drugs (see Results, Fig. 4). Similarly, reports that normal and hyperactive humans respond qualitatively similarly to therapeutic doses of methylphenidate (Ritalin) and D-amphetamine (Rapoport et al. 1978; Aman et al. 1984; Solanto 1998, Solanto et al. 2001) is not inconsistent with inverse rate dependency (Robbins and Sahakian 1979). As pointed out by Millard and Standish (1982), the mechanistic explanation for inverse rate dependency is not known. Thus, rate dependency is not a suitable explanation for the "paradoxical" effect that stimulants have on individuals at either end of the activity continuum, but rather is a description of an empirical observation (Millard and Standish 1982).

The fact that cocaine and GBR 12909 did not produce an average increase in total wheel revolutions in the control-line animals is not surprising because the drug trials were conducted at night, during peak activity (see Methods). Typically, drug trials are conducted during the day when nocturnal rodents are normally sleeping (Reith 1986; George 1989; Ichihara et al. 1993; Womer et al. 1994; Irifune et al. 1995). During the day, cocaine and GBR 12909 are known to stimulate activity in rodents (Kelley et al. 1989; Gainetdinov et al. 1999). However, baseline levels of activity are near zero during the day (Gainetdinov et al. 1999), and a floor effect limits the possible direction of response. At night, mice could respond by either increasing or decreasing activity levels. For example, in male ddY mice, 40 mg/kg cocaine suppressed night-time wheel running (Iijima et al. 1995). Interestingly, male ddY mice exhibit relatively high levels of spontaneous wheel running [8.7 km/day, estimated from raw data from Iijima et al. (1995) versus 5.8 km/day in our control-line females and 5.0 km/day in our control-line males (data from generation 24, as presented in Koteja and Garland 2001)].

Behavioral profiles of hyperactive animals

It is useful to compare the behavior of our selected-line animals with the DAT knockout mice because both are hyperactive. If behavioral profiles are similar, then we might infer that the hyperactivity in our selected lines is caused by impaired DAT. However, behavioral profiles are not similar. First, the difference in activity between the DAT knockouts and the wild-type controls decreased with trial duration in a 3-h test using photobeam activity cages (217×268×104 mm), such that hyperactivity in the DAT knockouts was most apparent in the novel environment (at the beginning of the experimental trial; Giros et al. 1996). In contrast, hyperactivity in our selected lines was most apparent in the habituated environment (on the second day of photobeam testing; Fig. 5). Second, Gainetdinov et al. (1999) concluded that cocaine calmed the DAT knockouts through its actions on the serotonin system, whereas cocaine appeared to act on the dopaminergic system in our lines (based on comparison with results of GBR 12909 trials). Thus, comparison of the DAT knockout mice with our high wheel-running mice suggests that hyperactivity may come in different forms with potentially different underlying mechanisms.

A selection experiment for open-field behavior (DeFries et al. 1970) and interspecies comparative data provide further evidence that hyperactivity in the habituated versus novel environment is controlled by different underlying mechanisms. Lines of mice selected for increased activity in an open-field arena did not exhibit increased spontaneous wheel-running activity (DeFries et al. 1970) and our high-running lines (which also display hyperactivity in photobeam cages after 24 h of acclimation) are not hyperactive in the open-field arena (Bronikowski et al. 2001). Further, as noted by Bronikowski et al. (2001), across 12 species of muroid rodents, the correlation between open-field activity and wheel running is not significantly different from zero. Thus, all studies to date support the view that spontaneous activity in a habituated environment and locomotor behavior in a novel open-field environment are not controlled by the same underlying mechanisms.

What form of hyperactivity is exhibited by people diagnosed as having ADHD? According to Porrino et al. (1983), ADHD children exhibit 24-h hyperactivity, including during sleep. However, ADHD children may not exhibit hyperactivity in the novel or stressful environment, such as during an experimental trial or at the doctor's office (Sleator and Ullmann 1981; Sagvolden and Sergeant 1998). Hyperactivity in humans is primarily treated with Ritalin and D-amphetamine, drugs which act more similarly to cocaine and GBR 12909 than to fluoxetine. However, fluoxetine (Prozac) is occasionally given to ameliorate hyperactivity in humans (Barrickman et al. 1991). We are currently conducting drug trials with Ritalin to further validate the selected lines as a model for human genetic hyperactivity.

With respect to implications for ADHD, one unusual feature of the present experiments is that we studied female mice, even though hyperactivity is two- to ninefold more prevalent in male children (Andersen and Teicher et al. 2000; but note that ADHD may be more similarly represented in male and female adults, and some argue that ADHD may be over-diagnosed in male children relative to female children, Biederman et al. 1994). We decided to study females to make use of the fact that selected-line females increase their total number of revolutions primarily by increasing the speed of running, not the number of minutes spent active, whereas males show a greater increase in duration of activity, although they too mainly show increased speed (Swallow et al. 1998, 1999; Koteja et al. 1999; Rhodes et al. 2000; Koteja and Garland 2001). Also, female mice generally run more total revolutions than males (previous references), which may enhance the ability to detect drug effects.

Consideration of pharmacokinetics

Both pharmacokinetic (rate of absorption, distribution or excretion of drugs) and pharmacodynamic (neurochemical) variables could have contributed to the divergent responses of animals from our selected and control lines (Benuck et al. 1987; Henricks et al. 1997; Wiener and Reith 1990). For example, one trait that has diverged between selected and control lines, and which might affect pharmacokinetics, is body mass (hyperactive animals are smaller: Swallow et al. 1999). However, all statistical analyses were conducted with body mass as a covariate, thus effectively removing its influence from group comparisons.

Evidence from the literature also argues against a pharmacokinetic explanation of divergent drug responses among animals that differ in baseline activity (Benuck et al. 1987). Benuck et al. (1987) reported no correlation between baseline activity and brain cocaine concentrations measured 12, 22, and 32 min after i.p. injections of 25 mg/kg cocaine in the BALB inbred mouse strain. These results may not be relevant if the physiological basis for the variation in baseline activity differs in the BALB mice relative to our genetic lines. The possibility that pharmacokinetic differences contributed to the divergent responses reported here cannot be ruled out entirely.

Conclusion

Results presented here are consistent with the hypothesis that genetic hyperactivity is associated with altered dopaminergic function (Carey et al. 1998; Sagvolden and Sergeant 1998; Papa et al. 2000; Russell 2000; Grace 2001; Solanto 2001). In future studies, we will quantify dopaminergic function using microdialysis (Damsma et al. 1992; Meeusen and De Meirleir 1995) or by measuring dopamine and the primary dopamine catabolite (DOPAC) concentrations in micro-dissected brain regions using high-performance liquid chromatography (Berridge et al. 1999). Pharmacological manipulation combined with direct measurement of concentrations of neurochemicals in regional areas of the brain are powerful tools; when applied to our replicate, selectively bred, hyperactive lines of mice, strong inference regarding the neural basis of genetic hyperactivity will be possible.

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