Pharmacology Biochemistry & Behavior, Vol. 21, pp. 237–244, 1984. © Ankho International Inc. Printed in the U.S.A. 0091-3057/84 $3.00 + .00

Systematic Comparison of Apomorphine-Induced Behavioral Changes in Two Mouse Strains With Inherited Differences in Brain Dopamine Receptors[1]

THOMAS W. SEALE,*[2] KIM McLANAHAN,* PAMELA JOHNSON,*
JOHN M. CARNEY† AND OWEN M. RENNERT*

Departments of Pediatrics and Pharmacology,† University of Oklahoma Health Sciences Center
Oklahoma City, OK 73190*

Received 19 September 1983

SEALE, T. W., K. McLANAHAN, P. JOHNSON, J. M. CARNEY AND O. M. RENNERT. *Systematic comparison of apomorphine-induced behavioral changes in two mouse strains with inherited differences in brain dopamine receptors.* PHARMACOL BIOCHEM BEHAV **21**(2) 237–244, 1984.—Dosage and time dependencies of apomorphine-induced changes in stereotyped behaviors (climbing, gnawing and sniffing), locomotor activity and rearing activity were compared in young adult male mice of two inbred strains, DBA/2 and C57BL/6. These two strains are known to differ in their genetically specified brain dopamine receptor number. Apomorphine administered intraperitoneally at dosages of 0.5–20 mg/kg failed to induced stereotyped climbing in DBA/2 at any of the doses tested but markedly increased climbing in C57BL/6 at higher dosages. Apomorphine-induced stereotyped gnawing occurred in both strains at higher dosages although the latency was shorter and maximal effect greater in C57BL/6. Stereotyped sniffing was induced in both strains to a comparable degree at doses ≥2.0 mg/kg, and the duration of this stereotypy was indistinguishable between strains. Locomotor activity was inhibited maximally in DBA/2 at an apomorphine dosage of 2 mg/kg and was inhibited to a greater extent than was C57BL/6. Rearing was inhibited in both strains by doses of apomorphine ≥0.5 mg/kg; however the duration of the effect was considerably greater in DBA/2 than in C57BL/6. These data suggest (1) that genetically determined differences in central dopamine receptors may have profound and selective effects on behaviors mediated by dopamine pathways; (2) that complex behavioral patterns, e.g., apomorphine-induced stereotypy, may be dissected in to individual components by identifying neuropharmaco genetic differences between strains; (3) that marked strain-specific, inherited differences in dopamine agonist-induced behavioral changes do occur among inbred, non-mutant mouse strains and that their occurrence in other mammalian species including man should be considered.

Apomorphine Dopamine agonists Locomotor activity Stereotyped behavior Inbred mouse strains
DBA/2 C57BL/6 Pharmacogenetics

APOMORPHINE is a classic dopamine agonist which exerts marked behavioral effects including the alteration of locomotor activity [8,21] and induction of stereotyped behavior in rodents [24, 25, 29]. However, within a species conflicting findings frequently have been reported for the dose-dependent action of apomorphine on locomotor activity suppression [4, 18, 22, 34, 36], stereotyped climbing activity [3, 28, 31] and stereotyped gnawing activity [7, 18, 30, 31, 35, 37]. These differences in dopamine responsiveness in some cases appear to have an inherited basis. Certain inbred strains of mice differ intrinsically from one another in the number of brain dopamine receptors [1,32]. At least in the case of strains C57BL/6 and DBA/2, this difference in receptor number is inherited in a simple Mendelian fashion [1]. The relative ability of dopamine agonists to induce behavioral changes in C57BL/6, DBA/2 [30, 32, 37] and other strains [32] has been attributed to such differences [1,32]. For example, CBA, which has 50% fewer striatal dopamine receptors than BALB/c, is less sensitive to apomorphine-induced stereotypy and more sensitive to haloperidol-induced catalepsy than BALB/c [32].

Three classes of dopamine receptors have been suggested to exist in the brain [13]. This diversity coupled with the probable involvement of multiple brain regions in the regula-

[1]These studies were supported in part by a Small Grant Award for Biomedical Research from the College of Medicine, University of Oklahoma Health Sciences Center, by a grant from the University Associates Program of the University of Oklahoma and by a research contract from the International Life Science Institute.

[2]Requests for reprints should be addressed to T. W. Seale, Department of Pediatrics, Room 2B-300, Oklahoma Children's Memorial Hospital, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190.

tion of some dopamine-induced behaviors [4, 5, 24] imply that single gene effects on dopaminergic pathways may have complex behavioral consequences. In principle, genetically specified alteration of the number of receptors of one type might either be ubiquitous or be specific to only one brain region. Present data indicate that receptor number may be under separate genetic control in different brain regions. Thus, a single, simple genetic difference between strains may affect a variety of apomorphine-induced behavioral changes, be restricted in its effect to only a specific subset of behaviors or even effect novel behaviors. Inbred strains, such as C57BL/6 and DBA/2 which differ from one another with regard to brain dopamine receptor number [1], are useful experimental subjects to identify common or separate mechanisms underlying specific dopamine-induced behaviors. Few studies simultaneously analyzing a variety of pharmacologically induced behaviors between two inbred strains have been made. Here we characterize the dosage dependency and time course of apomorphine effects on locomotor activity, rearing behavior, climbing activity, stereotyped gnawing and stereotyped sniffing in C57BL/6 and DBA/2 strains of mice.

METHOD

Animals

Adult male mice of inbred strains C57BL/6J and DBA/2J (Jackson Laboratory, Bar Harbor, ME) weighing approximately 25 g were housed in groups of 6 animals per cage on a continuous 12 hr light-dark cycle under constant temperature and humidity. Animals were used only once, i.e., for a single administration of drug. The litter used was kiln dried aspen wood chips (Sani-Chips, P. J. Murphey). Free access to a standard rodent pellet feed (Lab/Blox, Wayne) and water was given.

Behavioral Testing

Locomotor activity changes. Locomotor activity of individual animals (n=6 for each apomorphine dose) was measured in an automatic activity monitoring device (Digiscan, Omnitech Electronics) which used an infrared detection system. Activity was measured over a 1 hr period and determined in 10 min increments. A fixed volume (0.5 ml/20 g) of apomorphine (apomorphine hydrochloride, Research Biochemical, Inc.) dissolved in physiological saline immediately prior to administration was introduced into the mice by IP injection. Animals were immediately placed in the activity monitor and locomotor activity recorded in 10 min increments for 1 hr postinjection.

Rearing activity changes. Individual rearing events were scored in 5 min increments for 1 hr before and after apomorphine administration (n=6 for each dose). Control values for individual animals were determined at least several days prior to drug administration. A single event of rearing was defined to occur when an animal removed both forepaws from the floor of the cage and assumed a vertical or nearly vertical position. A second event of rearing was not scored until both forepaws were first replaced on the floor of the cage, i.e., the animal first assumed a normal horizontal position before initiating another rear. Rearing was distinguished from grooming events, and isolated grooming events were not scored as rearing. Rearing was scored in the cage described below.

Stereotyped behavior induction. Assessment of stereotyped sniffing, gnawing and cage climbing was conducted in a wire mesh cage (1/4 inch galvanized hardware cloth, 12×7×7 inches). Cage climbing activity was determined quantitatively by measuring the amount of time an individual had all four feet off the bottom of the cage, i.e., was positioned on the cage side or hanging from the wire on the roof of the cage. Climbing time was determined in 5 min increments for 1 hr after the introduction of the animal into the cage. Control values were determined in 18 mice of each strain several days before they were given IP injections of freshly prepared apomorphine solutions. Measurement of cage climbing activity, sniffing and gnawing stereotyped ac-

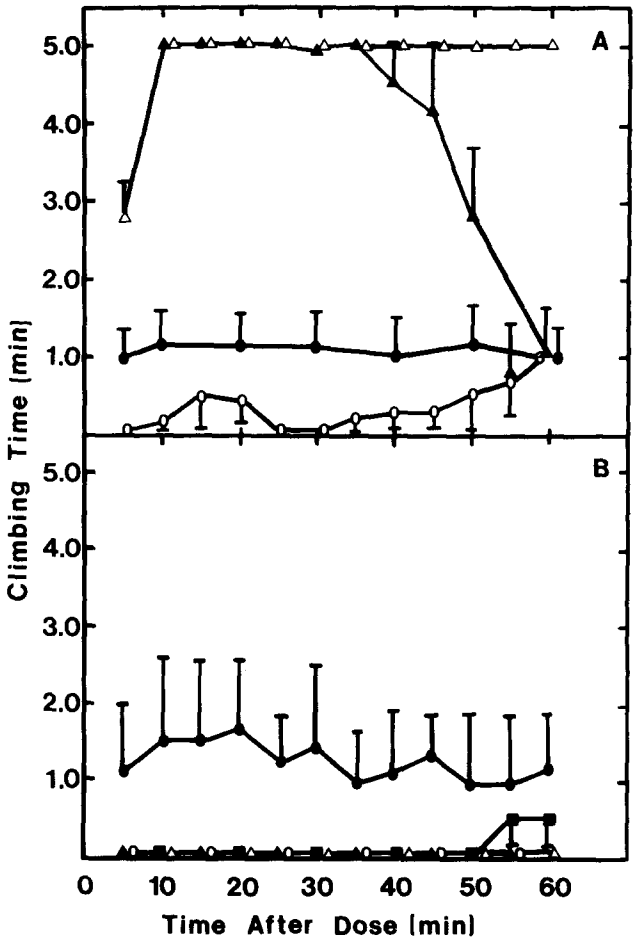

FIG. 1. Time-dependent effects on cage climbing activity elicited by apomorphine at different dosages. (A) C57BL/6 mice; (B) DBA/2 mice. Mice (n=6 for each dosage) were given IP injections of apomorphine and immeidately placed in a wire cage used for scoring stereotypy. (●) Saline control; (■) 0.5 mg/kg; (○) 2 mg/kg; (▲) 10 mg/kg; (△) 20 mg/kg. Values are the mean sum of the amount of time spent climbing off the cage floor per 5 min scoring interval ±SEM. The inhibition of C57BL/6 by 0.5 mg/kg from 5–20 min is significant at the 0.01 level. At 25 min climbing is not significantly different from basal level at 0.05 mg/kg. At 2 mg/kg C57BL/6 the inhibition is significant at the 0.01 level for 35 min but is not statistically different from baseline after 45 min. The stereotyped behavior seen in C57BL/6 at 10 mg/kg begins to decline at 40 min and is significantly different ($p<0.05$) from the maximal effect by 45 min.

TABLE 1

SUMMARY OF APOMORPHINE-INDUCED BEHAVIORAL EFFECTS IN C57BL/6 AND DBA/2 MICE

Behavioral Trait	Strain	
	C57BL/6	DBA/2
Cage climbing activity*		
Basal	22 ± 10%	24 ± 20%
Apomorphine treated	induced, 100% at 10 mg/kg	suppressed, 0% at 10 mg/kg
Gnawing activity		
Basal	random biting, infrequent	random biting, frequent
Apomorphine treated	stereotypy induced, more affected, latency <5 min at 10 mg/kg	stereotypy induced, less affected latency 15–20 min at 10 mg/kg
Sniffing activity		
Basal	continuous non-stereotyped	continuous non-stereotyped
Apomorphine treated	stereotypy induced, latency to maximum <5 min at 10 mg/kg	stereotypy induced, latency to maximum >15 min at 10 mg/kg
Locomotor activity level		
Basal†	10237 ± 2730	3252 ± 1199
Apomorphine treated	42 ± 6% of basal at 2 mg/kg	11 ± 3% of basal at 2 mg/kg
Rearing Activity		
Basal	21 ± 6	12 ± 5
Apomorphine treated	suppressed partially at doses ≤10 mg/kg	suppressed completely at all doses ≥0.5 mg/kg

*Cage climbing activity is expressed as percentage of time interval spent completely off the cage floor.
†Basal locomotor activity is expressed as activity monitor score.
Basal activities shown here were calculated from data on 18–36 animals.

tivities described below were initiated immediately after injection in previously untreated animals (n=6 for each apomorphine dose). We attempted to objectify the scoring of stereotyped gnawing and sniffing (each scored concurrently with cage climbing) and to assign a numerical score to the behavioral activity according to the following scheme: (0) no stereotyped behavior noted during the scoring interval; no qualitative change from basal activity; (1+) stereotypy present intermittently and infrequently (<1/3 of scoring interval); (2+) stereotypy present frequently (>1/3 of scoring interval) but not continuously; (3+) stereotypy present in exaggerated form and present continuously during the scoring interval. Animals (n=6) for each dosage were scored in 5 min increments for 1 hr by two independent observers. There was a high correlation between the scores determined by the two observers. To avoid biasing the outcome of these experiments by anticipation of expected results, experimental determinations of stereotypy at all doses were completed before any calculations and correlations were undertaken.

Statistics. Dose effect curves were compared through the use of an analysis of variance program (ANOVA). Comparison of individual data points was accomplished by student's *t*-tests [15]. Statistically significant results were considered to occur if a p value less than 0.05 was calculated.

RESULTS

Comparison of Apomorphine-Induced Stereotyped Behavior Activity

Cage climbing activity. Figure 1 shows the dose dependent effects of apomorphine on climbing activity in C57BL/6 and DBA/2 scored in 5 min increments for 1 hr after drug administration. A general comparison of these findings to the other behavioral effects induced by apomorphine in these two strains is summarized in Table 1. Before apomorphine administration, the two strains had comparable climbing times (20–25% of a given interval spent climbing) although the variance was somewhat greater for DBA/2 than for C57BL/6. Low doses (0.5–2 mg/kg) of apomorphine suppressed the basal climbing activity in both strains, but C57BL/6 (Fig. 1A) showed a more rapid return to the basal activity level than did DBA/2 (Fig. 1B). Climbing activity returned to basal level in 25 min at 0.5 mg/kg but not until 50–55 min at 2 mg/kg in C57BL/6. At a dosage of 10 mg/kg, there was a rapid increase in climbing activity in C57BL/6. In this strain climbing occupied 100% of the scoring interval over a period of 5–35 min following 10 mg/kg apomorphine administration. Induction of climbing behavior in C57BL/6 persisted for the entire 60 min when a dose of 20 mg/kg was given, but at 10 mg/kg, a decrease in climbing activity was noted by 40 min. Thereafter, climbing decreased rapidly and returned to basal levels by 55 min. In contrast, the climbing activity of DBA/2 was suppressed, not increased, at all dosages tested.

Stereotyped gnawing or biting. Untreated or saline treated controls from C57BL/6 bit the mesh of the cage wire in an infrequent, isolated, non-stereotyped manner. DBA/2 had more frequent isolated biting behavior which occasionally resulted in momentary fixed gnawing at a restricted section of the wire mesh. However, these infrequent events could be readily distinguished from stereotyped behavior in

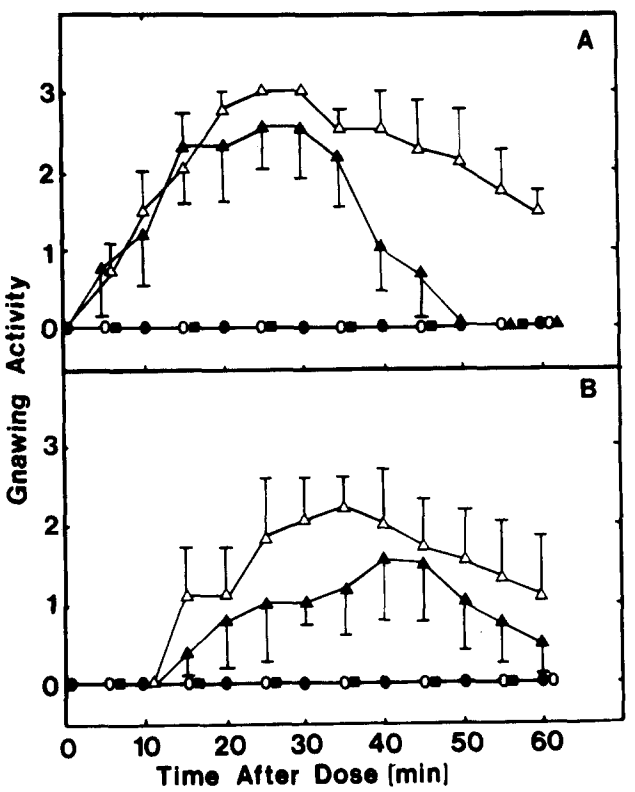

FIG. 2. Time-dependent induction of stereotyped gnawing activity elicited by apomorphine at different dosages. (A) C57BL/6 mice; (B) DBA/2 mice. Mice (n=6 for each dosage) were given IP injections of apomorphine and immediately placed in a wire cage used for scoring stereotypy, (●) Saline control; (■) 0.5 mg/kg; (○) 2 mg/kg; (▲) 10 mg/kg; (△) 20 mg/kg. Values are means derived from numerical scoring of qualitative classification of each mouse evaluated in individual 5 min scoring intervals ±SEM. At 10 mg/kg DBA stereotypy compared to baseline is statistically significant at the 0.01 level only from 25–50 min. The maxima reached by DBA at 10 and 20 mg/kg are not statistically different from one another but do differ at the 0.01 level from the maxima achieved in C57BL/6. The longer duration of the effect of 10 mg/kg in DBA is not statistically different from the response in C57BL/6.

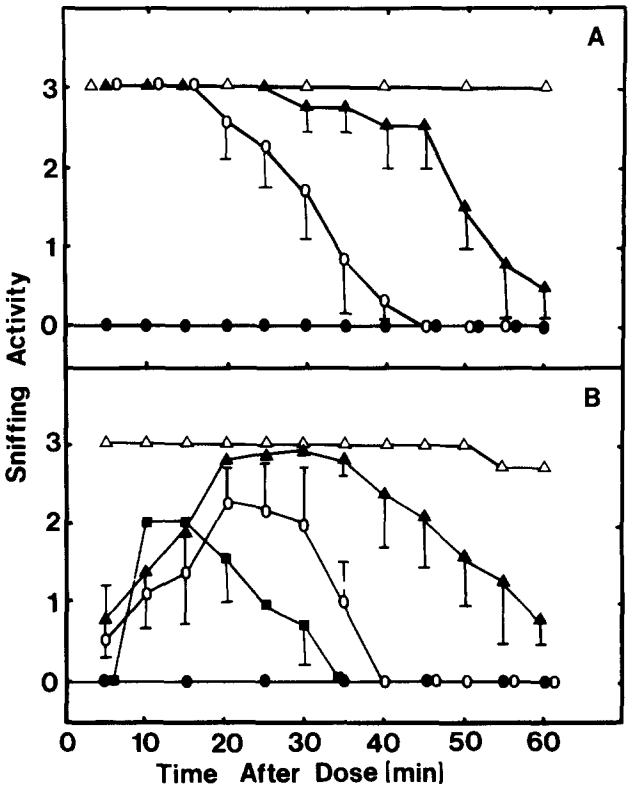

FIG. 3. Time-dependent induction of stereotyped sniffing activity elicited by apomorphine at different dosages. (A) C57BL/6 mice; (B) DBA/2 mice. Mice (n=6 for each dosage) were given IP injections of apomorphine and immediately placed in a wire cage used for scoring stereotypy. (●) Saline control; (■) 0.5 mg/kg; (○) 2 mg/kg; (▲) 10 mg/kg; (△) 20 mg/kg. Values are means derived from numerical scoring of qualitative classification of each mouse evaluated by individual 5 min scoring intervals ±SEM. In both C57BL/6 and DBA/2 the values ≥0.7 are significantly different from baseline at the 0.01 level. The positive responses of DBA and C57BL/6 were not statistically different from one another when compared for times >20 min. Sniffing was not scored in C57BL/6 at 0.5 mg/kg.

experiments in which the observer did not know whether a given experimental animal had been pretreated with saline or with apomorphine. At apomorphine doses ≤2 mg/kg, neither strain showed an increase in stereotyped gnawing (Fig. 2). At doses of 10–20 mg/kg, stereotyped gnawing was induced in both strains. All animals in both strains responded at these doses. However, the magnitude of the response was significantly less ($p<0.01$) in DBA/2 (Fig. 2B) than in C57BL/6 (Fig. 2A). Also, the latency of the onset of gnawing was increased in DBA/2 compared to C57BL/6 (Table 1 and Fig. 2).

Stereotyped sniffing. Under our conditions control animals of both strains show continuous random sniffing activity. Apomorphine induced stereotyped compulsive sniffing in a localized area by both strains at dosages of ≥2 mg/kg (Fig. 3). All animals of both strains showed stereotyped sniffing after drug treatments. In each strain the magnitude of the effect, the latency and the duration of the stereotyped behavior were doseage dependent. Latency of onset of response differed between DBA/2 and C57BL/6; latency to maximal effect was longer in DBA/2 (Fig. 3B; Table 1) than in C57BL/6 (Fig. 3A). Although the relative maximal values achieved were lower in DBA/2 than in C57BL/6, these differences were not statistically significant at times >20 min after apomorphine administration. The kinetics of return to non-stereotyped basal levels were indistinguishable between the two strains.

Comparison of Apomorphine-Induced Changes in Exploratory Activity

Locomotor activity. Basal locomotor activity in C57BL/6 was about threefold higher than that found in DBA/2 (Table 1). The overall dose-dependent effects of apomorphine on locomotor activity are shown in Fig. 4 and Table 1. Initially we characterized locomotor activity in 10 min increments for 60 min after drug administration (data not shown) to deter-

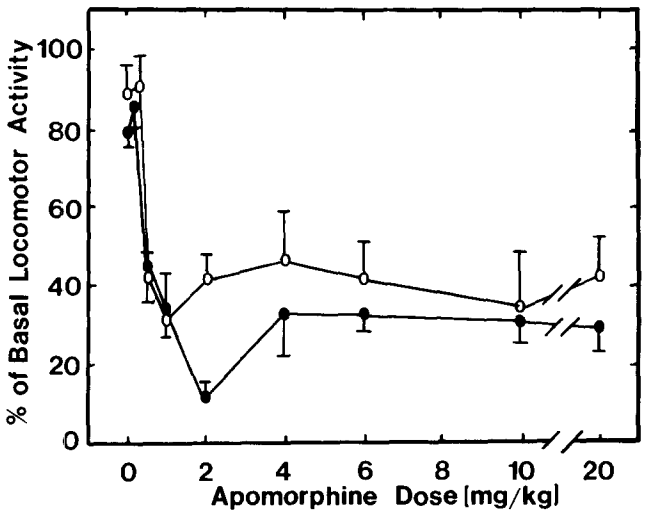

FIG. 4. Comparison of dosage dependent effects on locomotor activity elicited by apomorphine in C57BL/6 and DBA/2 mice. Activity levels were measured for 60 min post apomorphine administration. Values are the mean percentage change compared to untreated basal locomotor activity in the same animals ±SEM. Note that saline injected control animals of each strain had activity levels of 80–90% of uninoculated controls. When the two strains were compared, only the inhibition of DBA at 2 mg/kg was significantly different at 0.01 level from that observed in C57BL/6. (○) C57BL/6; (●) DBA/2.

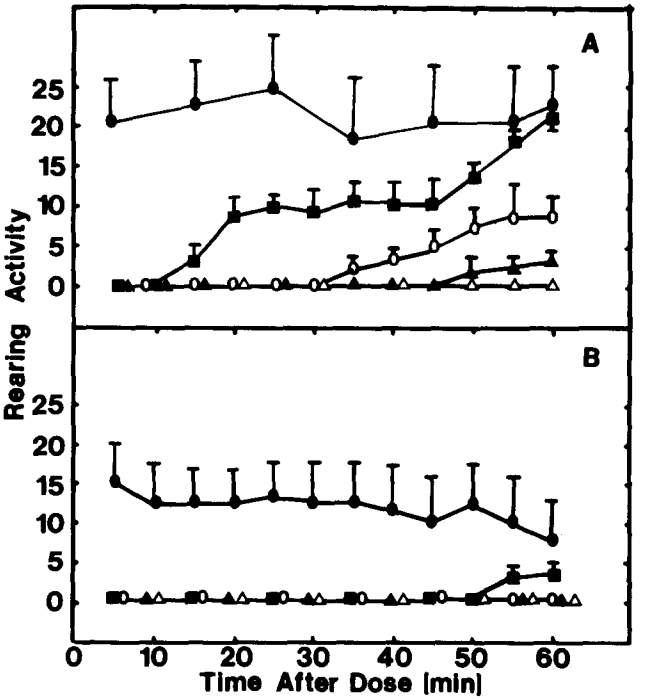

FIG. 5. Time-dependent effects on rearing activity elicited by apomorphine at different dosages. (A) C57BL/6 mice; (B) DBA/2 mice. Mice (n=6 for each dosage) were given IP injections of apomorphine and immediately scored in the wire cage used for scoring stereotypy. (●) Saline control; (■) 0.5 mg/kg; (○) 2 mg/kg; (▲) 10 mg/kg; (△) 20 mg/kg. Values are the mean sum of the number of individual rearing events occurring within each 5 min scoring interval ±SEM. Inhibition by all doses in both strains is statistically significant at the 0.01 level compared to control animals. The differences in return to basal level between the strains were significant ($p<0.01$) at 0.5 and 2 mg/kg doses.

mine if there was a significant difference between strains in the time dependence of the apomorphine effects. Whether locomotor activity was determined early (e.g., the first 20 min) or late (e.g., the last 20 min) after apomorphine administration, the results were essentially identical to those shown in Fig. 4. Neither strain was inhibited at a dose of 0.1 mg/kg. At an apomorphine dose of 0.5 mg/kg locomotor activity in both strains was inhibited about 40%. At 2 mg/kg DBA/2 was inhibited to a greater extent than was C57BL/6 ($p<0.01$). At doses $\geq$10 mg/kg, we found no significant difference between the two strains in the inhibition of locomotor activity by apomorphine.

Rearing activity. Basal rearing activity of control C57BL/6 and DBA/2 mice differ significantly from one another (22±7 and 12±6 rearings per 5 min increments respectively) over the 60 min period of assessment (Fig. 5, Table 1). The rearing activity of both strains was suppressed completely by apomorphine (at doses ranging from 0.5–20 mg/kg) within the first 10 min after drug administration. However, at lower dosages (e.g., 2 mg/kg), C57BL/6 returned to normal or nearly normal rearing activity by 60 min (Fig. 5A) whereas rearing in DBA/2 (Fig. 5B) was still completely suppressed at this time.

DISCUSSION

The neuropharmacological complexity of each individual apomorphine-induced behavioral change as well as the potential mutual interactions of these behaviors requires cautious interpretation of our findings. To put these results in context, we will first review individual behaviors as entities before discussing our overall interpretation of these new data.

Stereotyped behaviors induced by increased central dopamine transmission are characterized by the apparently purposeless repetition of small sequences of behavior [25,29]. Stereotyped cage climbing in mice is relatively specific for the dopaminergic agonist action of apomorphine and related compounds [3, 24, 28]. However, marked response differences between strains occur. In Swiss albino and BKW mice the threshold for induction of climbing is about 0.1 mg/kg with a maximal effect occurring at about 1 mg/kg [3,24]. In contrast, such doses of apomorphine (e.g., 0.5 mg/kg) did not induce cage climbing in our study with C57BL/6 and DBA/2 nor in the CD-1 strain of mice [28]. Low doses actually inhibited basal climbing rates under our conditions. Other strains require significantly higher doses of apomorphine to stimulate climbing, e.g., high levels of cage climbing occur in CD-1 at 10 mg/kg [28]. We found climbing stereotypy was induced in C57BL/6 at doses similar to CD-1 (10 and 20 mg/kg) but no enhancement of this activity occurred in DBA/2 at these doses. In C57BL/6 the duration of cage climbing activity induced by apomorphine was dosage dependent. This was also reported to be the case in Swiss albino mice [24].

It is unlikely that this marked, isolated behavioral hyporesponsiveness of DBA/2 arises from reduced general

availability of apomorphine because other behavioral effects with similar dosage requirements remain largely intact in this strain. The striatum [19] and the nucleus accumbens [4,5] have been shown in lesioning experiments to be brain regions which have a significant role in apomorphine-induced climbing activity. DBA/2 previously has been shown to have a reduced number of striatal dopamine receptors compared to C57BL/6 [32]. B_{max} for (^{3}H) spiperone and (^{3}H) domperidone binding in striatum of DBA/2 is only 80% of that found in C56BL/6 [32]. Failure of apomorphine to induce stereotyped cage climbing in DBA/2 may be correlated with this 20% reduction in striatal dopamine receptors. The 20% fewer binding sites may reflect a generalized reduction in receptor synthesis or increased receptor biodegradation. It could easily represent the absence of a particular subgroup of receptors. A multiplicity of dopamine receptor subtypes have been proposed. The D_1 subtype is associated with dopamine-sensitive adenylate cyclase [14]. While this receptor subtype appears to regulate a cyclase, it does not appear to be involved in the behavioral effects of dopamine receptor antagonists and agonists [16,33]. Spiperone binding and dopamine agonist binding are used to identify D_2 receptors. This site appears to be correlated with the behavioral and therapeutic effects of neuroleptics [12,17]. The existence of functionally different receptor subpopulations is exemplified by the work of Niemegeers *et al.* [23]. They demonstrated in outbred rats that the various behavioral effects of spiperone occur at different doses and correspond to the fraction of receptors occupied. Thus, in the rat the hypermotility response induced by apomorphine appears to involve occupation of only 20% of the total apomorphine binding sites available. Thus, a relatively small decrease in the absolute number of receptors could in principle have a marked and specific effect on one behavior among the several mediated by a dopamine receptor agonist.

How does such an interpretation apply to the other effects of apomorphine in DBA/2 and C57BL/6?

Stereotyped gnawing activity in rodents has been proposed to be under tonic inhibitory control which can be released in an all-or-none manner by apomorphine [26]. This may reflect a release of mechanisms in the superior colliculus following a reduction in nigrally-mediated inhibitory control [26]. Quite conflicting results have been reported previously by various investigators with regard to apomorphine-induced stereotyped biting or gnawing in mice. Lapin [18] reported that apomorphine induced no stereotyped gnawing in five strains of mice including C57BL/6 at doses up to 40 mg/kg. Oliverio *et al.* [30,37] detected apomorphine-induced gnawing in DBA/2 mice under one set of conditions but not another. Under conditions in which stereotyped biting was observed in DBA/2, it was not observed in C57BL/6 mice [37]. Apomorphine administration in N.M.R.I. mice produced moderate biting [31] but not in Kausali mice [7] nor in an undefined strain [35]. By our method of scoring we found that apomorphine could induce stereotyped gnawing in both C57BL/6 and in DBA/2 strains, albeit with somewhat different latencies of onset, dosage-dependent maximal responses and duration of occurrence. Our semiquantitative findings in these mice are in general accord with the observations of Redgrave, Dean and Lewis [27] who designed an automatic measuring device to quantitate stereotyped gnawing behavior induced by apomorphine in the rat. The conflicting findings on apomorphine-induced gnawing in mice appear to reflect several variables including: (1) the intrinsic capacity of the strain to respond which may be strain specific; (2) the method of assessing the behavior and its changes; (3) the environmental conditions; (4) the dosage of apomorphine; (5) the time after apomorphine administration at which gnawing behavior is scored. We presume that either the method of scoring or the environment explains the differences in our results compared to others [18, 30, 37]. Assuming the accuracy of our stereotyped gnawing data (obtained under exactly the same conditions as climbing behavior was assessed) we suggest that the gnawing response is largely intact (although partially reduced). Thus, either the dopamine receptor primarily mediating this behavior is a different subtype from that involved in climbing behavior or the synthesis and distribution of the same receptor subtype are under separate genetic control for different brain regions. However, there is a partial reduction of the maximal effect in DBA/2 compared to C57BL/6. This might be taken as the component mediated by the receptor subtype whose deficiency is postulated to underlie the climbing hyporesponsiveness also found in DBA/2.

We found that neither DBA/2 nor C57BL/6 showed increased stereotyped gnawing or biting activity at 2 mg/kg apomorphine, a dose which appeared to induce stereotyped sniffing in both strains. Lapin [18] also observed stereotyped sniffing in the absence of gnawing in C57BL/6 and other strains. We found no differences between C57BL/6 and DBA/2 in the intensity or duration of apomorphine-induced stereotyped sniffing. Many authors have considered the various components of drug-induced stereotyped behavior—sniffing, repetitive head and limb movements, gnawing/biting, licking, climbing—to be expressions of a single behavioral complex mediated by a common central mechanism. In the rat stereotyped sniffing can be dissociated from other stereotyped behaviors on the basis of neuroanatomical localization of brain lesions altering the response [6] and by the respective profiles of sensitization and tolerance [9]. Stereotyped sniffing appears to involve a substantial mesolimbic dopamine component [2,6]. Our results also clearly dissociate sniffing from other stereotyped behaviors. The differences between DBA/2 and C57BL/6 which dramatically affect apomorphine-induced climbing behavior have little effect on stereotyped sniffing. One possibility is that these behavioral responses reflect the intactness of the dopamine receptor functions in the nucleus accumbens in contrast to the loss of inducible climbing in DBA/2 as a consequence of the reduction in the number of striatal dopamine receptors.

In the rat apomorphine at doses between 0.01 and 10 mg/kg exerts a biphasic dose-dependent effect on locomotor activity [11,21]. Doses below about 0.2 mg/kg are inhibitory, whereas increased doses stimulate locomotor activity. The low dose inhibitory effects have been attributed to a presumptive presynaptic receptor. This receptor type is distinguished from the receptors which mediate locomotor stimulation by its differential response to selected dopamine agonists [11]. A similar biphasic response with differential agonist effects is found in Swiss-Webster and N.M.R.I. mice [10,34]. We interpret our results to indicate that a fraction of the receptors which mediate increased locomotor responses is reduced in DBA/2 compared to C57BL/6. Such a receptor deficit also may account for the more marked inhibition of rearing activity in DBA/2 (i.e., an inhibitory effect resulting from activation of one receptor class is opposed by the activation of a second receptor class at a higher dopamine concentration in C57BL/6). Strain specific effects on mouse locomotor activity similar to those we observed at higher

doses have been reported by others [4, 18, 22, 30, 37]. In the rat, apomorphine-induced stimulation of locomotor activity also is dissociable from gnawing activity [18,19]. We found that low doses of apomorphine markedly inhibited locomotor activity in both DBA/2 and C57BL/6 without inducing any stereotyped behaviors. Since under our conditions marked locomotor inhibition was induced in DBA/2 and C57BL/6 by apomorphine without the induction of stereotyped gnawing, it seems unlikely that the induction of stereotypy itself produces locomotor inhibition [37].

Through the use of full dose response curves and multiple behavioral measures, we have attempted to detail similarities and differences in apomorphine-induced behavioral responsiveness between two inbred mouse strains known to differ in the relative number of their brain dopamine receptors. In our discussion we have suggested that the observed behavioral differences in apomorphine responsiveness relate to genetically determined dopamine receptor number differences. While this may be so, our existing data do not unequivocally establish the causal relationship between reduced receptor number and apomorphine response differences between these two inbred mouse strains. More complex neuropharmacogenetic differences may occur between these strains. For example, significant differences in the time course for restoration of basal climbing and rearing activity occur between C57BL/6 and DBA/2 after apomorphine treatment. Whether these represent differential disposition of the drug to/from selected brain regions, intrinsic neural compensatory mechanisms (e.g., receptor affinity state change) or other basic behavior-pharmacological differences remains unclear. It has yet to be established whether each or any of the differences in apomorphine responsiveness between DBA/2 and C57BL/6 are inherited in a simple Mendelian fashion and, if so, whether they co-segregate with the genetic determinant for reduced dopamine receptor number in the brain. It cannot be assumed that an apparent single gene difference in receptor number means a single gene difference in behavioral response. The results presented here now allow the systematic investigation of these questions in recombinant inbred strains derived from C57BL/6 by DBA/2 hybrids.

REFERENCES

1. Boehme, R. E. and R. D. Ciaranello. Genetic control of dopamine and serotonin receptors in brain regions in inbred mice. *Brain Res* **266:** 51–65, 1982.
2. Costall, B. and R. J. Naylor. Mesolimbic and extrapyramidal sites for the mediation of stereotyped behavior patterns and hyperactivity by amphetamine and apomorphine in the rat. In: *Cocaine and Other Stimulants*, edited by E. H. Ellinwood and M. M. Kilbey. New York: Plenum Press, 1977, pp. 72–96.
3. Costall, B., R. J. Naylor and V. Nohria. Climbing behaviour induced by apomorphine in mice: a potential model for detection of neuroleptic activity. *Eur J Pharmacol* **50:** 39–50, 1978.
4. Costall, B., R. J. Naylor and V. Nohria. Hyperactivity response to apomorphine and amphetamine in the mouse: the importance of the nucleus accumbens and caudate-putamen. *J Pharm Pharmacol* **31:** 259–264, 1979.
5. Costall, B., R. J. Naylor and V. Nohria. On the importance of mesolimbic mechanisms for the control of apomorphine induced climbing behaviour in the mouse. *Br J Pharmacol* **68:** 175P–176P, 1980.
6. Costall, B., C. D. Marsden, R. J. Naylor and C. J. Pycock. Stereotyped behaviour patterns and hyperactivity induced by amphetamine lesions of extrapyramidal and mesolimbic nuclei. *Brain Res* **123:** 89–111, 1977.
7. Dadkar, N. N., A. N. Dohadwalls and B. K. Bhattacharya. Possible role of dopamine in central effects of cocaine as measured by apomorphine gnawing test in mice. *Psychopharmacology (Berlin)* **52:** 115–117, 1977.
8. DiChiara, G. and G. L. Gessa. Pharmacology and neurochemistry of apomorphine. *Adv Pharmacol Chemother* **15:** 87–160, 1978.
9. Eichler, A., J. Antelman and C. A. Black. Amphetamine stereotypy is not a homongeneous phenomenon: sniffing and licking show distinct profiles of sensitization and tolerance. *Psychopharmacology (Berlin)* **68:** 287–290, 1980.
10. Gianutsos, G. and K. E. Moore. Differential behavioral and biochemical effects of four dopaminergic agonists. *Psychopharmacology (Berlin)* **68:** 139–146, 1980.
11. Goodale, D. B., D. B. Rusterholz, J. P. Long, J. R. Flynn, B. Walsh, J. G. Cannon and T. Lee. Neurochemical and behavioral evidence of a selective presynaptic dopamine receptor agonist. *Science* **210:** 1141–1143, 1980.
12. Gorissen, H. and P. Laduron. Solubilisation of high-affinity dopamine receptors. *Nature* **279:** 72–74, 1979.
13. Jenner, P. and C. D. Marsden. Multiple dopamine receptors in brain. In: *Metabolic Disorders of the Nervous System*, edited by F. C. Rose. Bath: Pitman Press, 1981, pp. 13–24.
14. Kebabian, J. W. and D. B. Calne. Multiple receptors for dopamine. *Nature* **279:** 93–96, 1979.
15. Kirk, R. E. *Experimental Design: Procedures for Behavioral Sciences*. Belmont, CA: Brooks/Cole Publishing Co., 1968.
16. Laduron, P. Dopamine receptor: from an in vivo concept towards a molecular characterization. *Trends Pharmacol Sci* **1:** 471–474, 1980.
17. Laduron, P. M., P. F. M. Janssen and L. Leysen. Spiperone: A ligand of choice for neuroleptic receptor. *Biochem Pharmacol* **27:** 317–321, 1978.
18. Lapin, I. P. Effects of apomorphine in mice of different strains. In: *Psychopharmacogenetics*, edited by B. R. Eleftheriou. New York: Plenum Press, 1975, pp. 19–32.
19. Ljungberg, T. and U. Ungerstedt. Differential behavioural patterns induced by apomorphine: evidence that the method of administration determines the behavioural response to the drug. *Eur J Pharmacol* **46:** 41–50, 1977.
20. Ljungberg, T. and U. Ungerstedt. Classification of neuroleptic drugs according to their ability to inhibit apomorphine-induced locomotion and gnawing: evidence for two distinct mechanisms of action. *Psychopharmacology* **5:** 239–247, 1978.
21. Maj, J., M. Grabowska and L. Gajada. Effect of apomorphine on motility in rats. *Eur J Pharmacol* **17:** 208–214, 1972.
22. Maj, J., M. Grabowska, L. Gajada and J. Michaluk. On the central action of apomorphine in mice. *Diss Pharm Pharmacol* **24:** 351–364, 1972.
23. Niemegeers, C. J. E. and P. A. J. Janssen. A systematic study of the pharmacological activities of dopamine antagonists. *Life Sci* **24:** 2201–2216, 1979.
24. Protais, P., J. Costantin and J. C. Schwartz. Climbing behavior induced by apomorphine in mice: a simple test for the study of dopamine receptors in striatum. *Psychopharmacology (Berlin)* **50:** 1–6, 1976.
25. Randrup, A. and I. Munkvad. Pharmacology and physiology of stereotyped behaviour. *J Psychiatr Res* **11:** 1–10, 1974.
26. Redgrave, P., P. Dean, T. P. Donohoe and S. G. Pope. Superior colliculus lesions selectively attenuate apomorphine-induced oral stereotypy: a possible role for the nigrotectal pathway. *Brain Res* **196:** 541–546, 1980.

27. Redgrave, P., P. Dean and G. Lewis. A quantitative analysis of stereotyped gnawing induced by apomorphine. *Pharmacol Biochem Behav* **17:** 873–876, 1982.
28. Riffee, W. H., R. E. Wilcox and R. V. Smith. Stereotypic and hypothermic effects of apomorphine and N-n-propyl-norapomorphine in mice. *Eur J Pharmacol* **54:** 273–277, 1979.
29. Robbins, T. W. and B. J. Sahakrain. Behavioural and neurochemical determinants of stereotypy induced by drugs. In: *Metabolic Disorders of the Nervous System*, edited by F. C. Rose. London: Pitman Press, 1981, pp. 294–297.
30. Sansone, M., M. Ammasari-Teule, P. Renzi and A. Oliverio. Different effects of apomorphine on locomotor activity in C57BL/6 and DBA/2 mice. *Pharmacol Biochem Behav* **14:** 741–743, 1981.
31. Scheel-Kruger, J. Central effects of anticholinergic drugs measured by the apomorphine gnawing test in mice. *Acta Pharmacol Toxicol* **28:** 1–16, 1970.
32. Severson, J. A., P. K. Randall and C. E. Finch. Genotypic influences on striatal dopaminergic regulation in mice. *Brain Res* **210:** 201–215, 1981.
33. Spano, P. F., S. Govoni and M. Trabucchi. Studies on the pharmacological properties of dopamine receptors in various areas of the central nervous system. *Adv Biochem Psychopharmacol* **19:** 155–165, 1978.
34. Strombom, U. Catecholamine receptor agonists. Effects on motor activity and rate of tyrosine hydroxylation in mouse brain. *Naunyn Schmiedebergs Arch Pharmacol* **292:** 167–176, 1976.
35. Ther, L. and H. Schramm. Apomorphin-synergismus (Zwangsnagen bei Mausen) als Test zur Differenzierung psychotroper Substanzen. *Arch Int Pharmacodyn* **138:** 302–310, 1962.
36. Thornburg, J. E. and K. P. Moore. A comparison of effects of apomorphine and ET495 on locomotor activity and circling behaviour in mice. *Neuropharmacology* **13:** 189–197, 1974.
37. Vetulani, J., M. Sansone and A. Oliverio. Analysis of the difference in the behavioral effects of apomorphine in C57BL/6 and DBA/2 mice. *Pharmacol Biochem Behav* **17:** 967–971, 1982.