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Role of Genotype in Brain Dopamine Metabolism and Dopamine-Dependent Behavior of Mice

JULIA A. SKRINSKAYA,[1] ELLA M. NIKULINA AND NINA K. POPOVA

Behavioral Phenogenetics Laboratory, Institute of Cytology and Genetics
Siberian Branch of the Academy of Sciences of Russia, 630090, Novosibirsk 90, Russia

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SKRINSKAYA, J. A., E. M. NIKULINA AND N. K. POPOVA. *Role of genotype in brain dopamine metabolism and dopamine-dependent behavior of mice.* PHARMACOL BIOCHEM BEHAV **42**(2) 261-267, 1992. – In mice of eight inbred strains – BALB/c, AKR/J, DBA/2, CBA, C57Bl/6, DD, CC57Br, and C3H/He – brain dopamine and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), in striatum and nucleus accumbens with tuberculum olfactorium, the structures of two main dopaminergic systems – nigrostriatal and mesolimbic – were determined. In both dopaminergic regions, no strain effect on either dopamine or DOPAC levels was found, while for HVA content a highly significant hereditary determination was shown. Influences of selective D_1 and D_2 dopamine receptor agonists – SK&F 38393 and quinpirole, respectively – as well as that of a mixed D_1/D_2 agonist, apomorphine, on general locomotor activity and stereotypic climbing were studied. By that, marked genotypic differences in dopamine-dependent behavior and dopamine receptor sensitivity were observed. Although both SK&F 38393 (5 mg/kg) and apomorphine (0.25 mg/kg) decreased locomotion, the effect being genotype dependent, in all strains of mice quinpirole (2.5 mg/kg) proved more potent in locomotor inhibition. SK&F 38393 (10 mg/kg) induced climbing, but 2.5 mg/kg apomorphine in most strains was much more effective. At the same time, quinpirole (up to 8 mg/kg) failed to induce this behavior. This suggests the crucial role of D_1 receptors in the generation of climbing, attracting, at the same time, attention to the importance of D_1/D_2 interaction. The observed drastic interstrain differences in dopamine receptor sensitivity demonstrate the essential role of genotype in the effects of dopaminergic drugs.

Brain dopamine metabolism Locomotor activity Climbing D_1 and D_2 receptors Inbred strains of mice

THE current neurochemical hypothesis of many psychomotor disorders, such as rigidity in Parkinson disease, dyskinesias in Huntington disease, hallucinations in schizophrenia, and oral dyskinesia in the elderly, is that they may arise from brain dopaminergic system impairments (1,12,19,32). Hereditary factors are believed important in a high proportion of cases of the above-mentioned diseases (6,9). However, relatively little is known about the genetic control of dopamine in the brain. In several strains of mice, there have been reported differences in the number of dopaminergic neurons and tyrosine hydroxylase activity (the key enzyme of dopamine biosynthesis) (28,37). Dopamine receptors are now mostly divided into two types – D_1, stimulating adenylate cyclase, and D_2, not influencing or inhibiting this enzyme (20,36); and in number and affinity of these dopamine receptor subtypes interstrain differences have also been shown (4,8,21,31).

This report was designed to investigate strain-dependent differences in brain dopamine metabolism and in some kinds of dopamine-dependent behavior. To obtain a comprehensive overview of potential genetic variation, dopamine and its main metabolites' concentrations in structures of two main dopaminergic systems – nigrostriatal and mesolimbic – striatum and nucleus accumbens with olfactory tubercules, respectively, were measured. The study included also assessment of the role of genotype in some types of behavior believed to be dopamine dependent – stereotypic climbing and locomotor activity (7,21,25,38). To clarify the specific differential roles of the two types of dopamine receptors in the regulation of locomotion and climbing, we utilized selective D_1 and D_2 agonists.

METHOD

Animals

Male mice of eight different strains bred up in vivarium of the Institute of Cytology and Genetics, Novosibirsk, were used: BALB/c, AKR/J, DBA/2, C57Bl/6, CBA, CC57Br, DD, and C3H/He. They were housed in groups of eight in 40 × 25 × 12 cm cages at standard room temperature (24

[1] To whom requests for reprints should be addressed.

TABLE 1

MEAN ± SEM CONTENT OF DOPAMINE AND ITS MAIN METABOLITES IN MICE OF EIGHT INBRED STRAINS (μg/g BRAIN TISSUE)

Brain Region	Number of Assays	Dopamine	DOPAC	HVA	HVA/Dopamine
Striatum	63	8.81 ± 0.49	3.48 ± 0.22	0.56 ± 0.10	0.064
Nucleus accumbens with tuberculum olfactorium	63	2.92 ± 0.21	1.85 ± 0.09	0.64 ± 0.20	0.220

± 1°C) and humidity (60-62%) levels, under natural day/night cycle, with free access to food and water. Animals used were 3-4 months old, weighing 24-32 g. Experiments were performed under white light, in a quiet room, between 1000 and 1300 h, during the autumn-winter period. To abolish social interaction influences, mice were housed individually for 3-4 days before the experimental procedure.

Biochemical Assays

After rapid decapitation, brains were removed quickly in the cold and the dopaminergic structures were dissected. Striatum and nucleus accumbens with tuberculum olfactorium—representing the nigrostriatal and mesolimbic dopaminergic systems, respectively—were stored for less than 2 weeks before

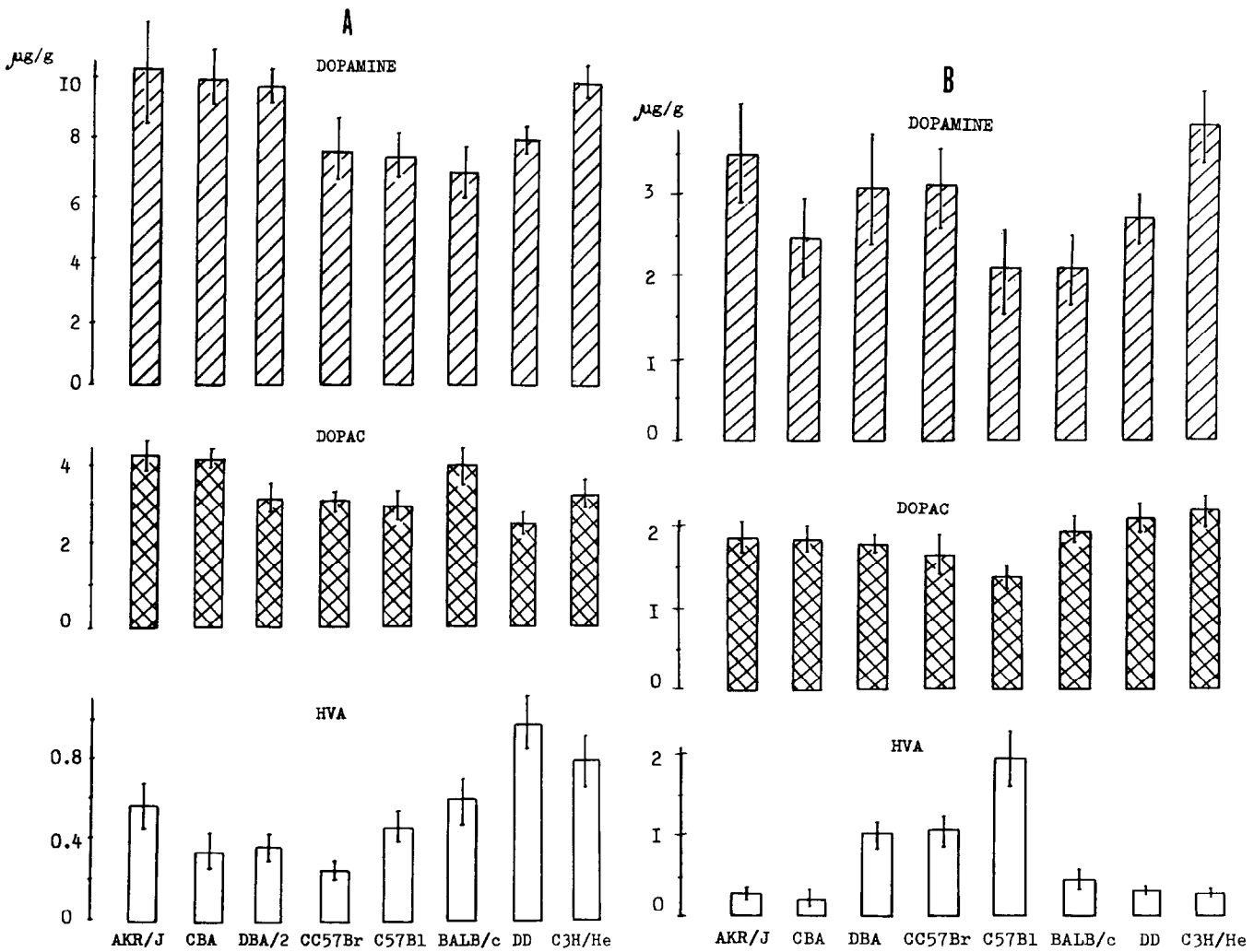

FIG. 1. Mean ± SEM levels of dopamine, DOPAC, and HVA in dopaminergic structures of inbred mice (μg/g brain tissue). (A), striatum; (B), nucleus accumbens with tuberculum olfactorium.

the biochemical assays at −40°C. They were analyzed fluorimetrically for content of dopamine and its main metabolites in the brain—3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) (15). Brain tissues were prepared by homogenizing in 1 ml 0.4 N $HClO_4$. KOH/HCOOH buffer was added to precipitate excess perchlorate ions. After centrifugation, the supernatant was poured onto chromotographic columns packed with Sephadex G-10 resin for dopamine, DOPAC, and HVA isolation. After fluorophorescein development, the dopamine samples were read on a Hitachi MPF-4 (Japan) at λ 330 ex-λ 370 em, DOPAC at λ 390-370, and HVA at λ 320-425.

Behavioral Tests

Locomotor activity. Locomotion of control animals, as well as of those after drug treatment, was assessed during 20 min in six activity chambers (18 × 18 × 20 cm) called actometers, each equipped with two photocell counters that recorded the number of beam crossings of the animal.

Stereotypic climbing. Mice were placed individually in circular 12 × 14 cm cages with wire mesh cage walls. Mice were observed for a total period of 20 min, during which each min they were given a score according to the position assumed during more than half the observation period (i.e., 30 s): 0, animal on all fours on the floor, not touching the walls with his forepaws; 1, animal touching the walls with one paw, most of the body on the floor; 2 and 3, animal standing erect, grasping the walls with both forepaws and one hindpaw; 4, animal clinging to the walls, no contact with the floor. This scale is a slight modification of that suggested by the authors (26) of the test. The final 20-min climbing score of each animal was obtained by adding the scores for each minute; thus, maximal climbing was rated 80 and minimal 0.

Drugs

A mixed D_1/D_2 agonist, apomorphine (Sigma Chemical Co., St. Louis, MO), was used SC for stimulation of either pre- (0.25 mg/kg) or postsynaptic (2.5 mg/kg) dopamine receptors (14,31). A highly selective D_1 dopamine receptor agonist, SK&F 38393 (Smith, Kline & French Labs, Philadelphia, PA), was injected SC in doses of 5 and 10 mg/kg (13). A selective D_2 agonist, quinpirole (LY 171555, Eli Lilly & Co., Indianapolis, IN), was administered intraperitoneally 2.5 and 8 mg/kg (5,27,35). All drugs were dissolved in distilled water (apomorphine immediately prior to each session) and injected in a volume of 10 ml/kg either immediately before testing—for evaluation of locomotor activity—or 10 min prior for climbing assessment.

Statistics

All data are expressed as means ± SEM and analyzed by one-way analysis of variance (ANOVA) except locomotor activity after drug administration. In this case, two-way ANOVA was utilized, the factors being strain and treatment. Also, correlation analysis for group means was used. Biochemical assays and climbing assessment were performed on eight animals of each strain; each group for locomotor activity testing consisted of nine animals.

RESULTS

Dopamine Metabolism

General characteristics of brain dopamine metabolism in mice of all genotypes studied are summarized in Table 1. They keep in approximately the same range as reported elsewhere (18). The dopamine content in the striatum is three times higher than in the nucleus accumbens with tuberculum olfactorium. The DOPAC level is two times higher. The HVA concentrations in two dopaminergic regions are nearly the same, but the variability is much greater in the mesolimbic system.

Interstrain differences in dopamine and DOPAC content either in the striatum or nucleus accumbens with tuberculum olfactorium proved nonsignificant (Fig. 1). At the same time, for both brain regions ANOVA showed highly significant strain effects for HVA concentrations: in the striatum, $F(7, 47) = 9.0$, $p < 0.001$, and in the nucleus accumbens with tuberculum olfactorium, $F(7, 46) = 11.0$, $p < 0.001$. The highest HVA level in the striatum was found in the DD mice, and it was almost five times higher than in CC57Br.

In the nucleus accumbens, HVA content was the highest in C57Bl/6 and lowest in CBA, the range of variation being tenfold.

No significant genotypical, within-strain, or phenotypical correlations were found between striatum and nucleus accumbens concentrations of dopamine, DOPAC, and HVA. The only reliable relationship found was a correlation between DOPAC and HVA levels in the nucleus accumbens with tuberculum olfactorium (Table 2): The higher the DOPAC content, the lower is that of HVA, genetical r being -0.847, $p < 0.05$.

Influence of Dopamine Agonists on Locomotor Activity

Behavioral tests showed significant genotype-dependent diversity in stereotypic climbing and locomotor activity.

Locomotion of mice, characterized by maximal (CC57Br) and minimal (DD) general locomotor activity, differed ap-

TABLE 2

CORRELATIONS BETWEEN DOPAMINE AND ITS METABOLITES CONTENTS IN DIFFERENT BRAIN REGIONS

	Striatum (A)		Nucleus Accumbens with Tuberculum Olfactorium (B)
Dopamine-DOPAC	+0.504		+0.393
Dopamine-HVA	+0.078		−0.286
DOPAC-HVA	−0.446		−0.847*
Dopamine (A-B)		+0.644	
DOPAC (A-B)		−0.010	
HVA (A-B)		−0.430	

*$p < 0.05$.

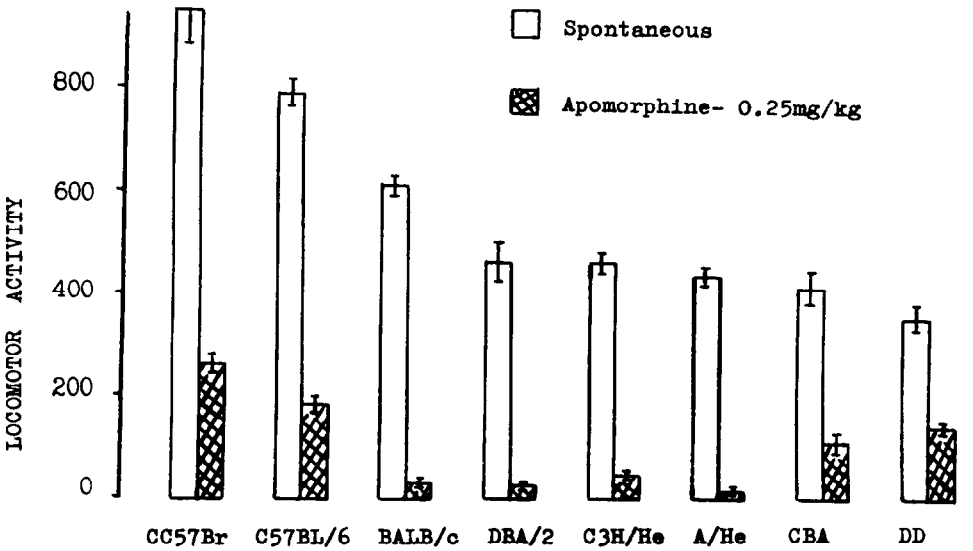

FIG. 2. Influence of mixed D_1/D_2 receptor agonist apomorphine on locomotion of inbred mice in actometers. Locomotor activity was measured during 20 min.

proximately three times (Fig. 2), one-way ANOVA showing highly significant differences; $F(8, 70) = 8.7, p < 0.001$. The low dose of apomorphine (0.25 mg/kg), which stimulates presynaptic dopamine receptors, caused a noticeable decrease of locomotion (Fig. 2), the manifestation of this effect, however, being different in different strains of mice. Two-way ANOVA (strain × treatment) showed a significant treatment main effect, $F(1, 125) = 7.5, p < 0.01$, as well as a highly significant strain × treatment interaction, $F(7, 125) = 46.5, p < 0.001$, indicating the effect of apomorphine itself to be genotype dependent. The most marked inhibitory influence was found in BALB/c, DBA/2, and A/He mice: Locomotion decrease was 18- to 25-fold, while in DD it was reduced only 2.5 times.

The highly selective D_1 dopamine receptor agonist SK&F 38393 decreased locomotion in all mice except C3H/He (Fig. 3). This inhibitory effect, however, was not so marked in CC57Br, C57Bl/6, and BALB/c as it was in DBA/2, CBA, and DD mice. Two-way ANOVA showed a significant strain × treatment interaction, $F(7, 120) = 44.3, p < 0.001$. Administration of the specific D_2 agonist LY 171555 definitively reduced locomotion in all strains studied, ANOVA showing

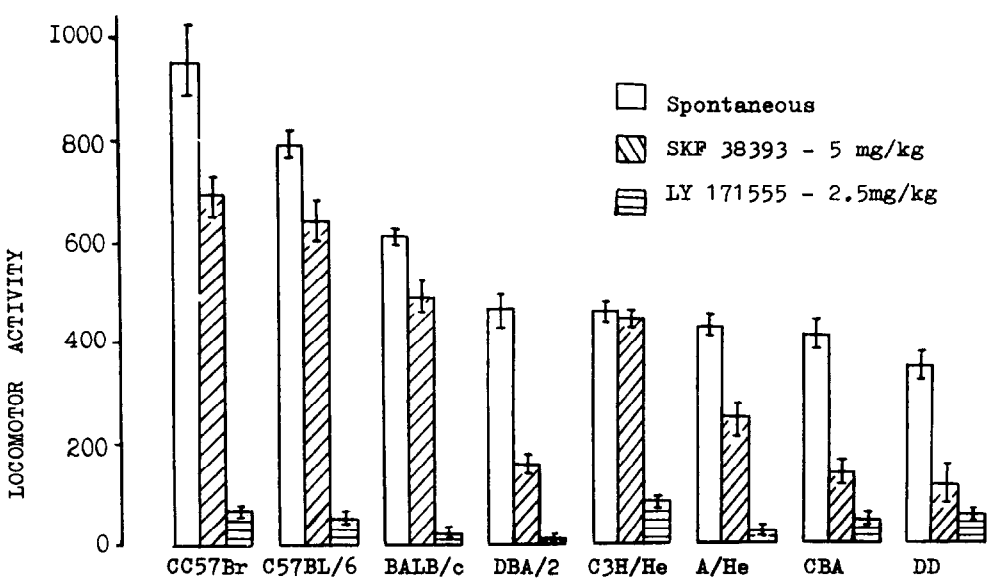

FIG. 3. Locomotor activity of inbred mice after selective D_1 (SK&F 38393) and D_2 (LY 171555) dopamine receptor stimulation. Locomotion was measured during 20 min.

a significant strain × treatment effect, $F(7, 124) = 41.3$, $p < 0.001$. Strain main effect was highly significant in all cases.

Influence of Dopamine Agonists on Stereotypic Climbing

Stereotypic climbing, induced by a large dose of apomorphine, acting mostly on postsynaptic dopamine receptors (2.5 mg/kg), varied over practically all the scale (Fig. 4): from 4 scores in DBA/2 mice up to 75 in CC57Br, ANOVA giving $F(7, 55) = 15.9, p < 0.001$. The distribution of mouse strains according to their climbing scores did not coincide with their locomotion scores (Figs. 3 and 4), for example, minimal locomotor activity was characteristic of DD mice, while minimal climbing was registered in DBA/2. Statistical analysis also did not reveal significant correlation between stereotypy and locomotion $r = 0.611, p > 0.05$.

The highly selective agonist of D_1 dopamine receptor SK&F 38393 at a dose 10 mg/kg, acting mostly on postsynaptic receptors (11), also induced climbing behavior varying in different strains of mice, $F(7, 54) = 8.4, p < 0.001$. In most strains (except CBA and BALB/c), climbing after SK&F 38393 administration was far less intensive than after apomorphine.

Injection of the D_2 dopamine agonist quinpirole (2.5 and 8 mg/kg) failed to induce this form of stereotypy.

Statistical analysis revealed no significant correlations between the effects of D_1 and D_2 dopamine receptor agonists in different behavioral tests.

DISCUSSION

No significant strain effect on dopamine and DOPAC content was found either in nigrostriatal or in mesolimbic dopaminergic systems. Thus, the levels of dopamine and DOPAC—product of dopamine deamination by brain monoamineoxydase—seem to be influenced more by ambient rather than genetic factors.

At the same time, for both systems the marked strain differences in the levels of the end product of brain dopamine degradation (3), HVA, were shown, suggesting a pronounced role of genotype in the regulation of catechol-*O*-methyltransferase (COMT) activity. The evidence of a more strict genotypical control of a certain way of neurotransmitter metabolism is of special interest because, namely, metabolism is supposed to reflect adequately neural cell activity (29,34).

The lack of correlation between concentrations of dopamine and its main metabolites observed in the nigrostriatal system is in accordance with the data obtained in rats (24).

Some peculiarities of brain dopamine metabolism in mice were found. DOPAC content was much higher than HVA level. In the striatum, dopamine and DOPAC content were much higher than in the nucleus accumbens with tuberculum olfactorium. At the same time, the activity of COMT, indirectly assessed by HVA/dopamine ratio, was considerably greater (threefold differences) in the second brain region. These differences and the absence of significant correlations between levels of neurotransmitter and its main metabolites in two dopaminergic regions confirm the hypothesis of independent genetic control of nigrostriatal and mesolimbic dopaminergic system parameters (23).

Both D_1 and D_2 dopamine receptors are shown to participate in the control of locomotor activity and stereotypic climbing. However, their relative importance in the regulation of these types of behavior is different. D_1 dopamine receptors seem to play a leading role in the generation of stereotypic climbing. This fact is worth separate attention because earlier D_1 receptors were not supposed to be important for the regulation of dopamine-dependent behavior (33). However, recently this suggestion has been proven doubtful (2,10,16,30). Our data concerning the key role of D_1 dopamine receptors in the regulation of stereotypic climbing also favor the revision of this concept.

At the same time, the necessity of interaction between the two types of dopamine receptors for the generation of a valid behavioral response should be underlined. Thus, in our experiments selective activation of D_2 receptors failed to produce stereotypy, but evidently played a facilitating, potentiating role: The concomitant D_1/D_2 receptor stimulation appeared to be more effective in inducing climbing. So, functional interaction between two types of dopamine receptors is shown to be crucial for the generation of maximal behavioral response, as it has been recently reported also for some other kinds of dopamine-dependent behavior (17,24,39,40).

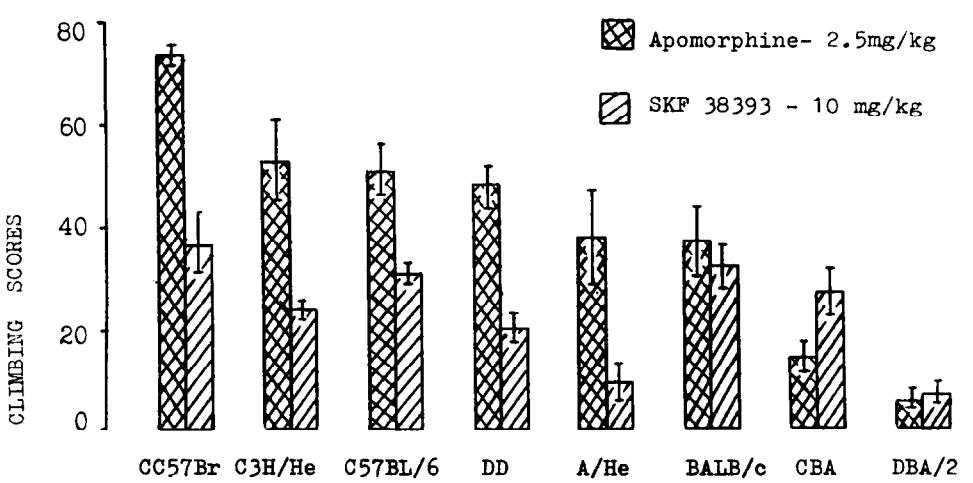

FIG. 4. Effects of mixed D1/D2 agonist apomorphine and highly selective D1 agonist SK&F 38393 on stereotypic climbing of inbred mice. Climbing was assessed during 20 min.

D_1–D_2 dopamine receptor interaction is also evident in the regulation of locomotor activity: Inhibitory effect of a mixed D_1/D_2 stimulation (apomorphine administration) is, in mice of most strains, intermediate between the influences of separate D_1 and D_2 receptor activation (by SK&F 38393 and LY 171555, respectively). This regularity demonstrates, however, a distinct genotype dependence. It seems also interesting to mention that our data concerning greater locomotor inhibition produced by quinpirole (in comparison to SK&F 38393) coincides, evidently, with its reported higher cataleptic capacity (27).

The lack of correlation between general locomotor and stereotypic activity in eight strains of mice is in accordance with data obtained earlier on three mouse strains (7). This fact is likely to reflect the involvement of different dopaminergic structures in control of different types of dopamine-dependent behavior. As for climbing and locomotor activity, there is no general conception of whether nigrostriatal or mesolimbic dopaminergic systems are more important for their regulation (12,22).

Mouse strains with peculiarities in brain dopamine-dependent parameters were revealed. According to the genotype-determined HVA concentrations, particular attention is attracted to the following four strains: 1) CC57Br and DD, characterized by minimal and maximal HVA level in the striatum, respectively. By that, CC57Br demonstrates highest general locomotor activity and climbing both after apomorphine and SK&F 38393. In contrast, having maximal HVA DD mice showed lowest locomotion and minimal climbing after SK&F 38393. 2) C57Bl/6, characterized by the highest, and CBA, with the lowest, HVA content in the mesolimbic system. By that, CBA had maximal SK&F 38393 locomotor inhibition and climbing response so that the latter after apomorphine was even lower than after SK&F 38393 (the only exception among eight strains!).

Thus, in mice of eight inbred strains data about brain dopamine metabolism as a function of genotype are obtained. Highly significant hereditary determination of content of one of the main brain dopamine degradation products, homovanillic acid, is shown. Marked differences in brain dopamine receptors' sensitivity, as well as in spontaneous dopamine-dependent behavior, are found in inbred mice. This fact draws attention to the necessity of taking into account the existence of drastic genotype-determined differences in the effectiveness of influence of dopaminergic drugs that are widely used for clinical purposes. For further investigation, CC57Br, DD, CBA, and C57Bl/6 strains with peculiarities in dopaminergic system functioning seem to be especially interesting.

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