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Dopaminergic Brain System in the Quaking Mutant Mouse

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NIKULINA, E. M., J. A. SKRINSKAYA, D. F. AVGUSTINOVICH AND N. K. POPOVA. *Dopaminergic brain system in the quaking mutant mouse.* PHARMACOL BIOCHEM BEHAV **50**(3) 333–337, 1995.—Quaking mice (*qk/qk*), autosomal recessive mutants with central nervous system dysmyelinization, characterized behaviorally by abnormal locomotion and tremor, are found to have altered brain dopaminergic system parameters, in comparison with phenotypically normal heterozygous littermates. Dopamine metabolism is enhanced in structures of both nigrostriatal and mesolimbic systems, as revealed by increased metabolites content (that of homovanillic acid in striatum and concentration of 3,4-dihydroxyphenylacetic acid in nucleus accumbens with tuberculum olfactorium) along with unchanged neurotransmitter levels in *qk/qk* mice. D_1 and D_2 receptor analysis via radioligand binding using [^{3}H]-SCH 23390 and [^{3}H]-spiperone, correspondingly, showed an increase of D_2 receptor density with decreased affinity to D_2 ligand in striatum of mutants: both B_{max} and K_d were markedly higher. D_1 and D_2 receptor sensitivity in the quaking mouse was also altered. Stimulation of D_1 receptors by a highly specific agonist SKF 38393 (2.5 and 5 mg/kg) decreased locomotor activity only in mutants, but not in controls. In contrast, *qk/qk* were less sensitive than phenotypically normal *qk/+* mice to a selective D_2 dopamine receptor agonist, LY 171555 (quinpirole, 1 and 2.5 mg/kg). The alterations found in the brain dopaminergic system of *qk/qk* mice may be responsible for the behavioral expression of this neurologic mutation.

Dopamine metabolism D_1 and D_2 receptor binding Quaking mutation Locomotor activity
D_1 and D_2 dopamine receptor agonists

THE QUAKING mouse results from an autosomal recessive mutation in a single locus, in 17th chromosome. In this mutant absence of the enzyme adenosine-2′,3′-cyclophosphate-3′-nucleotidehydrolase leads to a failure of oligodendrocyte differentiation that produces a myelin defect in the central nervous system (1,27). Thus, quaking mutation represents a valuable model to test therapeutic ameliorative treatment designed to correct pathology due to dysmyelinization. Behaviorally, this mutant is characterized by abnormal locomotion, tremor of voluntary movements, and tonic-clonic seizures that may be either spontaneous or elicited by mild stimulation (20). These effects are observed only in homozygous *qk/qk* mice; heterozygous *qk/+* mice are phenotypically normal.

The locomotor impairments observed as the main phenotypical peculiarity in the quaking mutant mouse may arise from brain dopaminergic system dysfunction. Dopamine is known to play an important role in regulating both locomotor and stereotypic activity (6,16,31). The neurologic mutant, weaver (wv/wv), also exhibits both locomotor impairments and altered dopaminergic function: decreased dopamine concentration in striatum and forebrain, severe cell loss in substantia nigra (24,25), and increased specific D_2 dopamine receptor binding in striatum (15). Although the dopaminergic system has not been examined previously in the quaking mouse, neurotransmitter abnormalities are observed in the noradrenergic system, where neuronal number was increased in locus coeruleus (20). Here, we report the differences observed in the dopamine system between the quaking mutants and their phenotypically normal heterozygous littermates used as controls, including dopamine metabolism, as well as D_1 and D_2 dopamine receptor binding and sensitivity. We also studied locomotor activity after stimulation of dopamine receptors by a mixed D_1/D_2 agonist apomorphine (10,26), specific D_1 receptor agonist SKF 38393 (9), and selective D_2 receptor agonist LY 171555 (quinpirole) (4,23,29).

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METHOD

Animals

Quaking mutants were maintained on the CBA × C57Bl/6J hybrid genetic background. They were obtained by breeding homozygous quaking mutant females and heterozygous males, with the *qk/qk* males being sterile. Phenotypically normal heterozygous littermates served as controls. Male mice used in experiments were 3–4 mo old, as this mutation gets its full expression in 30-day-old *qk/qk* animals (20), weighing 23–28 g. Mice were housed in groups of four per cage (40 × 25 × 12 cm) at standard room temperature (24 ± 1°C) and humidity (60–62%), with food and water ad lib, under a natural day-night cycle, in an autumn-winter period (approximately 8 h light and 16 h dark). Experiments were performed in a quiet room, between 10 and 13 h. To abolish social interaction influences, mice were placed into individual cages of the same size 3 days before decapitation.

Biochemical Assays

Immediately after rapid decapitation, brains were extracted on ice, and structures corresponding to two main dopaminergic systems—nigrostriatal and mesolimbic (corpus striatum and nucleus accumbens with olfactory tubercles, respectively) were isolated. The brain regions were stored at −40°C before dopamine and metabolite determinations, or at −190°C in liquid nitrogen until dopamine receptor analysis.

Brain dopamine and its metabolites. 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) were determined fluorometrically after preliminary separation by chromatography on Sephadex G-10 (11).

Binding assays of dopamine D_1 and D_2 receptors were carried out according to the radioligand method (14) with minor modifications. Brain tissues were pooled from four mice for one estimation. They were homogenized in 20 volumes (w/v) of ice-cold potassium phosphate buffer (50 mM, pH 7.4) using glass homogenizers and centrifuged at 25,000 × *g* for 15 min. This procedure was repeated twice. Final pellets were resuspended in 100 (striatum) or 50 (n. accumbens with tub. olfactorium) volumes of potassium phosphate buffer (pH 7.4). [^{3}H]-SCH 23390 (spec. act. 72.2 Ci/mol; Amersham, UK) and [^{3}H]-spiperone (spec. act. 40 Ci/mol; NEN Chemicals) were used as radioligands for labeling D_1 and D_2 receptors, respectively. Six increasing concentrations (ranging from 62.5 pM to 2 nM) of selective antagonist of the D_1 receptors, [^{3}H]-SCH 23390, were used for equilibrium saturation experiments. Nonspecific binding was detected by adding 10 μM *cis*-flupentixol (Lundbeck, Denmark). D_2 receptors were determined in six concentrations (ranging from 43.75 pM to 12.4 nM) of [^{3}H]-spiperone using sulpiride (Sigma), a selective D_2 receptor antagonist, as a displacing agent, at 10-μM concentration. The kinetic parameters (B_{max} and K_d) of the D_1 and D_2 receptors were estimated by the Scatchard analysis, and points were assayed in duplicates, according to the method of Nelder-Mead (5). The protein content was determined by the method of Lowry (19).

Behavioral Tests

Locomotor activity was estimated for 20 min after drug injection in actometer (18 × 18 cm), equipped with two photocell counters (situated at 6 cm from each other) that automatically registered the number of times the mouse crossed two red beams. Six animals were simultaneously tested in six chambers. Locomotor activity was also assessed for 20 min in ANIMEX (LKB, Sweden). Standard open-field test was performed in a Plexiglas cube (80 × 80 × 25 cm) with 64 squares, 10 × 10 cm each. The animal was placed in the central area, and the number of squares it crossed during 5 min was recorded (7).

Drugs

The following drugs were used: the mixed D_1/D_2 dopamine receptor agonist apomorphine (Sigma) was administered subcutaneously; the highly selective D_1 agonist SKF 38393 (Smith, Kline & French Labs) and the selective D_2 agonist LY 171555 (quinpirole; Eli Lilly & Co.) were administered intraperitoneally. All drugs were dissolved in distilled water (apomorphine immediately before each session) and injected in a volume of 10 μg/mg of animals weighed before each injection. Control animals were injected with the same volume of saline.

Statistical Analysis

In studies of receptor characteristics, linear regression analysis (8) was used to obtain all values of K_d and B_{max}. Eight mice of each genotype (*qk/qk* or *qk/+*) were used for the determination of dopamine and metabolites, and 20 mice for binding assays. Every series of behavioral testing was carried out on five animals for the ANIMEX, eight for the open-field tests, and eight for actometers. Animal groups were compared by means of two-tailed Student's test.

RESULTS

Dopamine Metabolism

Dopamine determination in structures of nigrostriatal and mesolimbic systems (Table 1) revealed no changes in the neurotransmitter level in the mutant homozygous mice. However, the HVA level in the striatum, as well as that of DOPAC in the n. accumbens with tub. olfactorium, were significantly higher in the *qk/qk* mice (208 and 125%, respectively), reflecting the increased dopamine metabolism.

TABLE 1

DOPAMINE AND ITS METABOLITES CONTENT (MEAN ± SEM., μg/g) IN THE QUAKING MOUSE (*qk/qk*)

Brain Region	Genotype	*n*	Dopamine	DOPAC	HVA
Striatum	*qk/+*	8	8.42 ± 0.59	1.41 ± 0.20	0.37 ± 0.08
	qk/qk	8	8.82 ± 1.07	1.96 ± 0.19	0.77 ± 0.09*
N. accumbens with tub. olfactorium	*qk/+*	8	3.69 ± 0.38	0.63 ± 0.04	0.24 ± 0.07
	qk/qk	8	3.47 ± 0.39	0.79 ± 0.05†	0.34 ± 0.03

*$p < 0.01$ vs. control (*qk/+*), †$p < 0.05$.

TABLE 2

CHARACTERISTICS OF [^{3}H]SCH 23390 (FOR D_1 RECEPTORS) AND [^{3}H]SPIPERONE (FOR D_2 RECEPTORS) SPECIFIC BINDING IN STRIATUM AND LIMBIC STRUCTURES IN THE QUAKING MOUSE (*qk/qk*)

Brain Region	Receptor Subtype	Genotype	B_{max}, fmol/mg Protein	K_d (nM)
Striatum	D_1	*qk/+*	1362.2 ± 218.7 (100%)	1.57 ± 0.32 (100%)
		qk/qk	1429.9 ± 95.2 (105%)	1.51 ± 0.13 (96%)
	D_2	*qk/+*	92.4 ± 12.7 (100%)	0.13 ± 0.04 (100%)
		qk/qk	163.1 ± 25.7 (176%)*	0.23 ± 0.06 (177%)*
N. accumbens with tub. olfactorium	D_1	*qk/+*	472.7 ± 34.2 (100%)	0.84 ± 0.09 (100%)
		qk/qk	511.9 ± 35.3 (108%)	0.82 ± 0.08 (98%)
	D_2	*qk/+*	62.5 ± 8.5 (100%)	0.14 ± 0.04 (100%)
		qk/qk	67.3 ± 7.5 (108%)	0.11 ± 0.03 (79%)

Nonspecific binding was determined in presence of 10 μM *cis*-flupentixol for D_1 receptors or sulpiride for D_2 receptors. Specific binding was calculated as the difference between total and nonspecific bindings. The values represent mean + SEM. Five determinations were performed in each group. *$p < 0.05$ vs. control (*qk/+*).

D_1 and D_2 Dopamine Receptor Binding Assays

Specific [^{3}H]-SCH 23390 binding to D_1 dopamine receptors in the two dopaminergic structures studied did not differ in homozygous and heterozygous animals (Table 2). At the same time, D_2 receptor binding in striatum of *qk/qk* mice was significantly higher than in control *qk/+* animals: both B_{max} and K_d for [^{3}H]-spiperone binding were higher (176 and 177%, respectively), indicating an increased receptor density with decreased receptor affinity to the ligand.

No differences were obtained in D_2 receptors parameters in limbic structures.

Behavioral Tests

Homozygous *qk/qk* mice demonstrated higher locomotor activity in ANIMEX, than heterozygotes (Fig. 1). However, this device monitored all types of muscular movements—that is, both locomotion itself and specific tremor—so standard open-field test was also used. In this case, the number of crossed squares in neurologic mutants was almost threefold less than in control animals, indicating considerably lowered locomotor activity in *qk/qk* mice.

A mixed D_1/D_2 receptor agonist, apomorphine (0.25 mg/kg) significantly decreased locomotor activity in the open-field test in mice of both groups (Fig. 1).

A specific D_1 dopamine receptor agonist, SKF 38393, decreased locomotor activity registered in actometers in *qk/qk* mice at both 2.5 and 5 mg/kg doses; this effect was nonsignificant in *qk/+* mice (Fig. 2). LY 171555 administration inhibited locomotion in a dose-dependent way in mice of both groups, but *qk/qk* mice were less sensitive to D_2 receptor stimulation (Fig. 3). Although in heterozygous mice locomotor activity was influenced by 1 mg/kg of LY 171555, in homozygous mice a significant effect was observed only after a dose of 2.5 mg/kg.

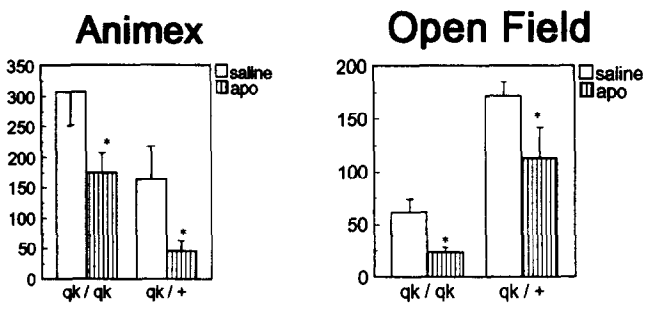

FIG. 1. Locomotor activity of mutant (*qk/qk*) and control (*qk/+*) mice. Locomotion was assessed in ANIMEX over 20 min (five animals in each group) and an open-field test over 5 min (number of squares crossed, eight animals per group). Locomotor activity was recorded 5 min after saline injection or 5 min after stimulation of D_1/D_2 dopamine receptors by 0.25 mg/kg of a mixed agonist, apomorphine. *$p < 0.05$ vs. saline.

DISCUSSION

We found that dopamine metabolism increased in both nigrostriatal and mesolimbic systems in homozygous quaking mice. In the striatum of *qk/qk* mice levels of HVA, neurotransmitter metabolite generated as a result of the action of two enzymes—catechol-O-methyltransferase and monoamine oxidase—were increased. Dopamine content, however, was unchanged. DOPAC levels were also slightly elevated. In the n. accumbens with tub. olfactorium the dopamine level was unchanged in *qk/qk* and *qk/+*, whereas the content of DOPAC, which results from the action of monoamine oxidase, was markedly elevated. The differences we observed in dopamine metabolites content lead us to suggest that neuronal activity in *qk/qk* mice is increased in both nigrostriatal and

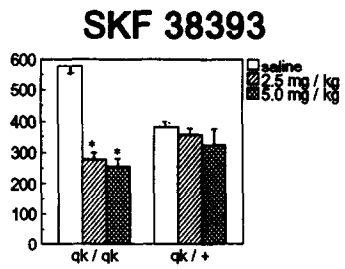

FIG. 2. Effect of selective D_1 dopamine receptor agonist, SKF 38393, on locomotor activity. Locomotion was recorded in actometers over 20 min (number of beam crossings, eight animals per group). *$p < 0.01$ vs. saline.

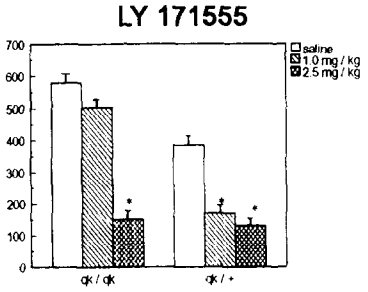

FIG. 3. Effect of selective D_2 dopamine receptor agonist, LY 171555 (quinpirole), on locomotor activity. Locomotion was recorded in actometers over 20 min (number of beam crossings, eight animals per group). *$p < 0.05$ vs. saline.

mesolimbic dopaminergic systems. This does not correspond to data obtained in another neurogenetic mutant with the weaver motor abnormalities, in which a severe dopamine decrease was observed in caudoputamen (24). However, weaver is characterized by massive losses of cerebellar granule and Purkinje cells, whereas quaking results from a failure of oligodendrocyte differentiation, leading to dysmyelinization.

The shift in dopamine metabolism in *qk/qk* mice was accompanied by alterations in some characteristics of dopamine receptor binding. Although D_1 dopamine receptor parameters were unaffected in the quaking mutant mice, D_2 receptor density in striatal membranes was increased by 77%, and ligand affinity was considerably decreased (by 76%). Curiously, in another neurogenetic mouse model with abnormal activity, weaver, alteration in dopamine D_1 binding sites in the striatum was found (22). The changes in D_2 receptors in the striatum of quaking mutant mice seem to be similar to those in the striatum of nontreated patients with Parkinson's disease, in which an increase of D_2 receptor density was also observed (17).

Similar to some behavioral characteristics, such as tremor and abnormal locomotion, neurologic mutant weaver was shown to have brain dopaminergic system changes different from those found in the quaking mouse. In contrast with data obtained in weaver, in which decreased metabolism in the dorsal part of striatum along with increased D_2 receptor density (15,24) was observed, we found that enhanced dopamine metabolism in striatum in *qk/qk* mice was accompanied by increased D_2 dopamine receptor binding, evidently reflecting upregulation of dopamine D_2 receptors. Thus, D_2 receptors, which are autoreceptors localized on presynaptic nerve terminals and control dopamine metabolism and release (3,18), are profoundly affected, in contrast with D_1 binding sites, which are found almost exclusively on intrinsic nondopamine neurons of striatum (14). We interpret that lack of change in D_2 receptors in mesolimbic structures of *qk/qk* mice to be consistent with the hypothesis that dopamine receptors in different brain regions experience independent genetic regulation (2).

The dopaminergic system plays a major role in regulating locomotor activity. Thus, in *qk/qk* mice, alterations of dopaminergic system decreased locomotor (and maybe also investigatory) activity in the open-field test. Low doses of apomorphine, which is known to act on the presynaptic dopamine receptors in striatum and to inhibit locomotion (21), produced decreased activity in both groups of mice. Furthermore, we observed differences in the sensitivity of D_1 and D_2 receptors in *qk/qk* and *qk/+* mice. The D_1 dopamine receptor agonist, SKF 38393, decreased locomotor activity in *qk/qk* mice, as it does in most inbred mouse strains (28). However, this agonist produced significant locomotor inhibition only in *qk/qk* mutants, indicating an increased sensitivity of D_1 dopamine receptors in these mice relative to control mice.

The D_2 dopamine receptor agonist, LY 171555, produced a dose-dependent inhibition of locomotion, an observation consistent with data obtained in laboratory rodents by others (13). However, the inhibitory effect was less pronounced in *qk/qk* than in *qk/+*. Because the behavioral depression observed associates with D_2 dopamine receptors, *qk/qk* mice appear to have decreased D_2 receptor sensitivity. We found increased dopamine metabolism in nigrostriatal dopaminergic system in *qk/qk* mice. Such a change could also contribute to decreased sensitivity to LY 171555, because D_2 receptor agonists stimulate autoreceptors in this brain region, and thus decrease dopamine release in striatum (12,30).

The changes observed in levels of dopamine and its metabolites may arise as secondary effects of the action of the neurologic mutant gene. They could, for example, represent compensation for general impairments of neurogenesis that arise from insufficient development or degeneration of brain cells. Thus, the behavioral changes observed in *qk/qk* appear to be a complex cascade of effects that begin as a primary myelin deficit and lead to various compensatory processes.

Abnormal locomotor activity in the quaking mutant mouse may result from changes in brain dopaminergic system, but these effects may be modulated by effects in other neurotransmitter systems. For example, *qk/qk* mutants exhibit enhanced noradrenergic function as well. A greater number of noradrenergic neurones is accompanied by higher levels of neurotransmitter and its metabolite and by changes in receptor sensitivity. Such changes in the noradrenergic system are believed to cause the tonic-clonic seizures observed in *qk/qk* mice (20).

Thus, alterations in both dopamine and noradrenaline catecholaminergic brain systems in *qk/qk* mice may represent a pleiotropic effect of the quaking mutation, not merely a consequence of dysmyelinization. However, the alterations we observed in the brain dopaminergic system of *qk/qk* mice appear to be responsible for the behavioral effects in the locomotor function of this neurologic mutation.

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