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Effects of Dopaminergic Agents and of an NMDA Receptor Antagonist on Motor Coordination in *Lurcher* Mutant Mice

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THULLIER, F., R. LALONDE AND F. LESTIENNE. *Effects of dopaminergic agents and of an NMDA receptor antagonist on motor coordination in* Lurcher *mutant mice.* PHARMACOL BIOCHEM BEHAV **63**(2) 213–219, 1999.—*Lurcher* mutant mice, characterized by an ataxic gait and olivocerebellar degeneration, were evaluated for motor coordination in the coat-hanger test after peripheral injections of two doses of dextromethorphan, a noncompetitive *N*-methyl-D-aspartate receptor antagonist, L-dopa/carbidopa, and SKF 77434, a dopamine D_1 receptor agonist. There was an improvement in the distance traveled on the suspended horizontal string after 25 and 50 mg/kg of dextromethorphan and 37.5 mg/kg of L-dopa/carbidopa, but not after SKF 77434. None of the drugs reduced movement times or increased latencies before falling. These results indicate that NMDA receptor antagonism or stimulation of some dopaminergic mechanisms partially improve genetically determined cerebellar ataxia in mice. © 1999 Elsevier Science Inc.

Motor coordination Ataxia Lurcher Dopamine receptor NMDA receptor Cerebellum

A progressive degeneration of cerebellar (Purkinje cells, granule cells) and inferior olive cells occurs in *Lurcher* mutant mice (5,14). Adult mutants are characterized by their ataxic gait and deficits of motor coordination (10) and exploration (22). This mutation represents a partial genetic model of olivopontocerebellar atrophy (OPCA), a degenerative cerebellar ataxia (15,23). Different neurotransmitters may be implicated in the mild therapeutic benefits of some experimental drugs on cerebellar disorders.

Clinical trials have shown that the administration of 5-hydroxytryptophan (5-HTP), or 5-HTP combined with benserazide, improves an ataxia score in some cerebellar syndromes. However, the slowness of action and the persistence of the effect indicate that the mechanism is in part independent of direct serotoninergic neuromediation (31). An improvement in bradykinesia was observed after administration of the combination of levodopa–carbidopa in OPCA patients with parkinsonian signs (12). In OPCA patients with no parkinsonian signs, an amelioration of movement initiation and movement completion has been discerned after chronic treatment with amantadine, a dopamine-releasing agent and antagonist of the *N*-methyl-D-aspartate (NMDA) receptor. A more limited improvement was found in patients with Friedreich's ataxia, a spinocerebellar disorder (3,4). These improvements were independent of the initial levels of homovanillic acid, a major metabolite of dopamine, indicating that the mechanism of action is not restricted to dopamine. In parallel with these clinical findings, pharmacological studies have been initiated with the *Lurcher* mutant for the purpose of ameliorating motor dysfunctions. The coat-hanger motor coordination test was used (22,23), in which mice are suspended upside down on a thin horizontal bar. Movement times (MTs) before reaching either diagonal bar and latencies before falling are measured. It was shown that amantadine reduced two-paw MT without changing latencies before falling. Moreover, a second NMDA receptor antagonist, ketamine, also improved two-paw MT (23).

Glutamate modulates the release of dopamine (24). It is known that interactions between dopamine and glutamate systems occur in the striatum, with functional consequences in motor behaviors such as locomotion (33) and in more com-

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plex sensorimotor tasks such as conditioned reaction time (1). Therefore, the actions of NMDA receptor antagonists may also implicate dopaminergic mechanisms (17).

In the present study, our goal was to evaluate the effects of L-dopa methyl ester, an analogue of L-dopa, SKF 77434, a dopamine D_1 receptor agonist, and dextromethorphan, a noncompetitive NMDA receptor antagonist on motor coordination in *Lurcher* mutants. The effect of SKF 77434 on motor activity level was also verified in an open-field test. As in a previous study (23), the coat-hanger was used, as this test provides the opportunity of evaluating the speed of execution of a response (MTs) and the ability to maintain balance without falling. Our purpose was to compare agents that facilitate dopaminergic transmission directly to an NMDA receptor antagonist at doses known to increase motor activity (L-dopa–methyl ester (13); dextromethorphan (8); and SKF 77434 (25), respectively). Because of the limited availability of *Lurcher* mutants, the same mice were used in all three experiments, with appropriate washout periods and measurements of baseline levels of performance.

METHOD

Animals

Mice were obtained by breeding normal females (+/+) of the B6CBACA/A^{W-J} strain with male mutants (Lc/+) from a stock originally purchased from Jackson laboratory (Bar Harbor, ME). The mice were kept in a room (14 L/10 D, lights on at 0700 h) with food and water available at all times in group cages. Groups were constituted at random from a pool of male and female mutants weighing 24 ± 3 g. The mice were 2–3 months of age at the time of testing. The procedures of the experiments were in compliance with the recommendations of the French Ministry of Agriculture (decree 87-848, October 19, 1987).

Apparatus

Coat-hanger test. The coat-hanger (22,23) consisted of a horizontal wire (diameter: 2 mm, length; 40 cm) divided into eight segments, terminating at each end by a diagonal bar (inclination: 35°, length: 19 cm) and suspended at a height of 80 cm from a cushion covered table. There were three trials per day (cutoff: 60 s) with an intertrial interval of 10 min.

Open-field test. During the final experiment (SKF 77434), motor activity was evaluated on the last day, immediately after the coat-hanger test. The open field was constituted by a circular wooden area (diameter: 50 cm, height of walls: 30 cm) divided into 36 equal sectors. For each mouse, the number of crossed sectors was recorded for 1 min.

Procedure

Each experiment was divided into two successive periods: (a) A 7–14-day period of adaptation in which the mice were exposed to the coat-hanger, allowing a stable performance level. (b) A 12-day period of treatment, with daily drug administrations.

The same mice were used in all three experiments but with different group distributions and a washout period of at least 3 weeks between each test study.

In the first experiment, we evaluated the effects of L-dopa methyl ester (37.5 and 75 mg/kg) preceded half an hour before by a injection of carbidopa (10 and 25 mg/kg, respectively) in comparison to placebo. In the second experiment, we compared the effects of placebo to 25 and 50 mg/kg doses of dextromethorphan. In the third experiment, the effects of SKF 77434 (10 or 20 mg/kg) were compared to placebo.

All drugs (RBI, Bioblock Scientific) were dissolved in NaCl 0.9% and injected via the IP route, with a volume of 2 ml/kg. Behavioral evaluation took place 30 min later, except for the SKF 77434 experiment where the tests were conducted 60 min after the injections. Mice in the placebo group received saline injections.

The mice were placed in the middle of the horizontal bar in an upside down position. In this situation, the mice are motivated to move along the bar to reach either diagonal bar and to reach an upright position.

Three types of movement time (MT) and latencies before falling were tabulated, together with the number of crossed segments (four-paw criterion). Two-paw MT was defined as the amount of time spent before reaching either diagonal bar with the two front paws. Three- and four-paw MTs were also measured.

Statistics

ANOVAs with repeated measures on the day factor were made after transformation of the raw data into log values, followed by post hoc comparisons using Fisher's test.

Nonparametric tests (Kruskal–Wallis and Mann–Whitney tests) were used for comparisons of the motor activity levels in the open-field test. Non parametric analysis of variance (Friedman test) was made to determine baseline levels of performance. The data are expressed as the cumulated sum of the three trials per day.

RESULTS

L-Dopa/Carbidopa

During the adaptation period (days 1–14), there was a progressive increase of latencies before falling and of the number of segments crossed (data not shown). By the first day of testing, the values of each behavioral measure were approximately equal for the three treatment groups. A 3×12 ANOVA with repeated measures on the second factor was made on each measure, with three drug groups and 12 days of testing. Figure 1A–E depicts the results for two-, three-, and four-paw MTs, latencies before falling, and the number of segments crossed. Because of unequal intergroup variances, the raw data were transformed into log values. In the case of segments crossed, the data were transformed into log+1 values because of the presence of null values.

There was no significant treatment effect, day effect or interaction for two-, three-, and four-paw MTs ($p > 0.05$). For latencies before falling, there was no significant treatment effect, $F(2, 26) = 0.32$, $p > 0.05$, or interaction, $F(22, 286) = 1.15$, $p > 0.05$. However, there was a significant day effect, $F(11, 286) = 4.19$, $p < 0.001$. As shown in Fig. 1D, there was a slight increase of latencies before falling by the placebo group and by the 37.5 mg/kg L-dopa/carbidopa group, but not by the 75 mg/kg L-dopa/carbidopa group. For segments crossed, there was a significant interaction, $F(22, 286) = 1.75$, $p < 0.05$. At the end of testing, the 37.5 mg/kg group had a higher number of segments crossed than the other two groups.

Dextromethorphan

Four mice were removed because of some weight loss during the intervening washout period. As shown in Fig. 2, there was no significant treatment effect, day effect or interaction for two-, three-, and four-paw MTs ($p > 0.05$). Neither were

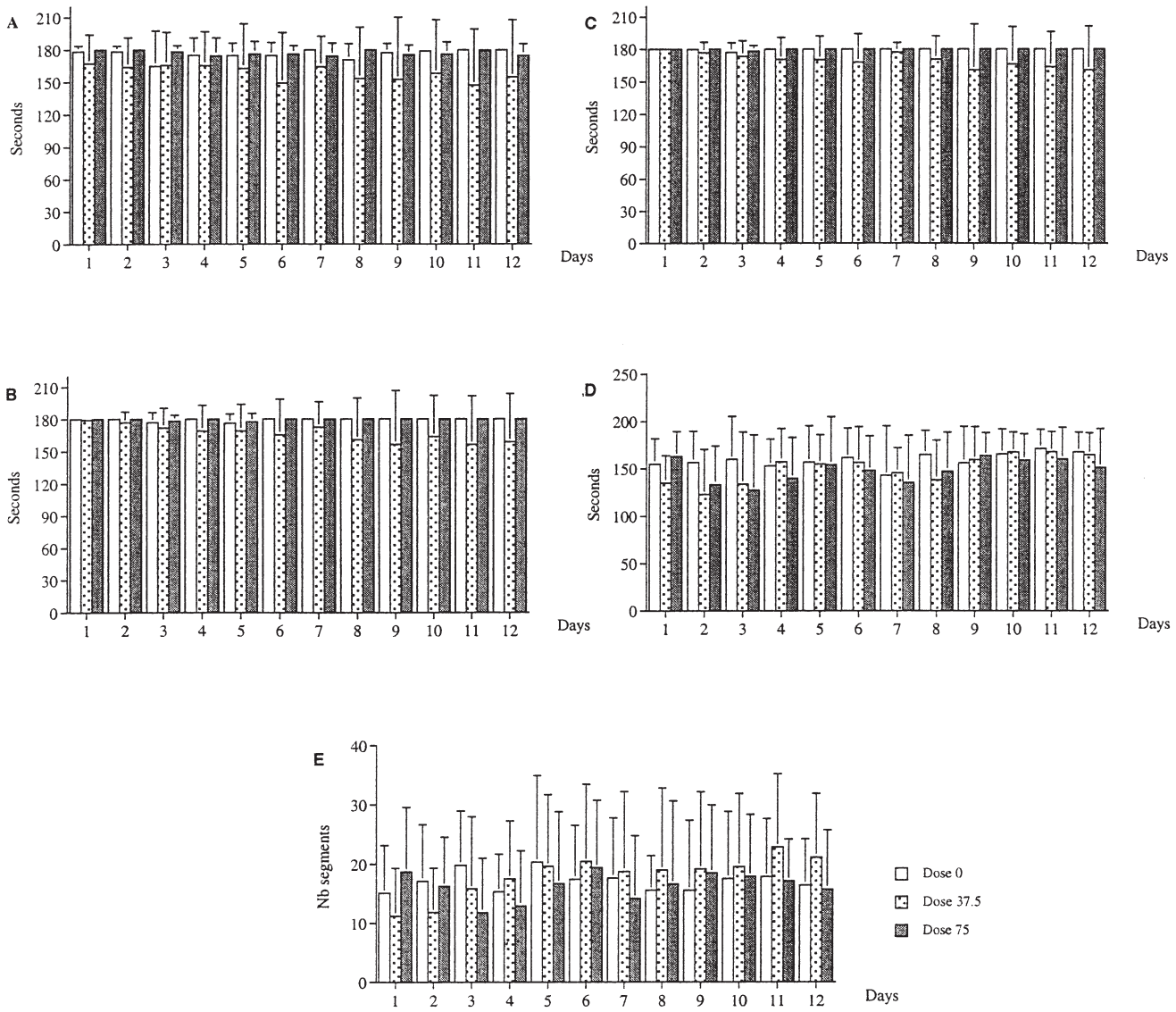

FIG. 1. Effects of IP administrations of L-dopa methyl ester/carbidopa, on two- (A), three- (B), or four-paw movement time (C), latencies before falling (D), and the number of segments crossed (E) on the horizontal bar of the coat-hanger test in *Lurcher* mutant mice. Data are expressed as the sum of the three trials. Values represent group means ± SD. Doses are shown as mg/kg: Dose 37.5 = 37.5 mg/kg (n = 10), dose 75 = 75 mg/kg (n = 9), dose 0 (placebo) = 0 mg/kg (n = 10).

there significant treatment, $F(2, 22) = 1.91$, $p > 0.05$, day, $F(11, 242) = 1.55$, $p > 0.05$, or interaction, $F(22, 242) = 1.13$, $p > 0.05$, effects for latencies before falling. In terms of segments crossed, there was a significant treatment effect, $F(2, 22) = 7.401$, $p < 0.01$ and interaction, $F(22, 242) = 2.47$, $p < 0.001$. The number of segments crossed was higher in either group injected with dextromethorphan than in the placebo group, the effect being stronger toward the end of training.

SKF 77434

As shown in Fig. 3, there was no significant treatment effect, day effect or interaction for any of the dependent variables. To verify that this drug is behaviorally active, on the final days of testing the mice were placed in the open field. As shown in Fig. 4, the Kruskal–Wallis test revealed a significant treatment effect, $H = 9.25$, $p < 0.01$, as either SKF 77434 group had a higher number of squares crossed than the placebo group (Mann–Whitney test: $z = -2.649$, $p < 0.01$ $z = -2.539$, $p < 0.05$, respectively, in the comparisons dose 0/dose 10, dose 0/dose 20).

DISCUSSION

The aim of this study was to evaluate the effects of a dopamine metabolic precursor, a D_1 receptor agonist, and an NMDA receptor antagonist on motor coordination in *Lurcher* mutant mice. Previous findings had indicated a shortening of two-paw MT in these mutants after administration of amantadine and ketamine (23). It was found that none of the three drugs affected any of the MT measures or latencies before falling. At both dose levels used (25 and 50 mg/kg), by com-

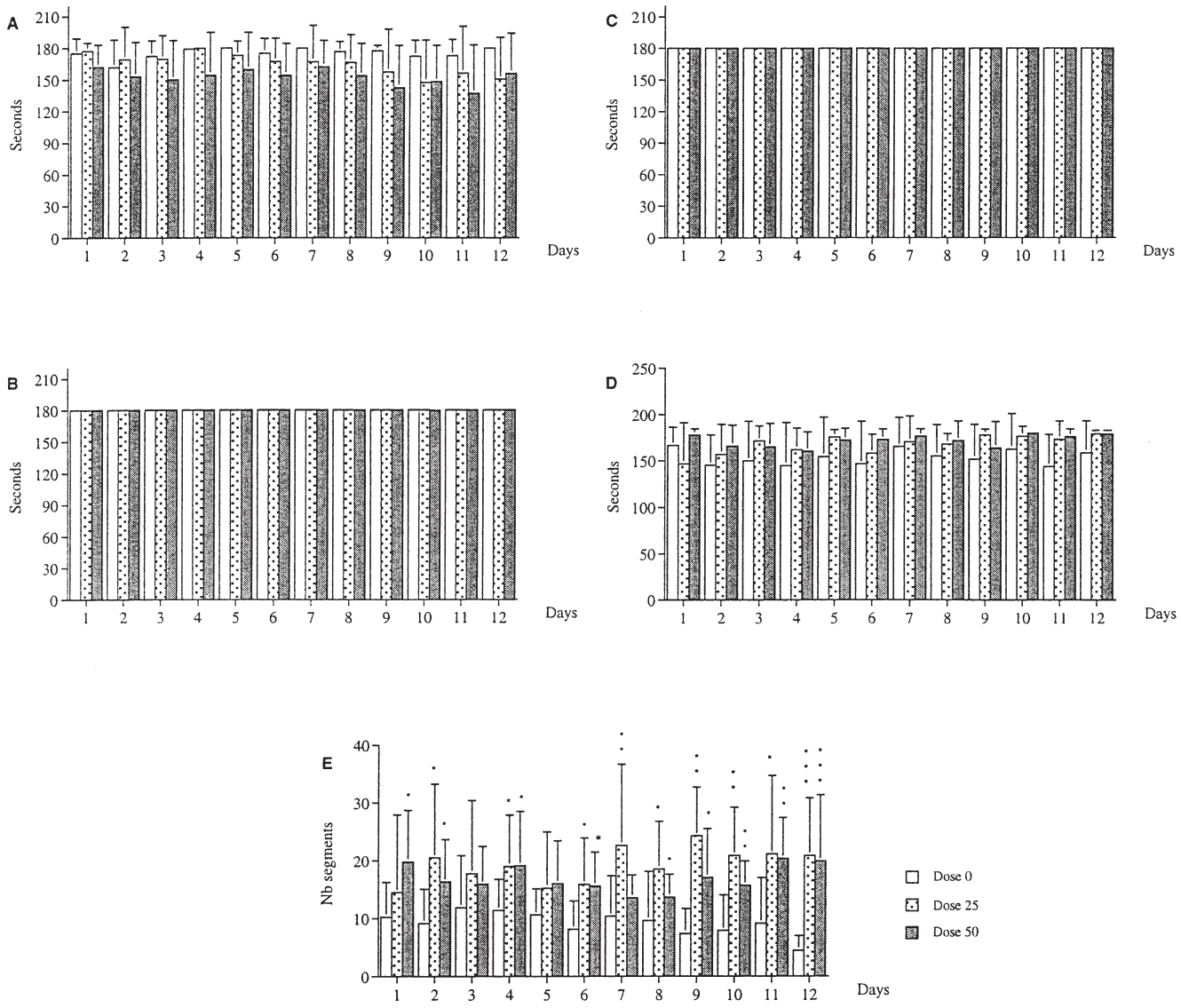

FIG. 2. Effects of IP administrations of dextromethorphan, on two- (A), three- (B), or four-paw movement time (C), latencies before falling (D), and the number of segments crossed (E) on the horizontal bar of the coat-hanger test in *Lurcher* mutant mice. Data are expressed as the sum of the three trials. Values represent group means ± SD. Doses are shown as mg/kg: dose 25 = 25 mg/kg ($n = 8$), dose 50 = 75 mg/kg ($n = 9$); $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ vs. placebo (dose 0, $n = 8$), Fisher *t*-test.

parison to placebo, dextromethorphan increased the number of segments crossed. A similar effect was detected with L-dopa/carbidopa, but at only one dose (37.5 mg/kg) at the end of testing. By contrast, the D_1 receptor agonist, SKF 77434, had no effect on the distance travelled on the horizontal bar at any dose. Thus, mild but significant improvements of motor coordination were observed in an animal model of heredodegenerative ataxia. An improvement was also seen after ketamine administration in a mouse model of Friedreich's ataxia (20).

The absence of an effect on two-paw MT differs from that seen with the previous drugs tested. Thus, it appears that various drugs facilitating dopaminergic transmission or antagonizing glutamatergic transmission have differential effects on separate measures of the coat-hanger test. It remains to be determined whether different transmitter interactions are involved in specific facets of motor function.

It is well known that dopamine is involved in locomotor activity (2,11). More recent studies have indicated that dopamine may be involved in cerebellar symptomatology (3,4,20,21). The possible role of dopamine in motor dysfunctions after cerebellar lesions may be explained by two factors: 1) cerebellar efferents to midbrain dopaminergic cell bodies (28), and 2) a small dopaminergic innervation of the cerebellum from the midbrain (16,26). Our present results with L-dopa/carbidopa indicate an amelioration of a motor coordination deficit, at least for the lowest dose tested, by means of selective facilitation of dopaminergic transmission in a cerebellar-lesioned mutant, but with a narrow dose range. By contrast, no amelioration was detected with the D_1 agonist. Further studies with other dopamine receptor agonists are indicated. On the other hand, SKF 77434 increased *Lurcher* motor activity in an open field. Because *Lurcher* mutants, in spite of ataxia, are not im-

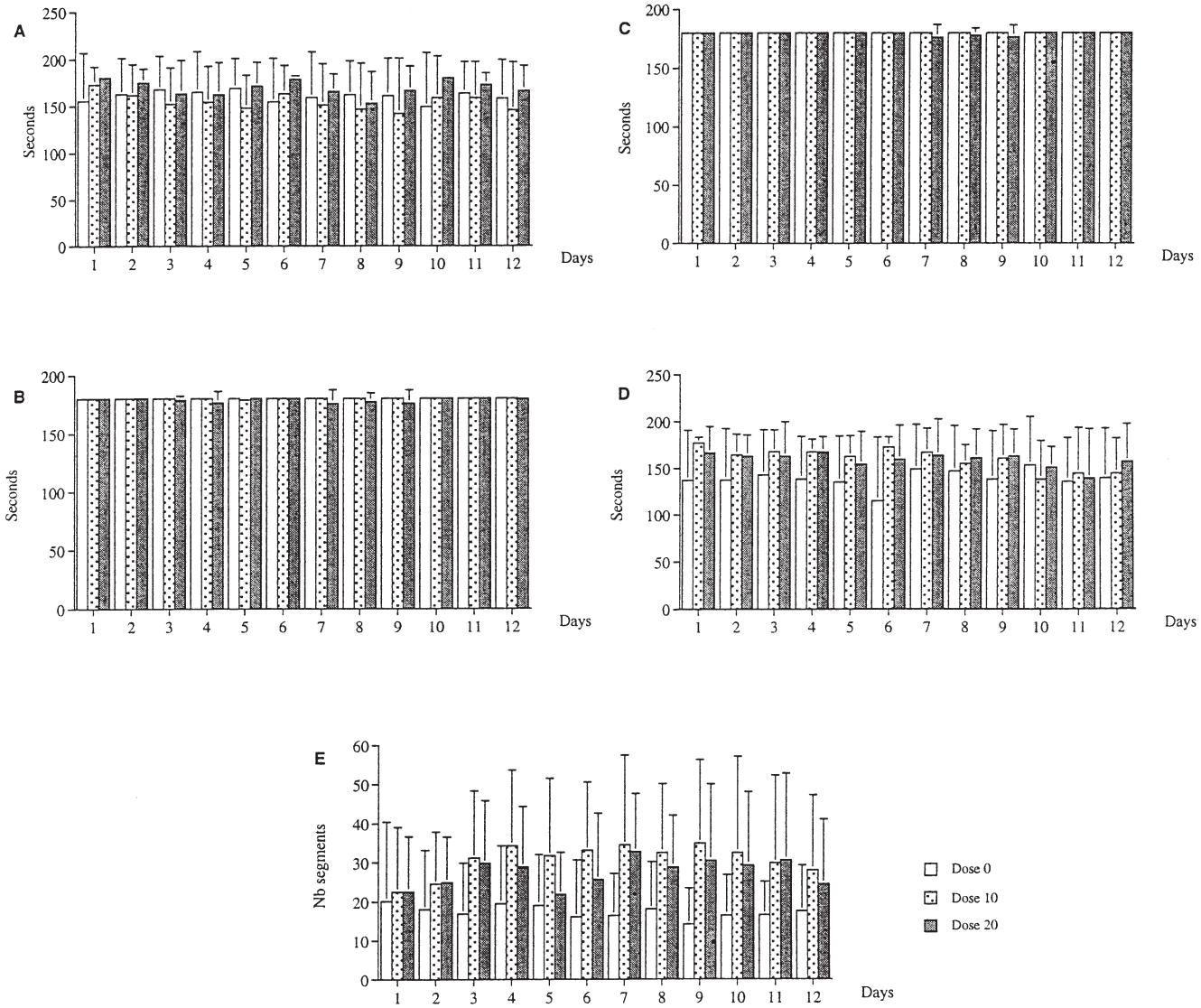

FIG. 3. Effects of IP administrations of SKF 77434, on two- (A), three- (B), or four-paw movement time (C), latencies before falling (D), and the number of segments crossed (E) on the horizontal bar of the coat-hanger test in *Lurcher* mutant mice. Doses are shown as mg/kg: dose 10 = 10 mg/kg ($n = 8$), dose 20 = 20 mg/kg ($n = 8$), dose 0 (placebo) = 0 mg/kg ($n = 8$).

paired in terms of motor activity by comparison to mice of the same background strain (22), the drug-induced augmentation of the locomotor score cannot be considered as a reversal of a cerebellar deficit.

Forebrain dopamine concentrations in *Lurcher* mutants were recently determined by high-performance liquid chromatography (27). No change of dopamine and its two main metabolites was found in any brain region, including the neostriatum and the cerebellum. However, a decrease of the presynaptic marker of the dopamine transporter, RTI-121, was seen in *Lurcher* mutants, but only in the subthalamic nucleus and not in the neostriatum (29). Thus, the slight amelioration observed after L-dopa/carbidopa may be partly due to subacute modifications of basal ganglia circuitry. Kinoshita et al. (18) likewise hypothesized that the improvement of motor dysfunctions in Rolling Mouse Nagoya, another cerebellar

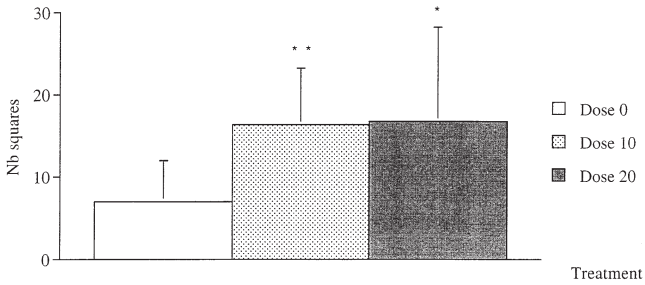

FIG. 4. Effects of IP administrations of SKF 77434 on the number of crossed squares in the openfield in *Lurcher* mutant mice. Doses are shown as mg/kg: dose 10 = 10 mg/kg ($n = 8$), dose 20 = 20 mg/kg ($n = 8$); $^*p < 0.05$, $^{**}p < 0.01$ vs. placebo (dose 0, $n = 8$), Mann–Whitney test.

mutant, after administration of thyroid-stimulating hormone was due to its activation of the dopamine system.

The involvement of glutamatergic transmission on locomotion has also been emphasized, in part by means of interactions with the dopamine system (6,7,9,17,19,30,33). The excitotoxic effects of glutamate have been suggested to be implicated in several neurodegenerative disorders including OPCA (15,32). In the adult cerebellum, NMDA receptors are located on granule cells, which undergo severe depletion in *Lurcher* mutants (5). The possible relationship between glutamate and cerebellar degeneration in *Lurcher* mutants is all the more plausible by the recent discovery of the *Lurcher* gene encoding the delta2 glutamate receptor (34).

Patients with heredodegenerative ataxias have higher reaction times (RTs) and MTs than normal controls (21). Both measures were improved in patients with OPCA and Friedreich's ataxia after chronic administration of amantadine, a dopamine-releasing agent. However, there was no difference in the outcome of patients with low concentrations of the major dopamine metabolite, homovanillic acid, in comparison to those with high concentrations of the same metabolite, indicating that other neurotransmitters may be involved, such as glutamatergic transmission, because amantadine is also an NMDA receptor antagonist (3,4). Such results indicate that selective disorders of the cerebellum may be amenable to NMDA receptor intervention.

In our study, dextromethorphan increased the distance traveled on the horizontal beam without affecting MTs and latencies before falling. Because the drug was administered over a period of 12 days in adult *Lurcher* mutants with severe granule cell depletion, it is unlikely that this improvement was caused by reversal of glutamate neurotoxicity. That hypothesis may more properly be tested with drug administrations during the period of neurodegeneration, i.e., the first postnatal month. Instead, the data indicate that NMDA receptor antagonism is at least partly effective after damage had occurred. In previous findings, a similar improvement of motor coordination after administration of either ketamine or amantadine was found (23). Our results are in agreement with the participation of glutamatergic pathways whether limited to the cerebellum or involving other brain regions. Further studies with other NMDA receptor antagonists in diseases of the cerebellum by comparison to other brain regions are warranted.

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