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Research report

Motor effects of delta 9 THC in cerebellar Lurcher mutant mice

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Abstract

The present study evaluated the effects of the principal active component of marijuana (delta 9 THC) on motor abilities and motor learning in mice with cerebellar dysfunction. For this purpose, spontaneous locomotor activity, equilibrium abilities, muscular tone, motor coordination and motor learning were investigated in Lurcher mutant and non-mutant B6/CBA mice 20 min after i.p. administration of 4 or 8 mg kg^{-1} of delta 9 tetra hydro cannabinol (delta 9 THC). The performances were compared to those obtained by Lurcher and non-mutant mice injected with vehicle (Tween 80).

The results showed that at the dose of 4 mg kg^{-1} but not at the dose of 8 mg kg^{-1}, the cannabinoid (CB) substance reduced deficits in motor coordination, equilibrium and muscular tone and facilitated motor learning in Lurcher mice. On the other hand, only a muscular strength decrease was observed in control B6/CBA mice injected with the dose of 8 mg kg^{-1} of delta 9 THC.

These results suggested that cannabinoid derivative could represent a new field of investigation concerning the treatment of cerebellar ataxic syndrome in humans.

Keywords: Lurcher mutant mice; Cerebellum; Delta 9 THC; Motor abilities; Motor learning

1. Introduction

Since the cannabinoid (CB) receptors and their ligands were discovered, numerous studies aimed at understanding the roles and the functioning of the cannabinoid system [2,14,26,38]. Today, according to the large panel of scientific data, we cannot overlook the fact that the cannabinoid system is one of the most potential therapeutic targets for many human pathologies [1,9]. It was demonstrated that cannabinoids exert antiemetic, appetite stimulation and analgesic effects in both animals and humans, more particularly in patients with tumors. The therapeutic potential of the cannabinoids was also investigated in neurological diseases such as multiple sclerosis, Gilles de Tourette syndrome, Parkinson and Huntington disease [1,9,10]. Although the efficacy of the treatment was not always clearly established, the undesirable effects observed were generally mild and well tolerated. The effects of the cannabinoids are mediated through their action on the CB1 and CB2 receptors [14], located in the whole body (i.e. in the gonads, blood vessels, immune cells and central nervous system). The CB1 receptors are highly concentrated in the basal ganglia and cerebellum [21], more precisely in the cerebellar cortex [20], and authors showed that their activation provoked behavioural modifications such as motor dysfunction [8,32,41,43–45]. For example, intracerebellar injection of delta 9 tetra hydro cannabinol (delta 9 THC) was associated with motor coordination and motor learning disturbances in the rotorod test [15]. In return no author undertook studies on the motor effects of cannabinoids in animals with cerebellar impairments.

Therefore, we investigated the effects of the delta 9 tetra hydro cannabinol, the principle active component of marijuana (*Cannabis sativa*), in the well-known cerebellar Lurcher mutant mice [47]. Because of their precocious cortico-cerebellar lesions, the heterozygous Lurcher mutant mice are widely used for an animal model of cerebellar degeneration and studied to emphasize the impact of cerebellar disorders on motor and non-motor processes [6,7,23,25,33]. The cerebellum degeneration model is useful to investigate some aspects of motor impairments observed in patients with cerebellar degeneration, such as severe ataxic gait and slow reaction and movement initia-

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tion [3] and the effects of drugs on cerebellar motor dysfunction [32,34,36,39].

The specific and complete degeneration of the cerebellar cortex in the heterozygous Lurcher mutant mice [4,5] and the retrograde degeneration of the olivo-cerebellar pathway are due to a mutation in gene codifying for the GluR delta2 (A654T) glutamate receptor [13,19,50]. This mutation was considered responsible for early and focused degeneration of all Purkinje cells in the cerebellar cortex [16,37,49]. The resulting severe motor impairments [17,22,24] did not prevent however the Lurcher mice from acquiring new motor equilibrium abilities in the rotorod task [7,22,28,29] and in the elevated unstable platform tests [36]. Nevertheless, it was showed that the performances of Lurcher after a specific training remained lower than those of controls. On the basis of these features, we expected that these mutant mice, also named Grid2 mice [47], were an ideal tool to investigate the effects of cannabinoid receptor agonists on cerebellar motor disturbances.

2. Experimental procedure

2.1. Drug and injections

The delta 9 tetra hydro cannabinol was obtained from Sigma–Aldrich. It was dissolved in 10% Tween 80 (Sigma–Aldrich) which, alone, served as vehicle control. The substances were injected to the mice via intraperitoneal (i.p.) route and in all cases the volume injected was about 0.2–0.3 ml.

2.2. Animals

Lurcher mutant mice (+/Lc) and normal controls (+/+) of the same strain (B6CBA) were born in our laboratory and were obtained by crossing +/+ females with +/Lc males. They were bred in standard conditions: 12-h light:12-h dark (light on at 00.00), 21–22 °C, food and water available ad libitum. All the mice were 3–4 months old at the beginning of the experiments. Before testing, the animals were randomly split into 6 groups containing, respectively, 8 or 10 Lurcher mice (+/Lc) and 10 controls (+/+) (sex ratio: 1/1). The research was realized within the guidelines established by "le Comité Consultatif National d'Ethique pour les Sciences de la Vie et de la Santé".

2.3. Experimental design

All the animals were handled every day for 1 week before the experiments, in order to reduce the stress due to manipulation. On the test days, the animals were weighed before i.p. injection of either vehicle (Tween 80) or delta 9 THC 20 min before the beginning of each test to obtain an optimal effect of the drug [12,27,48]. The dosage of the drug was established from preliminary experiments done in the laboratory: the Lurcher mice received a dose of 4 or 8 mg kg^{-1} of THC or an equivalent volume (about 0.2 ml) of the vehicle (that is 0 mg kg^{-1} of THC) (named Lurcher or +/Lc THC 4, THC 8 and Tween 80, respectively). The doses were not re-randomized for each test and each animal daily received the same dose. After the injection, each mouse was returned to its cage with its congeners. The same experimental procedure was followed with the non-mutant mice (named controls or +/+ THC 4, THC 8 and Tween 80, respectively). All the subjects were randomly tested in a simple blind procedure: the injected substances were only identified after the behavioural data collection (concerning genotype, a blind procedure was not possible because of the ataxic gait of the +/Lc mice).

The behavioural battery tests used in this study aimed at measuring motor abilities and motor learning in the Lurcher mutant mice as in previous studies [22,24]. They permitted to evaluate spontaneous locomotor activity (open field), muscular strength (hanging), equilibrium capabilities in dynamic conditions (wooden beam) and motor coordination (hole board). The equilibrium in static conditions and motor learning abilities of our mice were investigated with the unstable platform test. To allow comparisons between mutants and controls and between the different doses injected, all these tests were always conducted in the same order: openfield test, hanging test, wooden beam test, hole board test and unstable platform test. The animals had one test per day and after each experiment, each apparatus was cleaned with an alcohol solution (50%). The tests were completed between 02.00 and 04.00 p.m., (i.e during the active phase of the animals). For practical reasons, +/+ THC 8 and +/Lc THC 8 were tested after the mice of the other groups.

2.4. Openfield test

This test was aimed at measuring spontaneous locomotor activity of the mice and at detecting an eventual sedative effect of the substance. The test consisted of a wooden squared white painted box (60 cm × 60 cm × 12 cm). At the beginning of the test, the mouse was placed in the middle of the apparatus and, during 10 min, we measured the time spent walking.

2.5. Hanging test

The goal of this test was to evaluate muscular strength of the animals. The mice were hung by their two forepaws in the middle of a thin horizontal rope (2 mm in diameter and 30 cm in length), located 30 cm above the floor covered with a foam carpet to cushion the falls. The latency before falling was measured and the maximum time fixed was 180 s. Each animal had two trials spaced by a 3 min. interval, a pause including a return to its cage with its congeners.

2.6. Wooden beam test

The wooden beam test was used to evaluate the equilibrium abilities of the mice when their motion was not limited. The apparatus was a motionless wooden beam 3 cm wide, 1 m long at a distance of 80 cm above a foam carpet. At the onset of the single trial, each animal was placed in the middle of the beam, the animal's body axis being perpendicular to the longer beam axis. We recorded the latency before falling fixed to a maximum of 300 s.

2.7. Hole board test

This test was used to evaluate the motor coordination of the mice. The apparatus consisted in a wooden squared painted box ($L \times l \times h$: 29.5 cm × 29.5 cm × 19 cm) with a floor containing 36 holes (hole board). The holes were 1 cm deep, 2 cm in diameter and arranged in a 6 × 6 array. At the beginning of the single trial, each mouse was placed in the middle of the hole board. We collected, during 5 min, the time spent walking and the number of fore or hindpaw slips into the holes. Then, we calculated the slip frequency (number of slips per minute of walking).

2.8. Unstable platform test

The aims of this test were to evaluate the mice's abilities to maintain balance when their displacements were limited and their abilities to acquire motor equilibrium in these conditions (motor learning) [24]. The apparatus consisted of a light circular platform (diameter: 8.5 cm; weight: 16 g), fixed at its center on a vertical axis (1 m high) and which could tilt by 30° in either direction. This platform was covered with sticking plaster in order to avoid sliding and grasping. Each animal was subjected to six trials per day, 1 day out of 2, and returned to its cage during the intertrial intervals (about 3 min.). At the beginning of the trial, the mouse was placed in the middle of the board (horizontal situation). Only motions of the animal could provoke tilting of the platform and only adapted repartition of muscular strength in the limbs and the body could permit the mouse to restore equilibrium and to maintain balance. Each mouse was subjected to the trial in the following way: the animal was placed in the center of the horizontal platform. The trial ended when two or more paws of the mouse were out of the circumference of the platform or when the mouse reached the cut off period of 2 min. The mice were trained every other day until they

Table 1
Results of statistical analysis (2 ways ANOVA): genotype, Dose effects and Interaction between the two factors (F and p values) (n = number of mice tested)

Tests	Genotype effect	Dose effect	Interaction
Openfield (walking time)	$F(1.52) = 8.68$ $p < 0.001$	$F(2.52) = 1.07$ $p > 0.05$	$F(2.52) = 0.71$ $p > 0.05$
Wooden beam (latency)	$F(1.52) = 5.02$ $p < 0.05$	$F(2.52) = 0.33$ $p > 0.05$	$F(2.52) = 0.54$ $p > 0.05$
Hanging (latency)	$F(1.52) = 14.97$ $p < 0.0001$	$F(2,52) = 9.43$ $p < 0.0001$	$F(2.52) = 5.91$ $p < 0.001$
Hole board (slip frequency)	$F(1.52) = 11.68$ $p < 0.001$	$F(2.52) = 3.99$ $p < 0.05$	$F(2.52) = 3.53$ $p < 0.05$

reached the learning criterion fixed at two consecutive trials of 2 min. If they did not reach this criterion after 4 days, this training was stopped.

For each trial, we measured the time before falling and thereafter the daily mean performance of each mouse was calculated.

2.9. Statistical analysis

ANOVA and post hoc comparisons with Fisher's least significant difference test were used for the purpose of statistical analysis. In all instances, $p < 0.05$ was considered statistically significant.

3. Results

The weight of the animals was stable during the whole experimental period and no catalepsy was observed whatever the genotype or the substance injected. Table 1 summarizes the statistical results we obtained about ANOVA.

3.1. Motor abilities

ANOVA revealed that the locomotor activity (Fig. 1) was influenced by the genotype and the activity of the Lurcher mice was significantly higher than the control mice's activity. On the other hand, no sedative effect of the drug was observed regardless of the dose injected.

The latency before falling from the wooden beam was not significantly influenced by the drug received and it was noticed, as shown in Fig. 2, that the Lurcher fell sooner than the control mice, regardless of the dose injected.

The scores of the two trials in the hanging test (latency before falling) were averaged for each animal. The mean scores (±S.E.M.) were then calculated and are presented in Fig. 3.

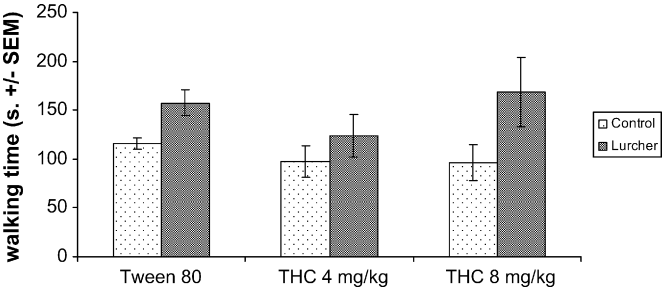

Fig. 1. Time spent walking in the openfield test.

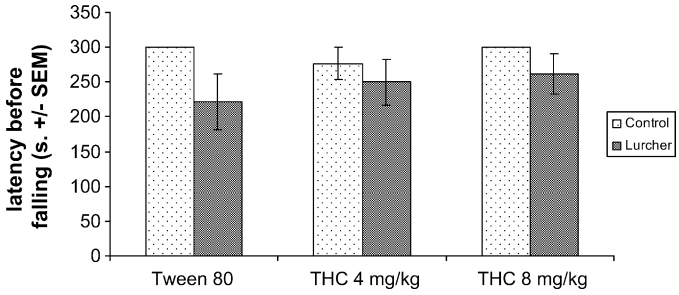

Fig. 2. Latency before falling in the wooden beam test.

The performances of Lurcher Tween 80 were significantly lower than those of the controls Tween 80 ($p < 0.0001$) whereas the performances of Lurcher THC 4 did not significantly differ from those of the controls THC 4 ($p > 0.05$). Moreover, since the performances of Lurcher THC 8 were similar to those of +/Lc Tween 80 ($p > 0.05$), the scores of Lurcher THC 4 were twice higher than those of the latter ($p < 0.01$). The muscular strength of control mice THC 8 was poorer than that measured in +/+ Tween 80 ($p < 0.0001$).

Concerning the motor coordination in the hole board test (Fig. 4), the ANOVA revealed that the influence of the drug was different according to the genotype (significant interaction between the two factors). As shown in Fig. 4, the motor coordination was not altered by the drug in +/+ mice ($p > 0.05$) while the frequency of slips in Lurcher mice was greatly reduced at the dose of 4 mg kg^{-1} (two-fold lower than that of the Lurcher Tween 80; $p < 0.01$). Thus, the motor coordination in the mutant was similar to that measured in +/+ mice ($p > 0.05$). This motor improvement was not observed with the dose of 8 mg kg^{-1}. The

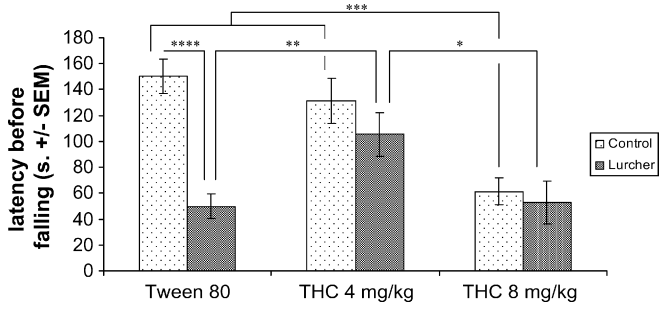

Fig. 3. Latency before falling in the hanging test ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ and $^{****}p < 0.0001$).

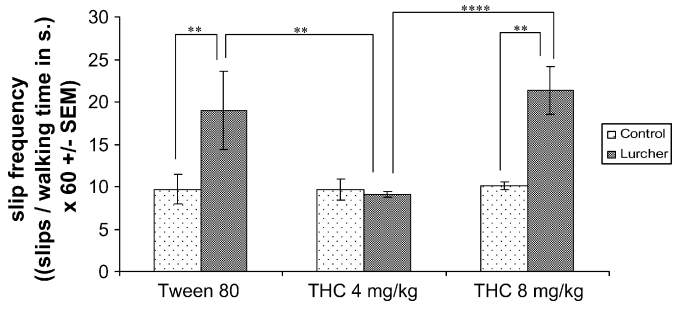

Fig. 4. Slip frequency ((number of slips/walking time in seconds) × 60) in the hole board test ($^{**}p<0.01$ and $^{****}p<0.0001$).

scores of the mutants injected with this dose were similar to those measured in the Lurcher Tween 80 ($p>0.05$) and lower than those measured in the +/+ mice ($p<0.01$ in all cases).

3.2. Equilibrium abilities and motor learning (unstable platform test)

As shown in Fig. 5, all the mice increased their performances with training (training effect: $F(3.156)=55.96$; $p<0.0001$). Such training effect was genotype dependent (interaction genotype × training: $F(3, 156)=47.47$; $p<0.0001$) but not significantly influenced by the dose of drug injected (interaction genotype × training × drug: $F(6.156)=1.40$; $p>0.05$). The effect of the drug (dose effect: $F(2.52)=12.05$; $p<0.0001$) was also different according to the genotype (interaction genotype × dose: $F(2.52)=13.04$; $p<0.0001$). The performances of +/+ THC-treated mice were not significantly altered by the drug, whatever the dose injected and the day of training ($p>0.05$ in all cases). The results were significantly different in the Lurcher THC-treated mice since all the mutants reached the learning criteria, as soon as the third day of training for the THC 4 and the fourth day for the THC 8. Their performances were similar to those measured in the control mice from the second day of training (Lurcher THC 4 versus +/+ THC 4; $p>0.05$) or the third day of training (Lurcher THC 8 versus +/+ THC 8; $p>0.05$). Moreover, the performances of the mice during the first day of training, reflecting the equilibrium abilities in static conditions, very impaired in Lurcher Tween 80 compared to controls ($p<0.0001$), were signifcantly improved in the mutant THC-

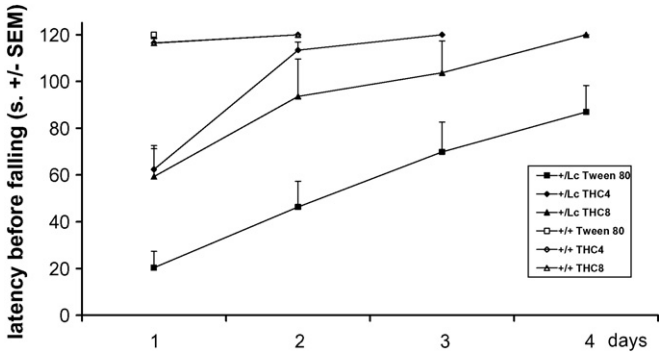

Fig. 5. Evolution of the scores of the animals, in seconds +S.E.M. (ordinates), when trained on the unstable platform for 4 days (abscissae).

treated mice. The latency before falling being three-fold higher in these mice compared to Lurcher Tween 80 (Lurcher THC 4 or THC 8 versus Lurcher Tween 80; $p<0.0001$).

4. Discussion

Lurcher mutant mice are widely used to study the roles of the cerebellum in motor abilities [17,22,24,30,35]. Many previous studies showed that in spite of their motor impairments, due to the degeneration of the cerebellar cotex and olivo-cerebellar pathway, these mutants are still able to learn an equilibrium motor task in the rotorod or in the unstable platform test, after a specific training [7,22,28,29,31,35,36]. The results we obtained in the present study corroborated such data since it was observed that the motor learning, although, reduced was not completely abolished in the mutant mice injected with the non psychoactive substance (Tween 80) while they were severely impaired in muscular tone, motor coordination and equilibrium abilities. Such results reinforced the idea that the cerebellar cortex did not play a crucial role for the acquisition of complex motor behaviour and that this structure played more likely a facilitating role. Furthermore, our results also confirmed that the key action of the cerebellum cortex was in the control of reactive postural adjustments [22,24,36].

Cannabinoid-induced motor deficits were wildly documented and it is well established today that such disturbances were mediated by activation of CB1 cannabinoid receptors highly concentrated in areas involved in motor regulation processes such as basal ganglia and cerebellum [8,11,43–45]. Unexpectedly, in the present study, injection of delta 9 THC failed to provoke motor coordination disturbances in wild type B6/CBA mice. Only muscular strength reduction was observed at the dose of $8\,mg\,kg^{-1}$. This lack of serious alteration of motor behaviours in the +/+-B6/CBA mice could be attributed to a "strain effect" comparable to that already observed in these hybrid mice with another pharmacological agent [36]. Nevertheless, the minor alteration of muscular strenght noticed in the controls injected with THC at the dose of $8\,mg\,kg^{-1}$ could herald more pronounced motor impairments at higer doses. The results were different in the cerebellar mutant mice, which exhibited a reduction of their motor deficits associated with a motor learning facilitation when treated with THC. Indeed, our results showed that, when administrated at the dose of $4\,mg\,kg^{-1}$, the major active component of marijuana permitted to enhance muscular strength, motor coordination and equilibrium abilities in static conditions in the mutants. Moreover, all the THC-treated mutants reached quickly the motor learning criteria. It is, therefore, very likely that the delta 9 THC facilitated the acquisition for a new equilibrium motor program on the elevated unstable board, by reducing motor abilities deficits and by improving successively the muscular synergies and the motor coordination. This argument was reinforced by the fact that the motor learning facilitation was more pronounced in Lurcher THC 4 than in Lurcher THC 8 mice, the former being less impaired than the latter in the hanging and hole board tests.

Immobility was required to balance on the unstable platform. Such immobility was not due to sedative effect of the

substance since no decrease in spontaneous locomotor activity was observed in the treated mice. The immobility was, therefore, more likely obtained by an adapted repartition of muscular tone in both the limbs and the body. With training, the mice became progressively motionless because they learned to anticipate the tilt of the platform. Therefore, they maintained balance through pro-active mechanisms corresponding to automatized anticipatory body adjustments, as well as those observed previously with the rotorod test [7,22].

Given the involvement of cerebellar or basal ganglia-located receptors in motor processes, it can be speculated that the dose-dependent improvements observed in the mutant mice were due to the action of the cannabinoid receptor agonist on these structures. Although the cerebellar cortex has completely degenerated in the mutants, one cannot completely exclude that there were resting cannabinoid receptors in this structure responsible for these motor alterations. On the other hand, given the functional integrity of the striato-pallidal system in the Lurcher mice [40,46], it is also possible that the alteration observed in the latter were the result of the local modulatory action of the delta 9 THC on neurotransmitters processes within basal ganglia [41], i.e. via the modulation of GABAergic and dopaminergic neurotransmission in these structures [8,18,42]. This hypothesis is consistent with that we previously proposed: basal ganglia would play a particularly important role in the motor processes in the Lurcher mice and their functional modulation could result in specific motor effects in these mutants [36]. Furthermore, such modulation by delta 9 THC would cause motor improvement at low dose but disruption at high dose (biphasic effect).

In summary, the results of this study showed that in spite of the complete cerebellar cortex and olivo-cerebellar pathway degeneration, a cannabinoid receptor agonist at the dose of 4 mg/kg can reduce the motor impairments in Lurcher mutant mice and consequently influence their motor learning abilities.

5. Conclusion

The present study was the first to determine the effects of the major active component of marijuana, the delta 9 THC, on motor abilities and motor learning in a rodent model of cerebellar degeneration. Our results showed that at low dose, injection of this substance enhanced the motor performances and facilitated the acquisition of a new motor task of equilibrium in the Lurcher mutant mice. Nevertheless, such improvements were less pronounced at 8 mg kg^{-1} suggesting biphasic motor effects of the drug. It is, therefore, obvious that, for a better understanding of such effects in the cerebellar deficient mice, further studies have to be undertaken to define precisely the localization of the receptors underlying them. Nevertheless, our data suggest that cannabinoid drugs could represent a new field of investigation concerning the treatment of cerebellar ataxic syndrome.

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