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Fine Motor Control in Rats is Disrupted by Delta-9-Tetrahydrocannabinol

PETER J. MCLAUGHLIN, CAREN E. DELEVAN, SCOTT CARNICOM, JOHN K. ROBINSON AND JASPER BRENER

Department of Psychology, State University of New York at Stony Brook, Stony Brook, NY 11794-2500

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MCLAUGHLIN, P. J., C. E. DELEVAN, S. CARNICOM, J. K. ROBINSON AND J. BRENER. *Fine motor control in rats is disrupted by delta-9-tetrahydrocannabinol.* PHARMACOL BIOCHEM BEHAV **66**(4) 803–809, 2000.—Evidence has suggested that cannabinoids such as THC, the active ingredient in marijuana, cause deficits in motor control and the production of movement. However, the specific components of motor control that are affected by cannabinoids have yet to be identified. The present study used an operant beam-press paradigm with a force criterion to determine the effects of THC on different parts of the force–time trajectory. Seven rats were trained to press a beam with at least 50 g of force to receive a sugar solution. THC was injected, as was apomorphine (APO), a selective dopamine D_2/D_1 receptor agonist that acts as an antagonist at low doses. Low doses of APO, which have been found to cause deficits in motor execution, were used as a control for the effects of THC. Average peak force of a given press, as well as rate of rise of force, were significantly lowered by THC, as well as by apomorphine. Past research suggests that deficits in the rate of rise of force that can be attributed to depletions of dopamine in the nigrostriatal pathway, as in the case of low doses of APO, reflect failures of motor unit recruitment rather than of motor memory. Similarities in the motor effects of THC and APO suggest that THC plays a role in recruitment and synchronization of motor neurons appropriate for a given task. © 2000 Elsevier Science Inc.

Basal ganglia Cannabinoids Dopamine Motor control Operant conditioning Sprague–Dawley

DELTA-9-TETRAHYDROCANNABINOL (THC), the main psychoactive component of marijuana, is known to produce a variety of behavioral effects in humans, including deficits in working memory, attention, perception, changes in appetite, and motor performance (6,9,17,18,23). Cannabinoid receptors are abundant throughout caudate, globus pallidus, substantia nigra, cerebellum, hippocampus, and cortices (13). The presence of receptors in motor areas suggests that a fundamental role of newly discovered endogenous cannabinoids such as anandamide may be in the modulation of motor behavior. Past research involving volunteers given THC in the laboratory have focused on a variety of motor tasks, including simulators [e.g., (31)] and tests of keyboard press accuracy and reaction time involved in cognitive tests (29) and coordination tasks (23). Recent surveys have shown that self-administration of marijuana is reported to alleviate motor symptoms found in Gilles de la Tourette syndrome (20), and in multiple sclerosis (7).

In rats, motor performance is usually measured in relatively nonselective tasks. The two standard measures of cannabinoid-induced motor impairments are the open field task (measuring spontaneous locomotion), and, at higher doses, catalepsy, measured in animals by immobility when placed on a horizonal ring (18). Dose-dependent ataxia has likewise been observed (4). However, long-term motor deficits have not been shown after chronic administration (27). Cannabinoids have also been found to increase press durations and interresponse times of operant lever pressing (3). However, virtually no studies have examined performance in rats on fine motor production tasks.

Although the behavioral link between injections of cannabinoids and dopamine agonists is not entirely clear, an eightfold increase of anandamide release in striatum has been seen after intrastriatal administration of the dopamine D_2 agonist quinpirole, but not the D_1 agonist SKF38393 (11). The effect of quinpirole was completely diminished with coadministration of the D_2 antagonist raclopride, which has also been shown to impair motor activity (10). Furthermore, activation of both the CB1 and D_2 receptors in cultured striatal neurons has been found to attenuate forskolin-stimulated cAMP accumulation (12).

Requests for reprints should be addressed to Jasper Brener, Department of Psychology, State University of New York at Stony Brook, Stony Brook, NY 11794-2500.

TABLE 1
COGNITIVE/ MOTIVATIONAL AND SECONDARY MOTOR FACTORS UNDER (A) THC AND (B) APO

	Doses of THC (mg/kg)				
A. Factors	Vehicle	0.5	1.0	2.0	3.0
Press of correct beam (%)	97.57 (2.43)	99.71 (0.18)	99.85 (0.14)	99.17 (0.54)	95.50 (4.50)
Transition to cued beam after time out (%)	96.71 (1.76)	96.43 (1.80)	99.14 (0.86)	98.40 (1.60)	100.0 (0.00)
Work per response (time integral of force, g×s)	8.91 (1.65)	10.84 (0.86)	10.83 (1.09)	8.37 (2.38)	8.41 (4.64)
Work per reinforcement (g×s)	20.52 (1.42)	21.40 (1.49)	24.26 (2.77)	28.02 (5.98)	30.08 (4.82)
Proportion of responses reinforced (%)	57.00 (6.64)	61.00 (4.25)	55.57 (6.52)	40.33 (11.82)	27.50 (16.61)
Latency to press after block has begun (ms)	2439.43 (285.77)	2386.86 (302.37)	2883.71 (430.35)	2794.00 (510.49)	11511.00 (5758.0)*
Inter response time (ms)	1187.14 (416.28)	1187.14 (259.65)	1097.86 (338.22)	1623.33 (560.80)	1991.25 (746.83)
Time per reinforcement (ms)	3641.70 (666.18)	2836.00 (115.76)	5009.34 (1748.72)	5673.23 (1484.58)	32419.41 (25569.8)*
Responses per reinforcement	2.06 (0.33)	1.76 (0.15)	2.09 (0.25)	2.59 (0.61)	1.95 (0.47)

	Doses of APO (mg/kg)			
B. Factors	Vehicle	0.01	0.03	0.2
Press of correct beam (%)	100.0 (0.00)	95.43 (2.76)	90.43 (6.31)	89.83 (5.34)
Transition to cued beam after timeout (%)	99.29 (0.71)	97.33 (1.86)	97.50 (2.00)	100.0 (0.00)
Work per response (time integral of force, g×s)	9.98 (0.98)	7.32 (1.99)	8.15 (2.43)	7.46 (3.42)
Work per reinforcement (g×s)	20.40 (1.82)	56.99 (24.40)	46.40 (11.61)	53.52 (15.49)
Proportion of responses reinforced (%)	60.43 (5.08)	33.29 (6.98)*	26.71 (7.34)*	19.33 (7.00)*
Latency to press after block has begun (ms)	2441.86 (248.97)	3164.50 (551.14)	4132.20 (701.17)	6212.00 (890.40)†
Inter response time (ms)	1171.43 (353.17)	1074.29 (363.02)	1554.29 (470.82)	1709.17 (732.66)
Time per reinforcement (ms)	3087.7 (317.06)	145334.5 (133212.3)	24435.5 (9350.75)	56506.5 (28160.7)
Responses per reinforcement	1.81 (0.21)	11.21 (7.99)	2.85 (0.26)	3.93 (0.95)

Values expressed are means (±SE). These factors are not affected by (a) THC or (b) APO, except that general motor depressions (e.g., latency) is seen at higher doses, and number of unreinforced presses increases, as subjects have greater inability to reach force criterion. All seven subjects recorded 200 reinforcements at each level, except that only five responded at the 2 mg/kg dose and only two at the 3 mg/kg dose of THC. Similarly, only six animals completed 200 reinforcements at the .2 mg/kg dose of APO. Tukey's HSD revealed no differences from vehicle at any dose with $p < 0.05$, except as noted, *$p < 0.05$, †$p < 0.005$.

Ultimately, to be able to understand the role that cannabinoid receptors play in voluntary motor behavior, one will have to work in animal systems combining behavioral and neural levels of analysis. Our laboratory has developed a fine motor control paradigm for rats that has revealed that lesions of the nigrostriatal dopamine system specifically impair the recruitment of motor units while leaving motor memory intact (16). In this operant task, rats are trained to press force-sensitive beams to a force criterion to receive reward. The force–time trajectory of each press is examined for changes in the way in which the beam is pressed. It is believed that these motor variables are vital components of gross motor behavior seen in tasks such as the open field and ring immobility (1,2,15,16,19,30). Additional cognitive measures were yielded by variants of the basic task, and are listed in Table 1 and discussed in the next section.

As a first step in studying the involvement of cannabinoid systems in motor production, the current study sought to examine whether this motor control paradigm was sensitive to the effects of THC. We assessed the effects of systemically administered THC on the ballistic and corrective components of reinforced motor responses. For comparison to previous published results (10–12), we also examine the effects of dopamine D_2/D_1 receptor agonist, apomorphine.

METHOD

Subjects ($n = 7$) were adult male Sprague–Dawley rats housed separately and weighing 370–450 g before training. During training and testing they were maintained at 87.5% of pretraining weights by monitored feedings of rat chow after daily sessions. Water was available ad lib throughout. They were housed with lights on from 2000 to 0800 h.

Apparatus

The two operant chambers each had three force-sensitive beams mounted on one wall [see (1) for a diagram of the apparatus]. Strain gauges bonded to each beam acted as linear transducers converting force to voltage. These voltages were sampled by a computer at 1 kHz via a 12-bit analog-to-digital converter. Beam presses were required to exceed a force of 1 g (9.76×10^{-3} N) to be classified as responses. Under each

beam was a food tray. Sugar solution (20 μl) (0.32 g/ml, with an energy value of 37 calories per reinforcement) was delivered into the middle tray for every correct press, via a syringe driven by a stepper motor housed outside the sound-attenuating chamber. The side trays were not used. A SoundBlaster 16 generated tones to indicate time-out intervals between blocks of presses. A piezo oscillator positioned behind the front wall emitted a click with each correct press, and concurrent with the press reaching a criterion of 50 g. Each rat was run in the same box throughout the study. Four small red lamps on each end of the box provided general illumination whereas three small lamps each positioned above a beam were used to identify the active beam during the session. A video camera housed above each box allowed observation of the rat from a monitor located in the control room.

Procedure

Training took place in four stages. In the first, all three lights were on continuously, and all presses over 1 g were rewarded. Subjects were required to make 150 presses, after which use of the center light was discontinued for the remainder of the study. One of the two side lights would illuminate to indicate the beam to be pressed. At this point, 12 reinforced presses were required to complete a block. Presses made on the beam beneath the illuminated lamp generated a click and the introduction of food into the center tray, whereas presses on either incorrect beam had no programmed consequences. At the end of each block, a 7-s time-out period occurred, during which time no presses were to be made. The time out was marked by the lamp above the beam and the house light turning off and a tone coming on. Each press during the time out would increase the interval by 5 s. Subjects were to achieve 50 reinforcements in this manner, in addition to the earlier 150, within 1 h to advance to the second stage.

In the second stage, subjects were to obtain 200 reinforcements under the same conditions as the last 50 presses in the previous session. Animals that did so in 1 h advanced to stage 3.

Beginning with the third stage, a force requirement was introduced gradually. Whenever a subject earned 12 reinforcements within 2 min at the prevailing force criterion, the force requirement increased by 3 g, to a maximum of 50 g. Subjects which completed one block of presses at the 50 g level moved on to the fourth stage. While on the third stage, subjects started each session with a force criterion 9 g less than the highest force criterion attained on the previous day.

In the fourth stage, animals were required to make 200 correct responses with a force criterion of 50 g within 30 min to complete the training. A random number generator selected a number between 5 and 15 inclusive, which then constituted the number of reinforcements required to complete a given block. The 50 g criterion was chosen because it is well below the maximal force a rat can normally achieve, but higher than the force level of default beam presses (3). Additionally, previous work has shown that fine kinematic adjustments to the force–time trajectory still occur at forces as high as 55 g (19). Following the end of training, animals ran each daily session with the criteria of the fourth stage.

Measures

Three primary motor measures were recorded for presses to all three beams. Their interrelationship is illustrated in Fig. 1. The first variable is peak force (PF) in grams (9.76×10^{-3} N), which is the highest force achieved during a response. Peak force is codetermined by two additional variables, rate of rise of force (*df/dt*) and time to peak force [Tpf; (26)].

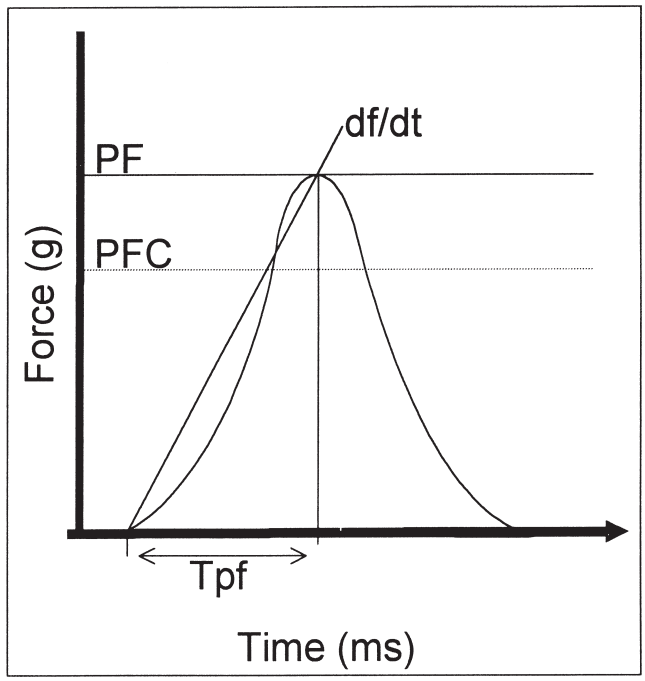

FIG. 1. This ideal force–time trajectory describes a single-peaked response in which the peak force (PF) exceeds criterion for reward (PFC). Also illustrated are the two codeterminants of PF, time to peak force (Tpf), and rate of rise of force (*df/dt*). An attenuation of peak force is seen if the slope, *df/dt* is lowered, while Tpf is held constant. Peak force can also be attenuated if Tpf is decreased and *df/dt* is held constant, or if both Tpf and *df/dt* are decreased (1,26).

Rate of rise of force (measured in g/s) corresponds to the slope of the force–time trajectory, and is believed to be related to the rate of recruitment and synchronization of an appropriate number of motor unites for a given task (30). Time to peak force (in ms) increases as a function of the number of corrective submovements needed in a press to reach criterion force (1,2). Because PF is codetermined by Tpf and *df/dt*, changes in response force are hypothesized to reflect changes in the number of feedback-based force corrections, or in the rate of motor unit recruitment, or a combination of the two (1,26).

If the PF of a press meets the force criterion, it is inferred that the memory trace for the motor task has been accessed and translated into a movement by coordination of the proper number and type of motor neurons. It is further inferred that presses that achieve the force criterion with no corrections and thus, minimal Tpf, have been generated in a feedforward manner (ballistically) and without reliance on feedback-based corrections (thus higher *df/dt*).

Changes in Tpf and *df/dt* also affect the area underneath the force–time trajectory, which has been shown to represent the amount of work performed per response (14,21). Thus, in addition to the three primary motor measures, secondary measures of motor control were recorded including work per response (measured by time integral of force), and work per reinforcement, plus time per reinforcement, number of re-

sponses per reinforcement, and proportion of responses reinforced. These measures vary with the animal's ability to reach the criterion force. They also vary with the number of presses on the correct beam, with the exception of work per response, which is measured for individual responses and, therefore, not affected by responses on an incorrect beam.

Additional discrimination-related measures were also recorded. These measures included proportion of presses on the correct beam, as well as proportion of correct beam transitions following time out. Both measures index the extent to which the subject responded on the beam signaled by the prevailing stimulus. Responding to the beam signaled by the visual stimulus presented after a time out (percent correct transitions) required the subject to attend to the visual stimuli. However, a high proportion of presses on the correct beam (percent correct discrimination) is possible by responding to the beam that yields reinforcements until it ceases to reward, then pressing another beam (a win-stay/ lose-shift strategy). By following this strategy animals may earn high discrimination scores without processing the prevailing visual stimuli. Additionally, Latency (LAT) to press after beginning of block and interresponse time (IRT) were taken as measures of motivation, but could reflect a motor deficit such as bradykinesia.

Drugs

Delta-9-tetrahydrocannabinol was delivered at a concentration of 200 mg/ml in ethanol. Equal parts of emulphor were added and diluted with 0.9% saline to doses of .5, 1, 2, and 3 mg/kg IP, which were administered in counterbalanced order to every animal. Pilot data (not shown) revealed that 3 mg/kg was the maximum dose that would permit performance on this task. Vehicle was prepared by mixing 0.3 ml emulphor with 9.6 ml saline and 0.1 ml ethanol. Animals were injected 30 min prior to each session every Tuesday and Friday.

Beginning 14 days after completion of the THC series, a series of apomorphine (APO) injections was used as a control. Doses of APO were 0.01, 0.03, and 0.2 mg/kg, and were dissolved in dilute ascorbic acid (0.2 mg/ml saline). Previous work (15) has shown that at doses of APO greater than or equal to 0.3 mg/kg, rats do not make beam presses reliably. Apomorphine was injected subcutaneously to the dorsal folds of the neck 7 min prior to sessions on Tuesdays and Thursdays. Order of drug in both repetitions was counterbalanced across subjects. Vehicle appropriate for each drug was used as a control Data from sessions in which animals failed to achieve 200 reinforcements were not included.

RESULTS

THC

A one-way analysis of variance was conducted on each of the three motor measures separately. As seen in Fig. 2a, peak force was significantly decreased with administration of THC in a dose-dependent manner, $F(4, 26)$ 3.81, $p < 0.05$. Of the

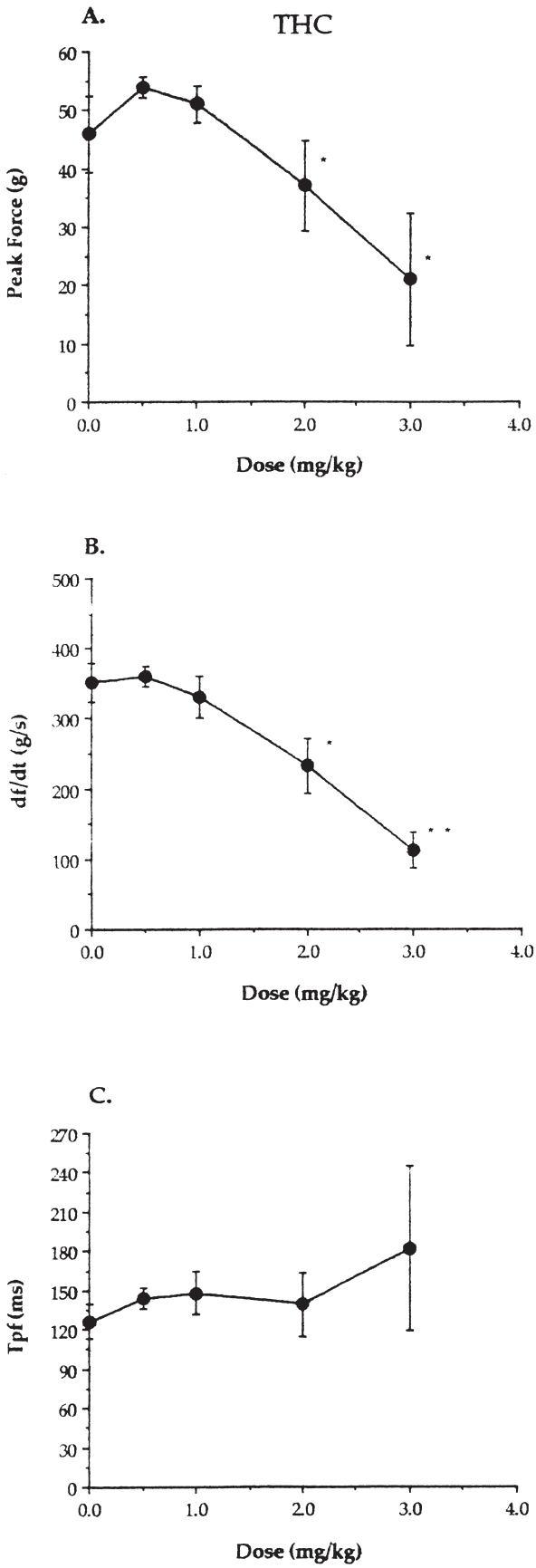

FIG. 2. THC is believed to impair execution of movement for lever pressing with force, as seen in dose-dependent decreases in (a) the maximum force attained during a given high-force press (PF), and (b) rate of change of force over time (*df/dt*), suggesting a deficit in recruitment of enough motor neurons to attain the 50 g criterion. (c) Time to peak force is not affected. Points represent group means and standard error of the mean; $*p < 0.05$, $**p < 0.01$.

two determinants of PF, *df/dt* was also significantly decreased, $F(4, 26)$ 10.33, $p < 0.00005$, while Tpf was not significantly changed, $F(4, 26) < 1$, NS.

Cognitive and secondary motor measures are summarized in Table 1a. It is noteworthy that neither percent correct discriminations, $F(4, 26) < 1$, NS, nor percent correct transitions to the cued beam after a time out, $F(4, 23) < 1$, NS, was significantly affected, indicating unimpaired discrimination. Also, work per response did not change, $F(4, 26) < 1$, NS.

Time per reinforcement (TPR) was significantly increased, $F(4, 23)$ 5.80, $p < 0.005$. Post hoc analysis using Tukey's HSD revealed that only the highest dose (3 mg/kg) was significantly different from performance at the other doses. Similarly, latency to press after a block has begun (LAT) was increased, $F(4, 23)$ 9.85, $p < 0.001$, but only at 3 mg/kg. Tukey's HSD revealed that the only significant comparisons were between 3 mg/kg and all other conditions. Not surprisingly, the session that yielded the dramatic rise in TPR did the same in LAT. Both measures tended to be in the range of a few seconds but have no ceiling, and can therefore be heavily influenced by one cataleptic subject, as will be discussed below. *t*-Tests were also conducted on each measure to compare the vehicle for THC with that for APO. No differences were found.

Apomorphine

Of the three kinetic measures, only Tpf (Fig. 3b) was not significantly changed, $F(3, 23) < 1$, NS. PF was lowered dose dependently, $F(3, 23)$ 5.30, $p < 0.01$, as was its other determinant, *df/dt*, $F(3, 23)$ 17.70, $p < 0.0001$.

There was also a decrease in the percent of presses that were reinforced, $F(3, 23)$ 7.25, $p < 0.005$. Post hoc analysis revealed significant differences to lie between the vehicle group and the 0.01 mg/kg group ($p < 0.05$), the 0.03 mg/kg ($p < 0.01$), and the 0.2 mg/kg group ($p < 0.005$). Also, of the motivation measures, only LAT was affected, $F(3, 18)$ 7.53, $p < 0.005$.

DISCUSSION

This study characterized the effects of a cannabinoid drug on a fine motor performance task. The force–time trajectory of the average beam press was summarized by three variables: PF, TPF, *df/dt*. THC was seen to dose dependently decrease PF and the rate of rise to PF (*df/dt*). The comparison drug (APO) was found to cause deficits in the same variables. Accordingly, APO caused a significant decrease in percentage of responses reinforced, and THC produced a strong downward trend in the same measure. Both produced a small dose-dependent increase in time per reinforcement that was significantly different from vehicle at the highest dose of THC. However, inspection of the data revealed that only two animals responded at that dose. One of these two subjects' TPR was not significantly different from vehicle, while the other's was 58,000 ms, almost four times greater than any other subject's TPR, at any dose. It is thus presumed to reflect a THC-mediated pause in responding in the range of several minutes, rather than an increase in subcriterion responding. This is supported by a nonsignificant change in responses per rein-

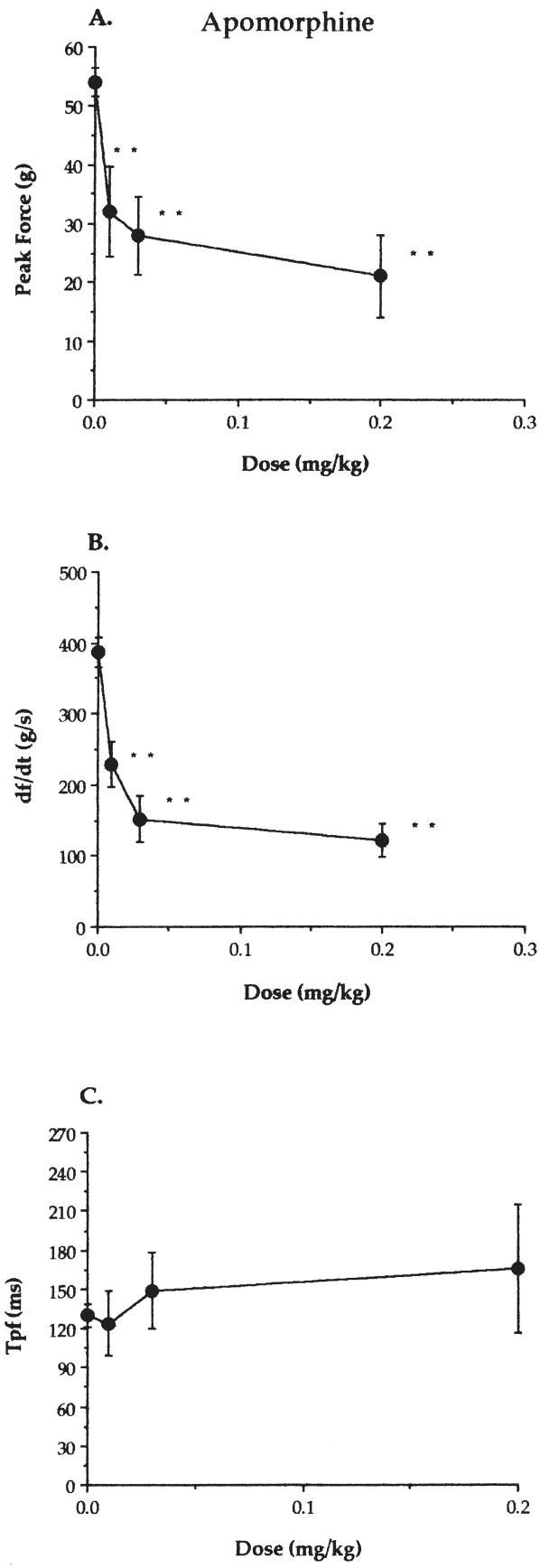

FIG. 3. APO evokes a similar pattern of deficits to THC, in that (a) peak force of a press, and (b) *df/dt* are reduced dose dependently, while Tpf (c) is not affected. Points represent group means and standard error of the mean; $*p < 0.05$, $**p < 0.01$.

forcement, and by a significant increase in latency to press at the beginning of a block at the 3 mg/kg dose.

That RPR is unchanged by THC in this task is surprising: this measure may be considered to represent a gross motor impairment as seen in the open-field task. However, there is a motivation for reward in learned tasks of behavior, such as in the current article, that is unseen in tasks such as the open field. This also presents a limitation on the current study's applicability to gross motor tasks in that criterion force output is abolished at doses commonly used in gross motor tasks (3,25), possibly resulting from difficulty in producing a learned force response. At doses above 3 mg/kg, subjects' responses are severely diminished; what little responses are made are far below criterion (data not shown).

Cannabinoids have already been found to increase response duration and interresponse time on an operant lever pressing task (3). A dose-dependent effect of several cannabinoids was found to be related to the binding affinity of each to the CB1 receptor. This may suggest that same weakness in beam pressing as observed in the present study. Also surprising was that IRT was not significantly increased, as has been seen in previous reports. However, the difficulty in producing the force requirement necessary for uncovering impairment in fine motor performance may engender a general fatigue that masks a dose-dependent change in IRT. However, there is a question as to what part of movement production has been impaired.

Previous work from the lab (16) has suggested that apomorphine acting in the nigrostriatal pathway serves to inhibit recruitment of a population of motor neurons adequate for generating high-force beam presses. Deficits in PF and *df/dt* were found for learned high-force responses (>50 g) of the sort studied in the current experiment. However, APO did not generate similar impairments for learned low-force beam presses (<3 g) indicating that the memory trace of the learned response is intact in the presence of APO, while generation of higher forces is impaired.

Although THC and APO showed the same force-related impairments, the question of the similarity of actions of the two drugs can only be speculated. However, as stated above, anandamide release has found to be stimulated eightfold by D_2 agonists, such as quinpirole. Of interest was the finding that intrastriatal quinpirole did not increase levels of the more abundant endocannabinoid, 2-arachidonylglycerol. Moreover, quinpirole was found to first impair, then increase motor performance, a finding attributable to activation of presynaptic D_2 autoreceptors, followed later by activation of postsynaptic D_2 receptors. The early performance deficit was attenuated by intraperitoneal injection of the CB1 antagonist SR141716A (11). Activation of D_2 autoreceptors is also believed to be the mechanism of behavioral effect of APO in the current study (15).

In striatum, it has been found that CB1 receptors are found largely on GABAergic medium spiny neurons, where they are believed to modulate GABA release (5,28) or uptake (24) presynaptically. It is, therefore, possible that the decrease of PF and *df/dt* involves dopaminergic activation of anandamide in striatum via D_2 receptors, that in turn, modulates GABAergic activity.

On the other hand, APO (as seen in Fig. 3), unlike THC, has a profound kinetic effect at even the lowest dose, indicating that dopamine plays a vital role in motor unit recruitment, while THC may be more involved in fine adjustment of that recruitment. Furthermore, it is uncertain that the THC-mediated deficits in PF and *df/dt*, while consistent with the effects of APO, even have a striatal site of action. Because systemic injections were used in the present study, it is possible that THC causes its effect on fine motor control at another site with high CB1 receptor density, such as cerebellum. Therefore, future studies can focus on microinjecting cannabinoids into neostriatum. Including a low-force press could be used to explore whether the effect of the cannabinoid is an impairment of motor memory or execution.

The similarity of the effects of THC to those of apomorphine may suggest that CB1 autoreceptors moderate recruitment of motor resources in the extrapyramidal system. At low doses, APO acts mostly at the presynaptic D_2 receptor (22), suggesting that DA in the nigrostriatal pathway moderates coordination of motor neurons to achieve peak force and rate of rise of force for a task. Likewise, anandamide, which causes hypomotility (8,11), may serve in the neostriatum to modulate application of motor resources to learned movements.

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