Behavioural Brain Research, 41 (1990) 161–166
Elsevier
BBR 01111

Short Communication

The NMDA antagonist dizocilpine (MK-801) reverses haloperidol-induced movement initiation deficits

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(Received 8 January 1990)
(Revised version received 25 July 1990)
(Accepted 25 July 1990)

Key words: Movement initiation; Haloperidol; Dizocilpine (MK-801); Reaction time; Force; Rat

The present study shows that systemic dopamine receptor blockade impaired movement initiation of rats, trained in a simple reaction time task for rapid initiation of locomotion in response to a combined optic/acoustic cue. Reaction time, movement time and the accelerative force were recorded for each initiation of locomotion. Results indicate a dose-related increase of reaction time following systemic administration of haloperidol (0.1, 0.15, 0.3 mg/kg i.p.). Measures derived from resulting force–time patterns showed a haloperidol-induced decrease (0.15 mg/kg i.p.) of the mean rate of force development, indicating a decreased initial acceleration. These effects were reversed by systemic co-administration of dizocilpine (MK-801) (0.08 mg/kg i.p.), a selective non-competitive *N*-methyl-D-aspartate (NMDA) antagonist. The haloperidol-induced movement initiation deficits in this task are in part comparable to akinesia seen in Parkinson's disease and their reversal by dizocilpine has implications for the treatment of this disease.

Blockade of central dopaminergic (DA) transmission by DA receptor antagonists in rats produces selective motor impairments. One hypothesis proposed to account for neuroleptic-induced disturbances of behavior is that these drugs predominantly affect animals' ability to initiate motor behavior[13]. This hypothesis is based on findings of neuroleptic-treated animals showing akinesia, catalepsy, prolonged reaction time and further impairments of motor control in a variety of other behavioral paradigms (for refs. see 1, 13), and these symptoms are, at least in part, due to a movement initiation deficit. The work reported here investigated the effect of haloperidol on initiation of locomotion of rats using a newly designed reaction time task. Neuroleptics are known to delay locomotor initiation in rats in an active avoidance paradigm and this impairment appeared not to be related to a disruption of sensory or motivational processes[9]. In our study, we examined initiation of locomotion using a rewarded reaction time task: food-deprived rats were trained in a modified runway for rapid locomotor initiation in response to a cue to get a food reward. Movement initiation was recorded by high performance video equipment and a force platform to detect ground reaction forces exerted by an animal on the surface. This device is espe-

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cially appropriate for evaluating time and force parameters of locomotor initiation and is therefore sensitive to akinesic effects in terms of reaction time, movement time as well as changes of force–time patterns. Since subtle changes of force production seem to be associated with DA dysfunction in rats and humans[5,6,16], analysis of force parameters may be a useful tool regarding neuroleptic effects on movement initiation. We further investigated in the paradigm used here, dizocilpine, a selective antagonist of the glutamatergic transmission mediated by *N*-methyl-D-aspartate (NMDA) receptors, which was recently found to have a marked anticataleptic activity[11] and pronounced stimulatory effects on locomotion[3]. As haloperidol was expected to act akinesic in the paradigm used here, dizocilpine should antagonize these deficits.

Eight male Sprague–Dawley rats, weighing 240–260 g were purchased from Interfauna (Tuttlingen, F.R.G.). The animals were housed in groups (4 per cage) and provided with 12 g rodent laboratory chow per rat each day and water ad libitum. The temperature in the colony room was kept constant at 22 ± 3 °C and lights were on between 6.00 and 18.00 h. Animals were trained on a newly designed reaction time paradigm[7]. Briefly, behavioral testing was conducted in a modified runway made of transparent perspex: it consisted of a start box (22 × 9 × 9 cm) and a runway (100 × 9 × 9 cm) terminating in a goal box (22 × 9 × 9 cm). The food-deprived rat was placed in the start box with the face to a guillotine door blocking the entrance to the runway. After a variable delay (3–10 s), a combined light/tone cue signalled the simultaneous opening of the front door. In response to the cue, a rat initiated from a starting position (upright posture, paws on the ground) rapid locomotion and moved straightforward through the runway to the goal box to receive a reward in a baited food cup (45 mg pellet, Noyes). Approximately 30 s later, the rat was replaced from the goal box into the start box for a new trial. The transition from stance to gait was recorded by means of high performance video equipment (Panasonic WV130 CCD camera, AG6200 recorder and WJ810 time generator) and evaluated by frame-by-frame analysis. In addition, dynamic indices of movement initiation were recorded with a sensitive biaxial force platform mounted below the start box: integrated force transducers (strain gauges) connected with an operation amplifier and PC-compatible oscilloscope (ITT-metrix OX750/2) provided an exact measurement of vertical and horizontal (anterior–posterior) ground reaction forces exerted by an animal on the surface. Force–time waveforms of each response emitted by the subjects showed a reproducible pattern and were used to analyse dynamic features of movement initiation. It has been shown that peak force and rate of force development (slope) of the anterior–posterior component of ground reaction forces are sensitive and reliable parameters for characterizing the initial acceleration in the forward direction. The following measures were recorded from each trial: correct reaction time (RT), defined as latency between cue presentation and movement initiation (first complete lifting of a paw from the surface) within a range of 100–1000 ms, correct movement time defined as latency from movement initiation up to leaving the force platform within a range of 100–1500 ms, peak force and rate of force development (force slope) of anterior–posterior ground reaction forces. Rats readily learned this task and a stable performance of all rats was established in 10 training sessions. One daily session consisted of 10 successive trials per animal. The following experimental design and analysis was used: after the training sessions, the experiment was performed on consecutive days with one daily session. The following drugs were used for intraperitoneal administration: saline solution (0.9% sodium chloride, 1 ml/kg i.p.); dizocilpine (MK-801) ([(+)-5-methyl-10,11-dihydroxy-5H-dibenz(a,d)cyclohepten-5,10-imine] hydrogen maleate) (Biotrend, Köln, F.R.G.) and haloperidol (Sigma, Deissenhofen, F.R.G.), dissolved in saline solution, respectively. Injections were given 30 min prior to the onset of individual behavioral testing (injection volume 1 ml/kg i.p.) according to the time–effect profile of both drugs[11]. The baseline performance of all animals (n = 8) was tested in 3 saline sessions (one initial and 2 intermediate sessions) and compared to the

performance in drugged sessions of the same animals. In the drug sessions one drug/drug combination was given at the following doses, respectively: haloperidol 0.1; 0.15; 0.3 mg/kg i.p.; dizocilpine 0.08 mg/kg. Reaction time was recorded of all sessions. As RT performances in saline sessions were not significantly different as revealed by ANOVA, saline RT data were pooled and compared to the performance in the drug sessions. Movement time and force data were recorded from a single dose/dose combination of the drugs (dizocilpine 0.08 mg/kg, haloperidol 0.15 mg/kg and co-administration at this dose) and compared with the data of the corresponding saline session. The results are presented as means of correct trials per session ($\pm$ S.E.M.). The data of saline and drug sessions were submitted to an analysis of variance (ANOVA), and, in case of significant differences of the means, followed by a Newmann–Keuls (NK) test for unequal n's and a posteriori pairwise comparison of differences. Statistical significance was admitted if the P-value was less than 0.05.

RT measurements indicated that performance of saline sessions remained stable and an analysis of variance confirmed that differences of means between saline sessions (222.2 $\pm$ 10.4 ms, $n = 80$; 233.3 $\pm$ 7.4 ms, $n = 77$; 229.5 $\pm$ 9.6 ms, $n = 72$) were stastistically insignificant ($F_{2,226} = 0.087$, df = 3.0, $P > 0.05$). As compared to performance in saline sessions, haloperidol induced a dose-related increase of RT. Analysis of variance revealed significant differences of drug and saline sessions ($F_{6,638} = 12.7$, df = 2.85, $P < 0.01$;) and the NK test showed that haloperidol induced significant RT deficits (0.1 mg/kg, $P < 0.05$; 0.15 mg/kg, $P < 0.01$; 0.3 mg/kg, $P < 0.01$). Dizocilpine (0.08 mg/kg), given alone, caused a modest decrease of RT ($P > 0.05$, NK-test) and completely antagonized the lower dose of haloperidol (0.15 mg/kg) ($P < 0.01$, NK-test). The RT deficit induced by the higher dose of haloperidol (0.3 mg/kg) was reduced significantly to about the same degree following dizocilpine coadministration ($P < 0.01$, NK-test). However, this antagonism was only partial, since RT remained significantly different from saline level ($P < 0.05$, NK-test) (see Fig. 1).

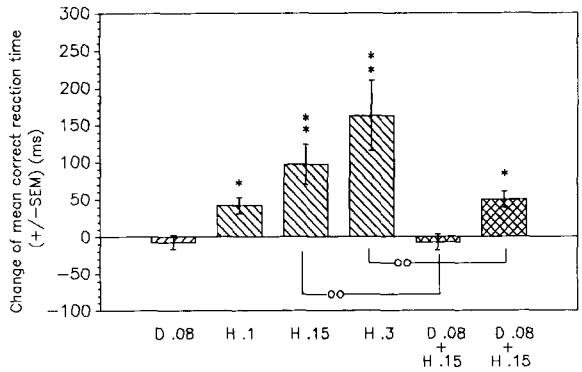

Fig. 1. Change of mean correct reaction time ($\pm$ S.E.M.) induced by systemic administration (i.p.) of haloperidol and/or dizocilpine tested in one session (10 trials per animal), respectively. The drug-induced changes refer to baseline performance of the same animals ($n = 8$) tested in one initial and two intermediate saline (1 ml/kg i.p.) sessions (mean reaction time of pooled saline sessions: 228.3 $\pm$ 9.5 ms, $n = 229$). Asterisks indicate significant differences between drug and saline sessions ($^*P < 0.05$, $^{**}P < 0.01$), circles indicate significant differences between drug sessions ($^\circ P < 0.05$, $^{\circ\circ}P < 0.01$) (ANOVA followed by Newmann–Keuls test). D 0.08: dizocilpine 0.08 mg/kg, $n = 80$; H 0.1: haloperidol 0.1 mg/kg, $n = 78$; H 0.15: haloperidol 0.15 mg/kg, $n = 58$; H 0.3: haloperidol 0.3 mg/kg, $n = 62$; D 0.8 + H 0.15: dizocilpine 0.08 mg/kg and haloperidol 0.15 mg/kg, $n = 75$; D 0.08 + H 0.3: dizocilpine 0.08 mg/kg and haloperidol 0.3 mg/kg, $n = 63$).

There was also a considerable reduction of the number of correct trials within the measured range from 100 to 1000 ms, as latencies often reached 1–5 s or animals failed to respond (see Fig. 1).

Movement time measures showed a mild decrease of mean movement time following dizocilpine administration (0.08 mg/kg) and an increase following haloperidol administration (0.15 mg/kg) as compared to the saline session (mean movement time: 610.8 $\pm$ 40.2 ms, $n = 64$). However, these effects were less marked and statistically insignificant ($F_{3,217} = 9.3$, df = 3.9 $P < 0.01$; haloperidol, $P > 0.05$; dizocilpine, $P > 0.05$; haloperidol + dizocilpine $P > 0.05$, NK-test) (see Fig. 2).

Haloperidol further impaired a dynamic capacity of the animals. As indicated in Fig. 3, haloperidol and/or dizocilpine in the dose tested, only mildly affected mean peak force during movement initiation as compared with saline treatment

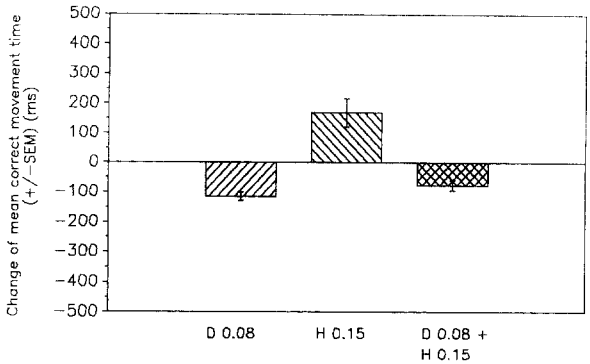

Fig. 2. Change of mean correct movement time (± S.E.M.) induced by systemic administration of haloperidol (0.15 mg/kg i.p., n = 39), dizocilpine (0.08 mg/kg i.p., n = 68) and co-administration of both drugs at this dose (n = 50) tested in one session (10 trials per animal), respectively. The drug-induced changes refer to baseline performance of the same animals (n = 8) tested in a saline (1 ml/kg i.p., n = 64) session (mean movement time: 610.8 ± 40.2 ms). The differences between drug and saline sessions are insignificant (ANOVA followed by Newmann–Keuls test). D 0.08: dizocilpine 0.08 mg/kg; H 0.15: haloperidol 0.15 mg/kg; D 0.08 + H 0.15: dizocilpine 0.08 mg/kg and haloperidol 0.15 mg/kg.

(mean peak force: 0.56 ± 0.04 N, n = 66), ($F_{3,230}$ = 6.06, df = 3.9, $P < 0.01$; dizocilpine, $P > 0.05$; haloperidol, $P > 0.05$; haloperidol + dizocilpine, $P > 0.05$, NK-test). In contrast, haloperidol induced a significant decrease of force slopes from saline level (mean force slope: 8.9 ± 0.7 N/s, n = 66) ($F_{3,230}$ = 4.98, df = 3.9, $P < 0.01$; haloperidol, $P < 0.01$, dizocilpine, $P > 0.05$, NK-test). Therefore the ability of rapid development of force to accelerate in the forward direction was impaired in a way that the time required to generate force is lengthened, as peak force was not altered. Dizocilpine reversed this effect in haloperidol-treated animals ($P < 0.01$, NK-test).

The simple reaction–time task presented here used rapid locomotor initiation as a paradigm to investigate movement initiation in rats. The task was rapidly learned by the animals and the rewarded nature of the task in combination with a gradual food-deprivation was sufficient to produce consistent responses. The device permitted the measurement of parameters known to be sensitive to DA dysfunction (see Introduction) and

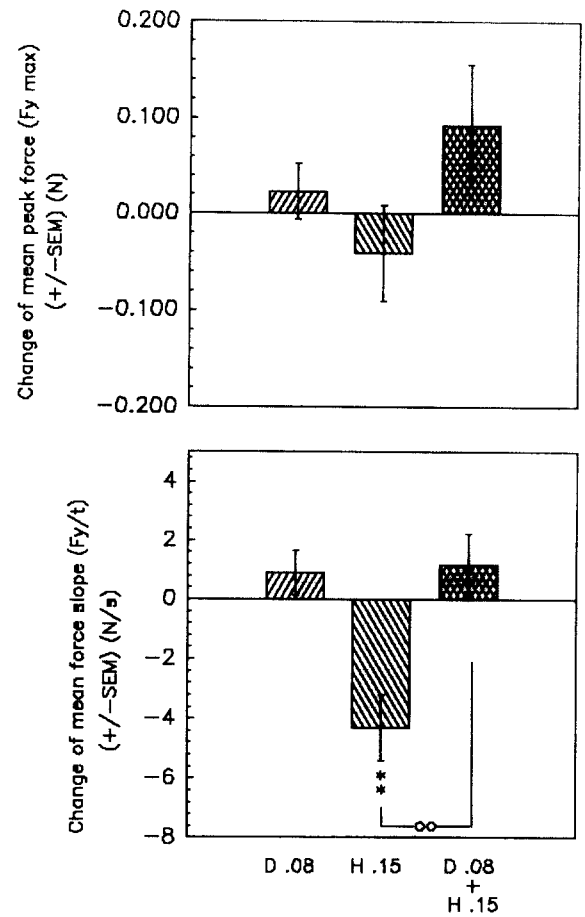

Fig. 3. Change of mean peak force (± S.E.M.) (top) and force slope (± S.E.M.) (bottom) of the accelerative force induced by systemic administration of haloperidol (0.15 mg/kg i.p., n = 29), dizocilpine (0.08 mg/kg i.p., n = 79) and co-administration of both drugs at this dose (n = 60) tested in one session (10 trials per animal), respectively. The drug-induced changes refer to baseline performance of the same animals (n = 8) tested in a saline (1 ml/kg i.p., n = 66) session (mean peak force: 0.56 ± 0.04 N; mean force slope: 8.9 ± 0.7 N/s). Asterisks indicate significant differences between drug and saline session (**$P < 0.01$), circles indicate significant differences between drug sessions (°°$P < 0.01$) (ANOVA followed by Newmann–Keuls test. D 0.08: dizocilpine 0.08 mg/kg; H 0.15: haloperidol 0.15 mg/kg; D 0.08 + H 0.15: dizocilpine 0.08 mg/kg and dizocilpine 0.08 mg/kg).

the results show that systemic DA receptor blockade by haloperidol impaired different aspects of locomotor initiation. Systemic coadministration of dizocilpine, a selective NMDA antagonist, improved these movement initiation deficits.

The RT of the animals measured in the saline condition (range 100–300 ms) of this task correspond well to the response latencies obtained in other paradigms[1,8,13–15]. Haloperidol treatment induced a dose-related increase of RT, accompanied by a decrease of correct trials (movement initiation within 1 s). These findings are consistent with earlier observations of neuroleptic actions on RT supporting the concept of a DA involvement in the initiation of movement[1,13,14]. Previous work using an active avoidance task has shown a similar deficit in the initiation of locomotion. In this study, chlorpromazine suppressed avoidance behavior which is due to a delayed locomotor initiation and not to a disruption of sensory or motivational processes[9]. Thus, the RT deficit seen here most probably reflects impaired movement initiation. However, a decrease of correct trials may indicate an attenuation of the rewarding properties of food reward. Although interference by reward attenuation cannot be ruled out, the animals did not neglect food reward in correct and even incorrect (latency over 1 s) trials. In addition, haloperidol was found to enhance feeding behavior of rats[2].

Regarding the effects of haloperidol on movement time, results indicate that haloperidol caused only a slight increase of movement time. This finding is in line with observations in a discriminated lever release (DLR) task where haloperidol was found to increase response duration due to a slowing in the animal's paw removal from the operandum[6]. However, the increase of movement time was less pronounced and therefore insignificant in our study.

In order to assess animals' dynamic capacities during initiation of locomotion, ground reaction forces were recorded by means of a force platform. Measures derived from resulting force–time patterns of the horizontal component showed a haloperidol-induced decrease of the mean rate of force development, while the mean peak force was not affected significantly. Thus, haloperidol reduced initial acceleration during locomotor initiation. However, a recent study using a DLR task shows that in rats haloperidol increased emitted peak force while pressing a force-sensitive manipulandum and prolonged the mean time for force to drop from its peak value during response termination[6]. These deficits are attributable to haloperidol's tendency to exaggerate static postural support mechanisms, e.g. to remain in the same postural position[4,6]. It is likely that the same underlying mechanism accounts for the different force deficit observed in the present paradigm, since an increase of postural support mechanisms could prevent an appropriate force development during transition from stance to gait. Lower rates of force development are also found in humans with PD tested in a force production task, suggesting a relation between DA dysfunction and deficient regulation of force and time parameters[16].

Dizocilpine, given alone, showed marked stimulatory effects on motor behavior, as indicated by mild but insignificant decreases of RT and movement time as well as slight increases in peak force and force slope. Furthermore, systemic coadministration of dizocilpine reversed haloperidol-induced movement initiation deficits. These findings are congruent with studies showing that dizocilpine antagonised haloperidol-induced catalepsy[11] and exerted locomotor stimulatory effects in monoamine-depleted mice[3]. Regarding underlying mechanisms mediating behavioral effects of NMDA antagonists, it has been proposed that DA and glutamate (via the NMDA receptor) exert opposite actions on striatally mediated behavior[10]. Thus, striatal NMDA receptor blockade antagonizes behavioral impairments due to DA deficits in rats, and these findings have implications for the treatment of PD[12]. Similar mechanisms may account for the antagonism observed here, since movement initiation is highly dependent on intact striatal DA transmission[8,14,15]. However, this conclusion is limited due to the systemic administration of drugs in the present study. Haloperidol-induced motor symptoms resemble in part those of PD in humans, and, therefore, neuroleptic-induced akinesia in animals is sometimes used as a model for this disease. The movement initiation deficits observed here following haloperidol treatment are reminiscent of symptoms in patients with PD and their reversal by dizocilpine further corroborates recent findings suggesting a therapeutic potential

of NMDA antagonists in the treatment of this disease.

The present results should be considered as preliminary awaiting more extensive studies with full dose–response characteristics. We wish to thank Dr. P. Lindenmüller, University of Stuttgart (Institute of Design and Production in Precision Engineering) for developing the force measuring unit. This research was supported by Deutsche Forschungsgemeinschaft (SFB 307).

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