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Destruction of the Noradrenergic System With DSP_4 Potentiates the Behavioral Effects of MK-801 in Rats

IZZETTIN HATIP-AL-KHATIB* AND FUNDA BOLUKBASI†

*Department of Pharmacology, Faculty of Medicine, Pamukkale University, Denizli, Turkey, and †Department of Pharmacology, Faculty of Medicine, Trakya University, Edirne, Turkey

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HATIP-AL-KHATIB, I. AND F. BOLUKBASI. *Destruction of the noradrenergic system with DSP_4 potentiates the behavioral effects of MK-801 in rats*. PHARMACOL BIOCHEM BEHAV **62**(2) 233–237, 1999.—In this study we investigated the effect of lesioning the noradrenergic systems on the behavioral effects of (5R, 10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo [a, d] cyclohepten-5,10-imine hydrogen maleate—MK-801, in rats. The noradrenergic system was lesioned with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride—DSP_4 (60 mg/kg IP). MK-801 increased the locomotor activity and rearing. DSP_4 significantly further increased the hyperlocomotor activity, circling (especially to the left side), sniffing, rolling, and falling that were induced by MK-801. These results showed that destruction of the noradrenergic system increased MK-801-hyperlocomotor activity, ataxia and stereotypy. © 1999 Elsevier Science Inc.

MK-801 DSP_4 Noradrenaline Hyperlocomotor activity Ataxia Stereotypy Rat

(+)-MK-801, (5R, 10S)-(+)-5-Methyl-10,11-dihydro-5H-dibenzo [a, d] cyclohepten-5,10-imine hydrogen maleate, is a highly potent and selective noncompetitive antagonist that acts at the *N*-methyl-D-aspartate (NMDA) receptors-operated ion channels as an open channel blocker. MK-801 dose dependently produces a variety of behavioral effects, such as increased coordinated and/or uncoordinated locomotor activities and stereotypy (2,7,37,46), by modulating several neuronal systems in the brain. MK-801 has been reported to increase serotonin level (48) dopamine and serotonin turnover in the nucleus accumbens, ACC (29,30), increase serotonin $5HT_{1A}$ receptor density in prefrontal cortex and hippocampus (45), and increase DOPAC level and dopamine release, but not noradrenaline or MHPG levels (5,32).

The involvement of different systems in the behavioral effects of MK-801 could be investigated by lesioning or depleting the concerned system. For this purpose various drugs that are known to deplete or lesion the noradrenergic, dopaminergic, or serotonergic system, such as reserpine and DSP_4, could be used. Reserpine induces release of the vesicular amines (catecholamines and indolamines) without any effect on the axonal terminals. Although interaction of reserpine with MK-801 had been demonstrated (46), different effects of short-term and long-term reserpinization had been elucidated (12,35,40,49). On the other hand, DSP_4 induces a selective and long-lasting degeneration of axonal terminals (leaving cell bodies unaffected) of noradrenergic neurons arising from locus coeruleus (14,15) and other brain areas such as hippocampus, frontal cortex, and hypothalamus (4,20,21,39). In addition, DSP_4 could also lesion serotonin and dopamine neurons, but to a lesser extent. It seems from the literature that while DSP_4 selectively affects the noradrenergic neurons, the effects (if any) on dopaminergic and serotonergic systems are somewhat inconsistent. Some studies suggest either no effect of DSP_4 on dopamine/adrenaline (24) and dopamine/serotonin neurons (20), or indicate that the reduction of dopamine and serotonin is only secondary to noradrenaline depletion (50).

In contrast to the well-known NMDA–dopamine interaction, NMDA–noradrenergic interaction has not been investigated to the same extent. In this regard, although most studies had used reserpine, no study of the effect of DSP_4 on MK-801 hyperactivity or MK-801 ataxia could be found in the literature. The validity of any proposed use of the noncompetitive antagonist in any neurodegenerative disease requires investi-

Requests for reprints should be addressed to Dr. Izzettin Hatip-Al-Khatib, Department of Pharmacology-Chairman, Faculty of Medicine, Pamukkale University, kinikli, 20020, P.O. Box 33 Denizli, Turkey.

gation of the effect after destruction of the presynaptic ends rather than exhausting the vesicules. Therefore, the present study aimed at investigating the effect of noradrenergic lesioning with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine hydrochloride—DSP_4, on the behavioral effects of MK-801.

METHOD

Animals

Male Wistar rats, reared in our laboratory, weighing 250–300 g at the time of the experiments were used in the present study. The rats were housed in groups of five in Plexiglas cages (42 × 26 × 15 cm) with litter. The room temperature and humidity were kept at 22 ± 2°C and 55 ± 5%, respectively. Lighting was maintained on a 12 L:12 D cycle (lights on at 0700–1900). The experiments were carried out in the light phase of circadian cycle (0900–1700). The rats had free access to food and water except during the experiments.

Lesioning Procedure

The noradrenergic system was lesioned by single injection of DSP_4 60 mg/kg IP (2 per 10 rats died 8 days after DSP_4 injection). A group of rats received 0.9% saline at a rate of 1 ml/kg and served as control for DSP_4-lesioned group. The dose of DSP_4 was chosen to adequately deplete the systemic noradrenergic terminals (21). Eight rats were included in each group.

Behavioral Studies

The behavioral effects of MK-801 (injected IP at a single dose) were studied 10 days after DSP_4. Of the behavior types the following were investigated: Coordinated locomotor activity (ambulation): movement with all four limbs, not accompanied by any ataxia or stereotypy, that alters the animals position in the cage; Rearing: animal standing with its hind limbs extended to the floor and the forelimbs are mainly in air (or resting on a wall); Circling: complete uninterrupted circle (rotation) with 360° turn of the pelvis and the whole body in one direction around the hind limb and with the support of forelimb ipsilateral to circling direction; Falling: repetitive falling down on rearing; Sniffing: rapid flaring and contracting of the nostril accompanied by movements of whiskers and flaring sounds, recorded as number of uninterrupted flares (not bouts); Rolling: side-to-side movements of the hind limbs not interrupted by crawling. The coordindated locomotor activity was quantified using activity cage (Ugo Basile, Varse, Italy) as mentioned in our previous study (2). Each rat was individually adapted for 15 min to the activity cage and before the start of the recordings, MK-801 was injected at a single dose; then the activity was directly measured, after completion of each injection, for 120 min. The recordings of locomotor activity and rearing were set in a manner so that data at each time point is for 15 min following that point. Rearing was also counted concomitantly with locomotor activity by an experimenter unaware of the treatment.

After measurement of locomotor activity and rearing, each rat was transferred immediately (without any further injection) to a Plexiglas cage and received a further 120 min test of ataxia (falling and rolling) and stereotypy (circling and sniffing). Of the ataxia observed in DSP_4 group received MK-801, the ataxic falling had predominated the other categories of ataxia. Each type of the ataxia/stereotypy was quantified by a separate experimenter, blind to experimental treatments, and the data were expressed as total number during each observation period.

Drugs

MK-801 hydrogen maleate (Dizocilpine maleate) and DSP_4 hydrochloride were purchased from Research Biochemicals International (RBI, Natick, MA). MK-801 and DSP_4 were dissolved in sterile isotonic 0.9% saline. The IP administration was at a volume of 1 ml/kg.

Statistical Analyses

The results of ambulation and rearing were analyzed by two-way analysis of variance (ANOVA) with repeated measure on one factor in the same animal (recordings replicated at each time interval) to evaluate the effect of dose, time and dose × time interaction followed by pairwise comparisons using Newman–Keuls post hoc test if significance ($p < 0.05$) was indicated. The independent factor is dose (subjects were injected once only) and the dependent factor is time (repeated measure). A check on the homogeneity was carried out by use of Bartlett's test. Data for ataxia, circling, and sniffing were expressed cumulatively for the experimental period (120 min). Circling (left-right) was analyzed by ANCOVA with *t*- and LSD (least significant difference) tests. Mean difference higher than the calculated LSD value indicates a significant effect. Falling, sniffing, and rolling were analyzed by Mann–Whitney *U*-test. All data are presented as means ± standard error of means with $n = 8$ per each group.

RESULTS

Effect of MK-801 in DSP_4-Lesioned Rats

Effects on locomotor activity and rearing. The effects of MK-801 at 0.01–0.30 mg/kg were investigated. The maximum hyperlocomotor and rearing-increasing effects were obtained at 0.1 mg/kg. This dose was chosen for investigating the effects of DSP_4 on MK-801. On the other hand, DSP_4-lesioned rats appeared asleep and aggregated at cage angles when in the housing cage, especially after the third day.

Figure 1 shows that DSP_4 reduced the locomotor activity during the 120-min period after administration, but the effect was significantly ($p < 0.05$) different from saline group for 60 min. This could be attributed to a decline in the motor activity of intact-saline group, possibly due to the effect of habituation. MK-801 produced a significant hyperlocomotion in both DSP_4-lesioned as well as in the intact rats. However, the effect of MK-801 in DSP_4-lesioned rats was significantly higher than its effect in the intact rats, $F(1, 14) = 9.12$, $p < 0.009$. The effect of MK-801 was increased by time, $F(8, 112) = 3.05$, $p < 0.004$. A significant lesion × time interaction was detected, $F(8, 112) = 1.88$, $p < 0.05$, indicating different profiles for the effect of MK-801 in intact and DSP_4-lesioned rats. The effect of MK-801 was decreased after 45 min in the intact rats. On the other hand, the effect of MK-801 exhibited two peaks in DSP_4 rats: the first one at 15 min, and the second one at 90 min. The effect then decreased after 105 min, perhaps due to prevalence of stereotypy. DSP_4 did not change the effect of MK-801 on rearing to any significant level.

MK-801-Induced Ataxia and Stereotypy in DSP_4-Lesioned Rats (Fig. 2)

Of the ataxia, MK-801 induced greater falling ($p < 0.001$) and rolling ($p < 0.01$) in DSP_4-lesioned rats compared with the intact rats. On the other hand, MK-801 evoked stereo-

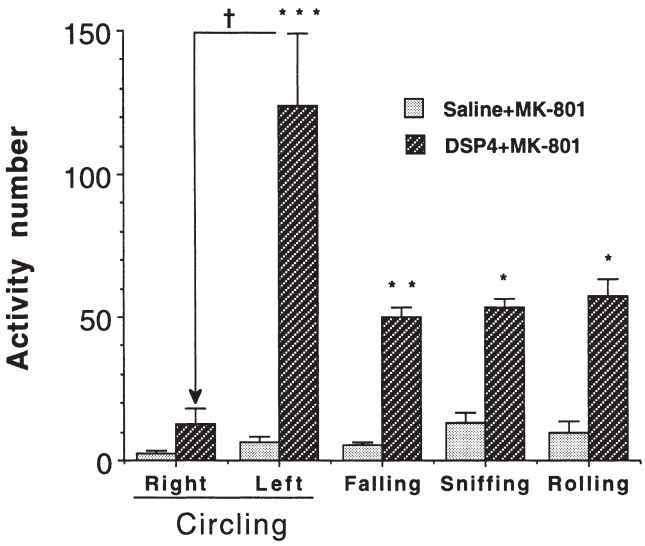

FIG. 1. Effect of DSP_4 (60 mg/kg IP) on the hyperlocomotor activity induced by MK-801 (0.1 mg/kg IP). The experiments were carried out 10 days after injection of DSP_4. Each point represents the mean ± SE obtained from eight rats per group. 0 indicates that the rats were placed in the activity meter and the locomotor activity was immediately recorded after injection of MK-801. Significant differences ($p < 0.05$): DSP_4 + MK-801 vs. intact (saline) + MK-801 (*); or saline + MK-801 vs. saline + saline (†); or saline + saline vs. DSP_4 + saline (#). The intact (saline) + saline group received isotonic 0.9% saline solution (1 ml/kg IP) and run in parallel with the DSP_4 group.

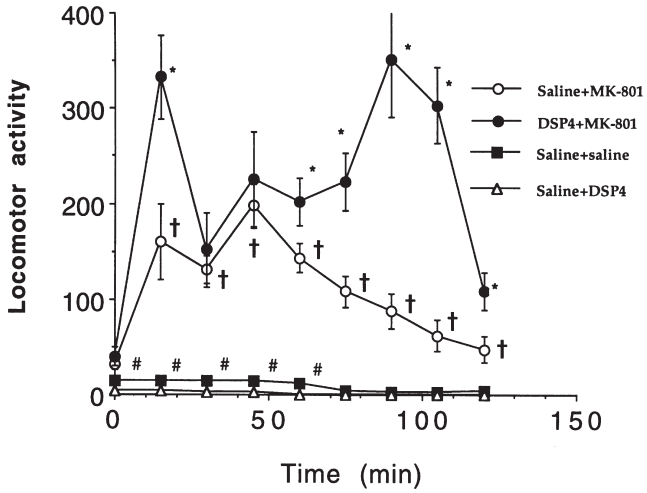

FIG. 2. Circling, falling, rolling, and sniffing induced by MK-801 (0.1 mg/kg IP) in rats, 10 days following pretreatment with either saline (intact rats) or DSP_4 (60 mg/kg IP). The values are expressed as mean ± SE, and represent cumulative data for 120 min; $n = 8$ rats per group. The observation was started after completing the 120 min duration of locomotor activity measurement. *$p < 0.01$, **$p < 0.001$, ***$p < 0.0001$ vs. saline + MK-801; †Indicates a significant difference ($p < 0.001$) from circling to right side of the same group.

typed circling in both intact and DSP_4-lesioned rats. However, DSP_4 significantly increased MK-801 circling, $F(1, 13) = 18.04$, $p < 0.001$, for the main effect. The results also showed that MK-801 induced a greater circling to the left side than to the right side, $F(2, 13) = 9.62$, $p < 0.003$. The circling bias to the left side (left side − right side ÷ total circling × 100 determined according to Ziegler and Szechtman, 1990) was 46.39 and 81.34% for intact and DSP_4-lesioned rats, respectively. In the intact rats the circling to the left side was higher than circling to the right side, but the result did not reach a significant level. On the other hand, in the DSP_4-lesioned rats the effect reached significant level [mean difference = 111.2, LSD = 30.47; $t(6) = 8.93$, $p < 0.001$]. Moreover, analyses of data showed that although a higher circling to the right side was observed in DSP_4 rats, compared with the effect in intact rats, the difference did not reach significant level. On the other hand, the circling to the left side that was induced by MK-801 in DSP_4-lesioned rats was significantly higher than that induced in intact rats [mean difference = 117.4, LSD = 31.55; $t(12) = 8.11$, $p < 0.0001$). MK-801 also increased sniffing ($p < 0.01$) in DSP_4-lesioned rats compared with the intact rats.

DISCUSSION

This study demonstrates that disruption of the noradrenergic system by DSP_4 intensified MK-801 hyperlocomotion in the first 2-h postinjection period, while produced motor syndrome thereafter.

The hyperlocomotor activity produced by MK-801 in this study is consistent with the results showing that MK-801 produced hyperactivity, not associated with stereotypy, during the first 2 h after injection (9,34,41,46). Moreover, our results are also in line with those in which it is reported that either hyperlocomotion (at the beginning, shortly after injection) or stereotypy (at higher doses or after 120 min) was produced by MK-801 (7,52). This activity is attenuated by prazosin (28). It seems to depend on the functional state of the monoaminergic system (44), and the association between dopamine and excitatory amino acids which occurs postsynaptically in ACC (36). Moreover, the hyperlocomotion produced by 0.1 mg/kg of MK-801 may involve a synergistic interaction with dopamine receptors (31).

DSP_4 has been shown to elicit a selective depletion of dopamine-β-hydroxylase (27). It reduces noradrenaline uptake (8) and its level by 60–80% (13). The effect of DSP_4 is specifically on the noradrenergic neuronal system and long lasting (22). At 60 mg/kg (the dose used in this study) the effect of DSP_4 is significantly obtained in locus coeruleus (14,15), hippocampus, frontal cortex, and hypothalamus (21). DSP_4 retards motor activity (6). In this study, DSP_4 also retarded motor activity of rats, especially during the first 60 min observation period. It did not decrease the effect of MK-801, but instead it further increased the effect of MK-801 on locomotor activity. This finding closely parallels the modification by DSP_4 of the effect of amphetamine (10). Moreover, the increase of MK-801 hyperlocomotion could be ascribed either to removal of the inhibitory effect of noradrenaline via α_2 receptors localized primarily on the afferent terminals (25,33), or to increased sensitivity of β-adrenoceptors induced by DSP_4 (11). The depletion of noradrenergic function could result in compensatory mechanism(s) or modulation of other neurotransmitters such as GABA, the stimulation of which (via $GABA_B$) within the dorsal raphe is reported to elicit hyperactivity (47). It could also be a kinetic one: elimination of MK-801 may be impaired by decreased blood pressure in DSP_4-lesioned rats. Moreover, although depletion of seroto-

nin does not alter rat baseline motor and exploratory activity, it may enhance MK-801 hyperlocomotor activity, but indirectly by displaying a synergistic disinhibition of MK-801-induced activation of dopaminergic neuron (38). This effect could also attribute to enhancement of MK-801 hyperlocomotor activity induced by DSP_4 in this study.

Modulation of the effect on the dopaminergic transmission consequent to lesion of noradrenergic neuronal system and depletion of noradrenaline seems to be of a prime importance in the effect of MK-801 in DSP_4-lesioned rats. This is because although MK-801 affects serotonergic mechanisms besides the dopaminergic mechanism, only the latter seems to be correlated with the MK-801 hyperactivity. MK-801 increases serotonin metabolites in dorsal striatum (30), which plays a lesser role than ACC in MK-801 hyperactivity (19), and only at high doses (32), which produce a variety of motor syndrome and decrease locomotor activity. Moreover, while all studies revealed the selectivity of effect of DSP_4 on noradrenaline, only minor depletion of serotonin (24) or dopamine and serotonin secondary to noradrenaline depletion (50) were reported.

It should be noticed that DSP_4 lesioning is different from reserpinization. In the latter, the axonal terminals are intact, and the duration of reserpinization seems important in modifying the effect of MK-801. Short-term reserpinization is reported to inhibit MK-801 hyperlocomotion, but long-term reserpinization did not inhibit MK-801 hyperlocomotion (12,35,40).

An interesting observation in this study was the circling and other stereotypes produced by MK-801 in DSP_4-treated rats. These categories of MK-801–induced behavior could be distinct from the hyperlocomotion. They exhibit different sensitivity to the drugs such as clozapine, which inhibits the hyperlocomotion but not the stereotypy induced by MK-801 (16).

MK-801 circling was characterized by a preferential circling to the left side. A circling asymmetry and endogenous hemispheric asymmetry had been reported in rats (23). An ipsilateral rotation had also been reported for MK-801 in rats with unilateral striatal lesions induced by transient occlusion of middle cerebral artery or by 6-OHDA (18). The MK-801–induced circling could be displayed mainly in the various parts of the basal ganglia such as striatum, globus pallidus, and subthalamus (42). However, the ACC also contributes to the locomotor components of drug-induced rotation (26). Although positive modulation of the dopaminergic activity is thought to greatly mediate MK-801 circling, sigma sites (by interacting with the dopaminergic pathways) also modulate circling of rats (3). The left-side preference observed in this study could be attributed to increased dopamine, DOPAC, and HVA in the globus pallidus (1). The dopaminergic activation could also take place in the striatum. It is unilateral and sets the directionality of turning independent of any hind-limb motor asymmetry (51). In this study, MK-801–induced dopaminergic activation may be preferentially displayed in the right side, because unbalanced dopaminergic activation on one side induces circling towards the opposite side (43). The glutamatergic neurons projecting to the ACC could also attribute to the circling behavior, in a different direction, depending on the degree of dopamine DA_2 receptor stimulation (44).

As to the falling, it is possibly correlated with affinities for PCP receptor (17). However, according to the results of the present study, it could be suggested that lesioning the noradrenergic system could enhance MK-801–induced falling.

In conclusion, the present results showed that depletion of the noradrenergic function facilitated the effect of MK-801 on the locomotor activity during the first 2-h period, and produced extensive circling to the left side besides falling, rolling, and sniffing thereafter. The increased effect of MK-801 by loss of the axonal terminals caused by DSP_4 could be an indication of the efficacy of MK-801 (and probably the other noncompetitive NMDA antagonists) in human neurodegenerative cases.

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