Effect of alpha1-adrenergic antagonist prazosin on behavioral alterations induced by MK-801 in a spatial memory task in Long Evans rats

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Summary

Animal models of neuropsychiatric disorders are current topics in behavioral neuroscience. Application of non-competitive antagonists of NMDA receptors (such as MK-801) was proposed as a model of schizophrenia, as it leads to specific behavioral alterations, which can be partly analogized to human psychotic symptoms. This study examined an animal model of schizophrenia induced by a systemic application of MK-801 (0.15 and 0.20 mg/kg) into rats tested in the active allothetic place avoidance (AAPA) task. Previous studies suggested that MK-801 may interact in vivo with other neurotransmitter systems, including noradrenergic system. Our experiments therefore evaluated the hypothesis that both locomotor stimulation and deficit in avoidance behavior In AAPA task induced by this drug would be reversible by application of alpha1-adrenergic antagonist prazosin (1 and 2 mg/kg). The results showed that both doses of prazosin partially reversed hyperlocomotion induced by higher doses of MK-801 and an avoidance deficit measured as number of entrances into the shock sector. Interestingly, no effect of prazosin on the MK-801-induced decrease of maximum time between two entrances (another measure of cognitive performance) was observed. These results support previous data showing that prazosin can compensate for the hyperlocomotion induced by MK-801 and newly show that this partial reduction sustains even in the forced locomotor conditions, which are involved in the AAPA task. The study also shows that certain parameters of avoidance efficiency may be closely related to locomotor activity, whereas other measures of cognition may more selectively reflect cognitive changes.

Keywords: prazosin, MK-801, place avoidance, memory, locomotion, animal model of schizophrenia

Introduction

Animal models of schizophrenia-like behavior based on the blockade of NMDA receptors have proven to be a very promising way of mimicking schizophrenic psychoses in the laboratory conditions. Application of NMDA receptor antagonists such as phencyclidine (PCP), ketamine, and MK-801 leads to specific alterations in behavior in both animals (Carlsson and Carlsson 1989, Deutsch et al. 2002, Becker et al. 2003) and humans (Bubenikova-Valesova et al. 2008a), which are being considered valid pharmacological models of psychotic illness (Andiné et al. 1999, Rujescu et al. 2006).

MK-801 is a non-competitive antagonist of NMDA subtype of glutamate receptors which acts by means of open-channel blockade. Systemic administration of MK-801 in laboratory rats results in a variety of behavioral symptoms, including stereotypical behaviors, hyperlocomotion, ataxia (at higher doses; Nilsson et al. 1991) and social withdrawal (at lower doses; Rung et al. 2005). These behavioral changes are reversible by antipsychotic medication applied to the animals and considered analogues of positive and negative symptoms of psychoses in humans. Recently, a cognitive deficit in the active place avoidance (Vales et al. 2006) and other tasks following the administration of MK-801 was studied more intensively (Mandillo et al. 2003, Vales et al. 2006), and it has been shown to be sensitive to treatment with atypical antipsychotics (Bubenikova-Valesova et al. 2008b). These findings suggest that the application of MK-801 may serve as an animal model of schizophrenia with highly predictive validity.

The active allothetic place avoidance (AAPA) task was designed in our laboratory about ten years ago (Bures et al. 1998), and is now used by our and other groups for evaluating the spatial cognition abilities in rats, including pharmacological influences on cognitive performance (Stuchlik and Vales 2005, Pastalkova et al. 2006, Stuchlik and Vales 2008). In this task, animals are required to move over a slowly rotating arena and to avoid a shock sector defined in the stable coordinate frame of the experimental room. The AAPA task has the advantage of testing the effects of given experimental manipulations on both locomotion and cognitive performance, and the performance in the task has been shown to require both allocentric spatial memory and cognitive coordination, dependent upon the hippocampus (Wesierska et al. 2005). The latter is usually referred to as an ability to segregate spatial stimuli of the environment into coherent representations of the arena and experimental room and to select the coordinate frame of the room as relevant for navigation (Kubik et al. 2006), as the to-be-avoided sector is defined in the room frame. Recent results have demonstrated that this task is a very suitable behavioral paradigm for testing the animal model of schizophrenia induced by the application of MK-801 (Stuchlik et al. 2004; Stuchlik and Vales 2005; Bubenikova-Valesova et al. 2008b).

The present study was aimed at further evaluating the behavioral changes induced by MK-801 and to determine to what extent these alterations are reversible with an antagonist of alpha1-adrenoceptors, prazosin. Previous research suggested that prazosin may interact with MK-801 in regulation of locomotor activity (Maj et al. 1992; Mathé et al. 1996) and in the present study we aimed at assessing the effect of prazosin on the MK-801-induced behavioral changes in active allothetic place avoidance (AAPA) task, which has an advantage of assessing locomotion and avoidance behavior simultaneously. Previously it was shown that changes in the locomotion may alter avoidance behavior in the place avoidance task; nevertheless, the present study employed two parameters of avoidance efficiency to determine which one would be more related to locomotor changes and which would describe the potential cognitive changes more specifically.

Methods

Animals

All animal manipulations were done in accordance with the Animal Protection Code of The Czech Republic and appropriate directives of the European Union (86/609/EEC). Seventy-two male adult Long-Evans rats (3-5 months old, weighing 300-400 g) obtained from the Institute's breeding colony were used in the experiment. Animals were housed in 30x30x40cm plastic transparent cages in pairs in a laboratory air-conditioned animal room with a constant temperature (21ºC) and 12:12h light/dark cycle (lights on at 7:00). Rats were implanted with a low-impedance subcutaneous needle piercing the rat's skin between its shoulders, removing the sharp end and creating a small loop on it with tweezers. The loop prevented the needle from slipping out and provided purchase for an alligator clip, which connected a shock-delivering cable. Water and food was available *ad libitum*.

Drugs and drug applications

Prazosin hydrochloride (prazosin) and MK-801 (dizocilpine maleate) were both purchased from the Sigma Aldrich, Czech Republic. Prazosin was dissolved in distilled water at concentrations 0.25 mg/ml and 0.5 mg/ml and injected i.p. at a volume of 4 ml/kg (corresponding to 1 mg/kg and 2 mg/kg) 21 min prior to behavioral screening. Saline (0.9% NaCl) at a volume of 4 ml/kg was injected as a control for prazosin, also 21 min before testing. MK-801 was dissolved in saline (0.15 mg/ml and 0.20 mg/ml) and injected intraperitoneally (0.15 mg and 0.20 mg/kg b.w.) 20 min prior to behavioral testing. Isotonic saline (0.9% NaCl; 1ml/kg b.w., i.p.) was injected as a control solution for MK-801. A control group (n=8) received two saline injections, 4 ml/kg (21 min before testing) and 1 mg/kg (20 min prior to testing). All groups thus received the same volume of liquid per 1 kg of body weight. Each group in the present study consisted of eight rats. A dose range used in this study was based on previous results of our and other groups (Mathé et al. 1996, Stuchlik et al. 2004, Stuchlik and Vales 2005, Stuchlik and Vales 2008), which established the effective doses of MK-801 and prazosin. Our previous studies and pilot experiments showed that in adult satiated Long-Evans rats, 0.15 mg/kg of Mk-801 is a threshold dose for eliciting an avoidance deficit, which appears to be accompanied by hyperlocomotion in this strain.

Apparatus and behavioral procedure

The active allothetic place avoidance (AAPA) apparatus was described in detail previously (Stuchlik et al. 2007). Briefly, it consisted of a smooth circular arena (82 cm in diameter), enclosed by a 30 cm high transparent wall and elevated 1 m above the floor of a 4 x 5 m room containing many extramaze cues. Each animal was initially placed onto the constantly rotating arena (1 rpm) opposite a shock sector. Animals had to avoid an unmarked, 60° sector defined solely by its relationships to distal room cues. The shock sector remained in a stable spatial position throughout the training. The rats wore a latex harness, which carried an infrared light-emitting diode. A computer-based tracking system (iTrack; Bio-Signal Group, USA) located in an adjacent room recorded the rat's position every 40 ms. Position time series were stored for off-line analysis (TrackAnalysis; Bio-Signal group, USA). Whenever the rat entered the to-be-avoided sector for more than 500 ms, the tracking system delivered a mild shock (50 Hz, 0.5 s, 0.4-0.7 mA) and counted an entrance. If the rat did not leave the sector, additional shocks were given every 1200 ms, but no more entrances were counted until the rat left the sector for more than 300 ms. Shocks were delivered through the implanted needle on rat's back and the arena floor (the highest voltage drop was between rats' paws and grounded floor, therefore animals perceived the shock presumably in their paws). This shocking procedure has previously shown to be very efficient, leading to rapid avoidance behavior (Kubik et al. 2006, Stuchlik and Vales 2008). The shock current was individualized for each rat to elicit an escape response. In most cases, animals responded appropriately to 0.5 mA. There were four daily sessions of AAPA training, each lasting 20 min, and carried out between 10:00 and 14:00.

Design of experiments and data analysis

There were four daily sessions of AAPA training, each lasting 20 min, and carried out between 10:00 and 14:00. Intervals between the beginnings of the sessions were 24 hours. Drugs or saline were injected prior to every session. Only the data from the fourth, last session were taken into analysis, as being representative of the asymptotic performance of the control animals. This design has previously shown to be very informative concerning drug effects on final stage of learning (Vales et al. 2006; Bubenikova-Valesova et al. 2008b). Moreover, close inspection of the present data (not shown) demonstrated that analyzing data from initial stages of learning yielded similar results as analysis of the final day of learning.

The following parameters were extracted from the offline processing and analyzed: **The total distance** traveled per final session reflecting the active locomotion was measured in the coordinate frame of the arena as a sum of linear distances of points recorded every second; this sampling eliminated non-locomotor movements such as shivering (Stuchlik et al. 2008). Two measures of spatial efficiency were the **number of errors** per final session (number of entrances into the shock sector) and maximum time between two entrances in a session (**maximum time avoided**), the latter reflecting maximum remembrance of the shock sector location. The data were analyzed with a two-way ANOVA (prazosin application x MK-801 application); the prazosin and MK-801 applications being independent factors. Post-hoc analysis was performed using a Newman-Keuls test. Data in the graphs are means ± S.E.M in the final session. Significance was accepted at a 5% level of probability.

Results

Visual inspections of the rats prior and after injections revealed no signs of discomfort in the animals, no vocalizations or increased defecation were observed. All animal responded to the shocks in the arena with mild startles, often accompanied by rapid escape reactions, directed towards the safe part of the arena. This suggests that the perception of the electric shocks was preserved, despite the application of drugs. Control rats and animals treated with prazosin alone rapidly learned to avoid a sector, and this avoidance was at an asymptotic level by the final day of training. Illustrative tracks of typical rats in the experimental groups are depicted in Fig. 1.

Effect of prazosin on the MK-801-induced hyperlocomotion

Analysis of locomotor activity measures the total distance walked in the final session revealed that it was affected by application of both MK-801 and prazosin. A two way ANOVA (prazosin application x MK-801 application) revealed a significant main effect of prazosin application ($F(2,63) = 14.35$, $P = 0.0001$), and a significant effect of MK-801 application ($F(2,63) = 8.42$, $P = 0.0005$). A significant interaction between these two factors was also found ($F(4,63) = 5.83$, $P = 0.0005$). However, post-hoc test revealed no differences between control group and groups with prazosin alone (Fig. 2, top panel). Therefore, prazosin co-applied with MK-801 was responsible for the overall significant effect of prazosin application. The post-hoc analysis of the single factor MK-801 application showed that higher dose of MK-801 (0.20 mg/kg) increased the locomotion significantly with respect to the control group ($P < 0.05$). Lower dose of MK-801 (0.15 mg/kg) also slightly increased the total distance walked (Fig. 2, top panel), but this elevation did not reach the statistical significance ($P=0.06$). More informative was a post-hoc analysis of the interaction, which revealed that both doses of prazosin (1 mg/kg and 2 mg/kg) significantly alleviated the locomotor-stimulating effect of 0.20 mg/kg of MK-801. No significant ameliorating effect of prazosin on the lower dose of MK-801 was found, probably due to the lack of significant increase in locomotion after this lower dose. However, a non-significant reduction of mildly increased locomotion in animals co-administered with 0.15 mg/kg MK-801 and prazosin was observed, as can be seen in Fig. 2, top panel. From the above mentioned it can be concluded that both doses

of prazosin were capable of partly compensating the locomotor stimulation induced by the higher dose of MK-801.

Effect of prazosin on the spatial avoidance deficit following MK-801 treatment

Analysis of the number of errors in the final sessions demonstrated that this parameter was affected by the treatment with both prazosin and MK-801. A two-way ANOVA (prazosin application x MK-801 application) showed a significant main effect of prazosin administration ($F(2,63) = 5.64$; $P < 0.01$) and MK-801 administration ($F(2.63) = 57.1$; $P < 0.00001$) and a significant interaction between these two factors ($F(4,63) = 3.13$; $P < 0.05$). Like in total distance, there was no difference between the control group and groups with prazosin alone (Fig. 2, middle panel); again indicating that prazosin co-applied with MK-801 was responsible for the overt main effect of prazosin administration. A post-hoc analysis of the MK-801 factor revealed that the higher dose of MK-801 (0.20 mg/kg) significantly increased the number of errors ($P < 0.001$) and thus decreased the spatial performance (Fig. 2, middle panel). The lower dose of MK-801 (0.15 mg/kg) only insignificantly decreased spatial performance measured by the number of errors ($P = 0.064$).

A post-hoc analysis of the interaction revealed that prazosin at doses of 1 mg/kg and 2 mg/kg decreased the elevated number of errors after 0.20 mg/kg of MK-801; however, this reduction did not reach the levels of the control group. We observed no effect of either dose of prazosin on the mild increase in the number of errors after the lower dose of MK-801, again probably due to the non-significant increase in errors after this dose. This suggests that similar to the locomotor activity, both doses of prazosin were able to partially alleviate the behavioral impairment observable after the higher doses of MK-801, however these results also suggest that this parameter is probably very closely correlated with locomotion (see Discussion).

Analysis of the maximum time avoided in the final session demonstrated that this parameter was affected by MK-801 application, but not by prazosin application. A two-way ANOVA found a significant main effect of MK-801 application ($F(2,63) = 42.89$; $P < 0.0001$), but no effect of prazosin application ($F(2,63) = 0.23$; $P > 0.05$). No interaction between the factors was found ($F(4,63) = 0.31$; $P > 0.05$). The post-hoc analysis of the single factor of MK-801 application indicated that both doses of MK-801 decreased the maximum time avoided and thus impaired the spatial avoidance in the AAPA task. Prazosin was found to have no effect on this parameter, either when injected alone, or in combination with MK-801, as is documented by an absence of interaction. There was a slight, but insignificant tendency to increased maximum time avoided in rats co-administered with 0.15 mg/kg MK-801 and prazosin.

It can be concluded that both doses of MK-801 dose-dependently impaired performance measured by maximum time avoided. However; prazosin was not capable of significantly alleviating the avoidance deficit measure by this parameter.

Discussion

Results of the present study show that systemic administration of MK-801 results in locomotor stimulation and deficit in the AAPA task performance in the rats. Prazosin (1 mg/kg and 2 mg/kg) was found to be capable of partly ameliorating the locomotor hyperactivity induced by higher dose of MK-801 (0.20 mg/kg). Elevated number of entrances into shock sector after this dose was also alleviated by both doses of prazosin (1 mg/kg and 2mg/kg).The findings of increased locomotion and avoidance deficit after MK-801 are in accordance with previous studies from our and other laboratories, which convincingly demonstrated behavioral alterations induced by MK-801 (Maj et al. 1991). It was proposed previously that application of MK-801 can serve as a suitable model of schizophrenia-like behaviors in rodents (Andiné et al. 1999). For example, Nilsson et al. (2001) found that application of MK-801 in mice induces hyperactivity and other changes, which

are reversible by antipsychotics. A recent study in our laboratory (Vales et al. 2006) pointed to the cognitive disturbances following the MK-801 application and showed that behavioral impairments following treatment with MK-801 can be induced in both Wistar and Long-Evans rats. The present results are also in agreement with another study from our laboratory (Stuchlik and Vales 2005), which described hyperlocomotion and a dose-dependent impairment of avoidance behavior after the application of 0.15 and 0.20 mg/kg of MK-801 in Long-Evans rats. The present data, together with the previous results, indicate that MK-801 induces specific behavioral changes in rats tested in the AAPA task, which appears to be a very promising behavioral paradigm for studying drug-induced deficits in laboratory rats.

Another finding of this paper is that prazosin alone did not significantly impair behavior and locomotion at the doses studied (1 and 2 mg/kg). This result is in accordance with the data in our recent study (Stuchlik and Vales 2008), showing that prazosin produces behavioral impairments in the AAPA task at higher doses (4 mg/kg). The effect of prazosin on other behavioral tasks was also studied by Puumala et. al. (1998) and it was found that stimulation of alpha1-adrenoceptors enhances memory in the Morris water maze, but blockade of the same receptors with prazosin had no effect on the performance. Administration of prazosin was also found to have a very weak or no effect on working memory (Puumala and Sirvio, 1997), which is also an important function necessary for the AAPA performance. These results suggest that application of lower doses of prazosin alone has a minor, if any; effect on the locomotion and cognitive functions tested in the spatial memory paradigms.

Prazosin was found to diminish the MK-801-induced hyperactivity in the present experiment, although not to the levels of intact animals. This finding supports the previous findings from other laboratories (Loscher and Honack 1992, Mathé et al. 1996) showing that pre-treatment with prazosin efficiently alleviates the hyperlocomotion induced by MK-801. However, the present study differs from previous ones in one important aspect. The AAPA task involves forced locomotor activity rather than spontaneous (since the animals are trained to move in a direction opposite to arena rotation) and therefore, it shows that the effect of prazosin on the hyperlocomotion is rather robust, lingering even in the forced locomotion condition. On the other hand, Maj et. al. (1991) reported no decrease of locomotor stimulation induced by MK-801 by prazosin, but at a different dose and time schedule than in our present study (3 mg/kg, orally, 90 min prior to testing; see also Maj et al. 1992). However, the same study (Maj et al. 1992) demonstrated that repeated prazosin treatment attenuated MK-801-induced hyperlocomotion. Our present results support the view that treatment with prazosin can partially reduce the locomotor stimulation induced by MK-801. The exact mechanism of effect of prazosin on this hyperactivity is not known, but it seems that this effect is related to the excessive release of dopamine in the mesolimbic areas following administration of MK-801, which has been demonstrated to be blocked by pre-treatment with prazosin (Mathé et al. 1996).

An amelioration of avoidance deficit induced by MK-801 by pre-medication with alpha1-adrenoceptor antagonist prazosin was observed in only one of the parameters measured (number of entrances). It should be pointed out that this parameter is likely closely related to the alterations in locomotor activity, henceforth the **relative reduction of number of errors cannot be simply interpreted as improvement of cognitive functions after application of prazosin**. **Our results also show that prazosin had no effect on the MK-801-induced impairment in another parameter of cognitive performance, maximum time avoided in the last session, in spite of decreased hyperlocomotion.**

The present study therefore suggests that maximum time avoided may be a substantially more sensitive measure of changes in cognitive efficiency, than the number of entrances into the shock sector, which was found to be very closely related to alterations in locomotor activity. In some sense, this finding is rather intuitive, because in the AAPA task, an animal is required to precisely move in the arena, walking in a

direction opposite to arena rotation, otherwise it would be always passively transported into shock sector. Hyper- or hypolocomotion may thus be closely correlated with increased number of entrances without selective influence upon cognitive function. The present results point to an importance of the parameter of maximum time avoided, as probably very sensitive measure of putative cognitive alterations.

The AAPA task might also be considered in relation with other behavioral paradigms used for examining the locomotor activity and navigational behavior in laboratory rodents. It should be emphasized that contrarily to classical tasks for studying the locomotion, such as the open-field, behavior in the AAPA task is more complex and includes more aspects which are mutually interrelated. First, the locomotion in the AAPA task is not purely spontaneous, as the animals are forced to move in a direction opposite to arena rotation, otherwise they would be passively transported to the shock sector (Stuchlik et al. 2007). Second, the locomotor activity and changes in number of entrances after particular pharmacological manipulation are most likely highly correlated (see above), therefore the alterations of avoidance efficiency must be interpreted carefully in case there are accompanying changes in locomotion. The spatial avoidance aspect of the AAPA task is also rather different from other spatial tasks, such as the Morris water maze, and from simpler memory tasks such as passive avoidance. The spatial accuracy demands of AAPA are lower than in other memory tasks, since the prohibited area occupies rather large part of the environment (consider the 60-degree sector in the AAPA vs. relatively small platform in the watermaze). Moreover, the navigation in the AAPA task was demonstrated to be highly dependent on the hippocampus, and requiring a "cognitive coordination" (Wesierska et al. 2005), which is usually explained as an ability to segregate both proximal and distal orienting cues from the environments into coherent representations of the arena and room, and to select the room frame as the only relevant for navigation.

It can be concluded that the present results support the current concept that antagonizing the alpha1-adrenergic receptors may partly compensate for the locomotor stimulation induced by a non-competitive NMDA receptor antagonist MK-801. The results also demonstrate that this ameliorating effect sustains also during forced locomotion condition (as is in the AAPA task), and it may project into certain parameters of spatial avoidance efficiency. The current findings also suggest under certain conditions, the parameter maximum time avoided may be selectively more informative of the specific changes in cognition than number of entrances, especially when there are accompanying changes in locomotion. The study also supports the notion that the active place avoidance task is a useful behavioral approach in the study of drug-induced locomotor and behavioral disturbances.

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Figure captions.

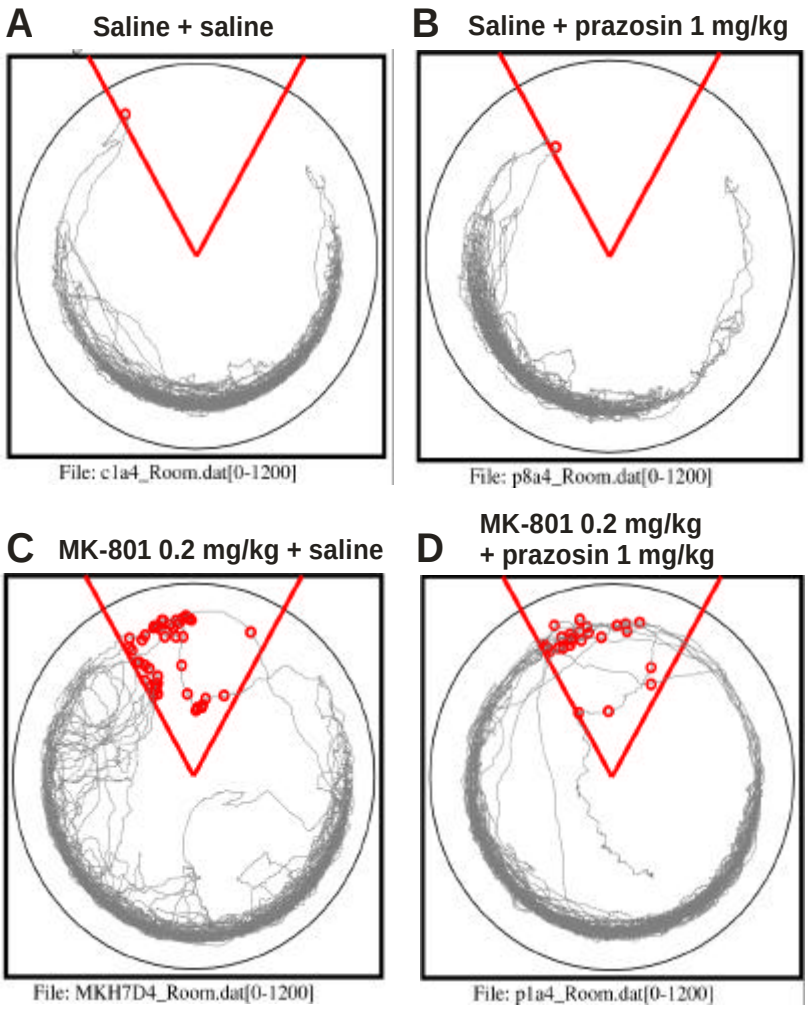

Fig. 1. Example of representative rats' tracks from the final session of active allothetic place avoidance (AAPA) task training. A rat from the control group (***Panel A)*** avoided the area efficiently, as well as a rat treated with 0.1 mg/kg of prazosin only (***Panel B***). An animal treated with MK-801 (0.20 mg/kg; ***Panel C***) exhibited poorer performance. ***Panel D*** shows the track of a rat treated with combination of 0.20 mg of MK-801 and 1 mg/kg of prazosin.

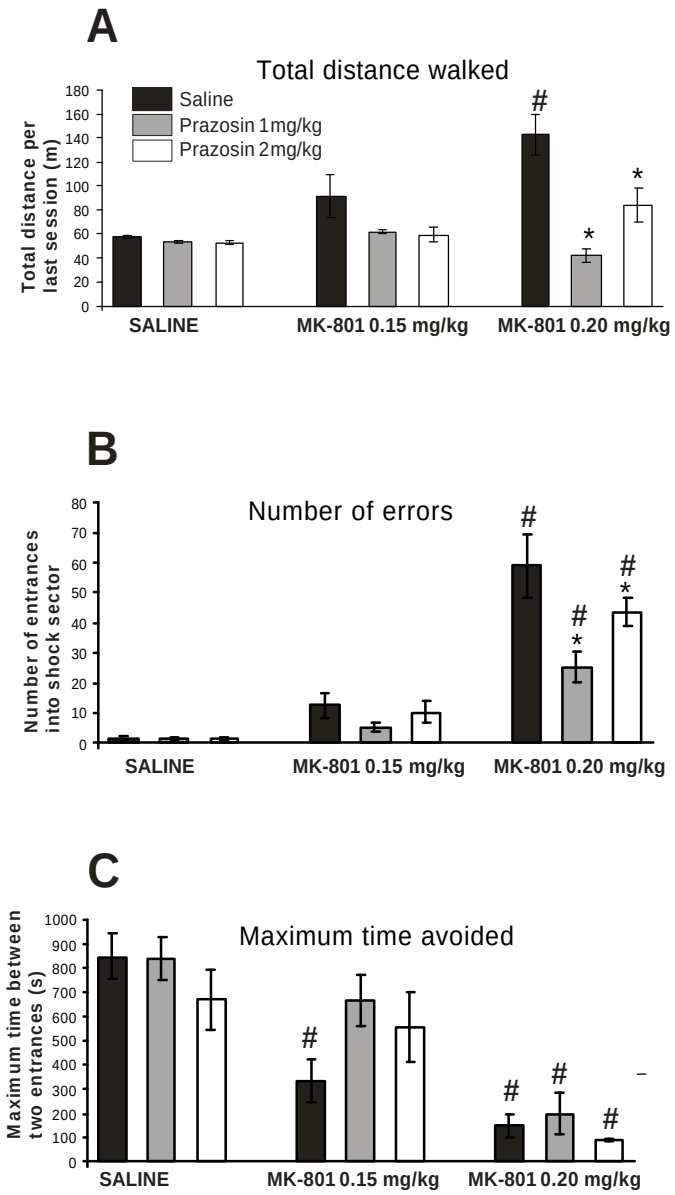

Fig. 2. ***Panel A:*** Effect of separate or combined administration of prazosin and MK-801 on the locomotor activity measured as total distance walked in the final session. Application of prazosin alone did not change the locomotion, whereas administration of MK-801 (0.15 mg/kg and 0.20 mg/kg) caused locomotor stimulation. Prazosin partially alleviated the hyperlocomotion induced by higher dose of MK-801 (0.20 mg/kg). ***Panel B:*** Effect of separate or combined treatment with prazosin and MK-801 on the number of errors. Prazosin alone did not change this parameter, whereas MK-801 (0.20 mg/kg) increased the number of errors significantly. Prazosin (1 and 2 mg/kg) partially ameliorated the disturbing effect of higher dose of MK-801 (0.20 mg/kg), although not to the level of control group. ***Panel C***: The effect of combined or separate administration of prazosin and MK-801 on the maximum time avoided, which was another measure of cognitive performance. MK-801 impaired this parameter dose dependently (0.15 mg/kg and 0.20 mg/kg); prazosin had no effect on it either separately or in combination with MK-801. * $P < 0.05$ with respect to MK-801 (0.20 mg/kg); # $P < 0.05$ with respect to control group.