The Role of NMDA receptors in rat propofol self-administration

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Research article

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Abstract

Aim Propofol is among the most frequently used anesthetic agents, and it has the potential for abuse. The N-methyl-D-aspartate (NMDA) receptors are key mediators of both neural plasticity and development, as well as of addiction and neurodegeneration. Herein we explored the role of these receptors in rat propofol self-administration. Methods Rats were trained to self-administer propofol (1.7 mg/kg/infusion) using an FR fixed ratio schedule of the course of 14 sessions (3 h/day). After training, rats were intraperitoneally administered the non-competitive NDMA receptor antagonist MK-801, and then 10 minutes later were subjected to a propofol self-administration session. Results: After training, rats had acquired the ability to self-administer propofol successfully, as evidenced by a significant and stable rise in active nose-pokes leading to propofol administration relative to control nose-pokes ($P<0.01$) and became stable. Relative to control rats, rats that had been injected with 0.2 mg/kg MK-801 exhibited significantly more propofol infusions ($F(3, 28)=4.372$, $P<0.01$), whereas infusions were comparable in the groups administered 0.1 mg/kg and 0.4 mg/kg. In addition, MK-801 failed to alter numbers of active ($F(3, 28)=1.353$, $P>0.05$) or inactive ($F(3, 28)=0.047$, $P>0.05$) responses in study groups. Animals administered 0.4 mg/kg MK-801 exhibited significantly fewer infusions than animals administered 0.2 mg/kg ($P=0.006$, $P<0.01$). In contrast, however, animals in the 0.4 mg/kg MK-801 group exhibited a significant reduction in the number of active nose poke responses ($F(3, 20)=20.8673$, $P<0.01$) and the number of sucrose pellets ($F(3, 20)=23.77$, $P<0.01$), with increased locomotor activity ($F(3, 20)=22.812$, $P<0.01$). Conclusion These findings indicate that NMDA receptors may play a role in regulating rat self-administration of propofol.

Background

Propofol (2,6-di-isopropylphenol) is an anesthetic agent that has been found to have the potential for recreational abuse, as its intake is associated with pleasant and euphoric feelings[1]. Indeed, one anesthesiologist that had been self-administering propofol in order to relieve stress eventually exhibited propofol-dependence[2]. Animal studies of both self-adminisration and conditioned place preference further support that propofol can provide reinforcement[3–5]. We have previously demonstrated a role for GABA receptors in the ventral tegmental area (VTA) in governing propofol self-administration[6]. We further found that the D1R antagonist SCH23390 was able to mediate a simultaneous dose-dependent reduction in propofol self-administration while also reducing p-ERK/ERK expression associated with D1R in the nucleus accumbens (NAc) [7, 8]. These previous results thus clearly indicate that propofol is susceptible to abuse, but the underlying mechanisms remain uncertain.

Glutamate is known to play key roles in both directly and indirectly controlling drug addiction via regulation of the dopaminergic system[9–11]. Glutamatergic inputs within the VTA increase dopamine release within the NAc and to increase dopaminergic cell activity[12], with glutamate further facilitating dopaminergic transmission, likely via acting at the presynaptic stage to regulate the release of dopamine[13]. Alcohol dependence and withdrawal have both been linked to elevated levels of glutamate

and associated neuroadaptation in rodent and human systems[14]. Dependence on other agents such as heroin, cocaine, and nicotine is similarly associated with clear changes in extracellular levels of glutamate in the VTA, NAc, PFC, and striatum [15, 16]. Propofol has similarly been suggested to alter glutamate levels, with multiple studies having indicated that propofol can inhibit glutamate receptor-mediated excitatory synaptic transmission[17, 18].

N-methyl-D-aspartate (NMDA) receptors are glutamate receptors that play a central role both in governing learning, neuroplasticity, and memory, while also facilitating drug additction. Studies of chronic neuronal exposure to ethanol demonstrated that NMDA receptor activity could be directly influenced by ethanol[19], with similar findings having been made in vivo[20]. The non-competitive NMDA antagonist MK-801 can be systemically administered to animals, and doing so has been shown to suppress the development of dependence upon and tolerance to opioids[21]. MK-801 can similarly inhibit the onset of morphine withdrawal syndrome[22], interfere with normal cocaine self-administration acquisition[23], and alter conditioned place preference study outcomes[24]. Antagonism of NMDA receptors can also change or able responses to other psychostimulant compounds including amphetamines and alcohol[25]. Work in vitro has demonstrated that propofol can drive NMDA receptor inhibition, thereby resulting in the hallucinations that are known to occur following propofol anesthesia[26]. Additional work suggests that when used at an anesthetic dose, propofol can disrupt normal calcium entry into cells induced by agonists of NMDA receptors[27, 28]. These findings thus strongly suggest that there is a link between the NMDA receptor and propofol dependence.

We therefore hypothesized that NMDA receptors play a role in regulating propofol addiction, and to test this we developed a rat propofol self-administration model. Using this model, we then intraperitoneally administered rats with MK-801, and assessed the effects of such administration both on general and propofol-specific activity in these animals.

Methods

Subjects

A total of 80 male Spague-Dawley rats (280–300 g) from the Slac Laboratory Animal Center of Shanhai (Shanhai, China) were obtained and individually housed in a temperature-controlled facility with a 12 h light/dark cycle and free food/water access.All animal protocols were approved by the Animal Care and Use Committee of Wenzhou Medical University (wydw2015–0121, Zhejiang, China).At the end of the study, animals were euthanized using sodium pentobarbital (100 mg/kg, IP).

Drugs

Animals were injected intravenously with propofol (10 mg/mL; Diprivan, Astrazeneca, Italy), with drug preparations made immediately prior to use. The 1.7 mg/kg per infusion dose of propofol used in the

self-administration model was chosen based on a previous report[29]. MK-801 was obtained from Sigma-Aldrich (USA), and was prepared using sterile water.

Apparatus

Twelve customized plexiglass operant boxes (Ningbo Addiction Research and Treatment Center, China) were used for propofol training studies, as detailed in previous reports[30]. These boxes contained two nose-poke holes at a height of 5 cm containing yellow LED light. In addition, a larger light was present on the wall over these holes (28 V, 0.1 mA). Drugs were delivered to animals via Tygon tubing, with a leash assembly used to protect the tubing and a plastic swiveling apparatus used to guide tubing through the ceiling. Animals worse jackets containing a customized fluid connector that attached to the leash assembly. A 5 mL syringe pump was attached to the tubing, delivering fluids at a 1.2 mL/min rate. A MED Associates interface on an IBM PC was used for experimental control, using software written internally using Borland Delphi 6.0.

Surgery

Sodium pentobarbital (50 mg/ml) was used to anesthetize animals, after which incisions were formed on the chest above the right jugular vein and at the mid-scapular level on the back. Next, a chronically indwelling silastic jugular cannula was implanted so as to extend from the back of the animal [30]. A total of 0.2 mL saline-heparin solution (25 U/mL heparin) was flushed through these cannulas each ay so as to maintain patency, while infections were prevented via administering animals sodium penicillin daily for 5 days after surgery. Prior to study initiation, animals were given a 7 day post-operative recovery period[29].

Propofol Self-administration

Training for the self-administration of propofol was performed as in previous reports [30]. Briefly, after surgical recovery animals were placed into the customized operant boxes and infusion lines were attached as appropriate. At the start of each session, the yellow LED within the active nose-poke hole was lit. Once rats completed the active nose-poke ratio requirement (FR1), they were administered one 1.7 mg/kg infusion of propofol. This administration was paired to house light illumination for 5 s, in addition to the noise made by the infusion pump apparatus. After this time a 15 s timeout period was activated, during which time responses were recorded but did not induce any changes in drug administration. At the end of this 15 s period, the yellow LED within the active nose-poke hole was again illuminated. Any responses to the inactive nose-poke hole failed to result in any consequences. Sessions were allowed to continue until either 3 h had elapsed or 100 propofol infusions had been administered.

Specific Experiments

The 32 rats in the study were trained once daily to self-administer propofol (1.7 mg/kg per infusion). Once rats had exhibited a stable response (± 5%) for 5 consecutive days, they were intraperitoneally administered MK-801 (0, 0.1, 0.2, or 0.4 mg/kg; n = 8/group) 10 minutes before starting the next session, as determined based on previous reports[31]. Animal responses over a 1 h self-administration period were then recorded, after which animals were euthanized for IHC sample collection.

Sucrose Self-administration

For sucrose administration tests, rats were placed in 30 × 20 × 24 cm operant conditioning chambers and trained with a FR1 schedule using food reinforcement (45 mg pellets; Noyes, NH, USA) over a period of 7 days. For these chambers, two nose-poke holes were present with a light above each and a food dispenser between the two holes. In addition, a house light was present on the opposite wall. Food pellets were delivered only upon pressing of the active hole during nose-poke tests, while there was no programmed outcome for inactive hole responses. Tests were allowed to proceed either for 3 h or until 100 food pellet had been acquired.

After rats exhibited stable sucrose acquisition responses, they were i.p injected using MK-801 (0, 0.1, 0.2, or 0.4 mg/kg) 10 minutes before the next session, and numbers of active/inactive pose-poke responses and sucrose pellets obtained were recorded via computers over a 1 h session period.

General Activity Test

To explore the ability of MK-801 to non-specifically influence general activity in rats, animals were i.p administered MK-801 after which locomotion in a novel context was analyzed. In total, 24 naive rats (n = 6/group) were administered MK-801 (0, 0.1, 0.2, or 0.4 mg/kg), after which they total distance traveled (cm) was measured and assessed via the MED Associates SOF-811 Open-field Activity Software.

Statistical analysis

One-way ANOVAs were used to measure any differences in active/inactive nose-poke responses during self-administration assays. Newman-Keuls multiple comparison tests with a 0.05 or 0.01 alpha level were employed for post hoc comparisons of group means.

Results

Acquired self-administration propofol in rats

Over the course of propofol self-administration training, numbers of active nose-pokes rose significantly relative to inactive nose-pokes ($P < 0.01$)(Fig. 1). Using this FR1 schedule of propofol self-administration (1.7 mg/kg per infusion), rats exhibited stable responses after a total of 14 training sessions.

Effects Of Mk-801 On Propofol Self-administration

We observed no significant difference in numbers of active ($F(3, 28) = 1.353$, $P > 0.05$) (Fig. 2A) or inactive ($F(3, 28) = 0.047$, $P > 0.05$) (Fig. 2A) responses among groups when NMDA receptor activity was antagonized. We did however observe a significant difference in the number of infusions per session following MK-801 administration ($F(3, 28) = 4.372$, $P < 0.01$) (Fig. 2B), with a significant increase in number of infusions for animals pre-treated with 2.0 mg/kg MK-801 relative to saline controls ($P = 0.003$,$P < 0.01$).

Acquisition Of Sucrose Self-administration Responses In Rats

Using an FR1 schedule, rats acquired a stable sucrose self-administration response following a total of 7 sessions. There was a significant increase in numbers of active but not inactive nose-poke responses over the training period (Fig. 3A), and after 4 days rats were stably acquiring 100 food pellets per training session (Fig. 3B)

Effects Of Mk-801 Pretreatment On Sucrose Self-administration

We observed no changes in the numbers of active or inactive nose-poke responses for rats treated with MK-801 (0.1 or 0.2 mg/kg, ip) during sucrose self-administration testing, whereas animals administered the higher 0.4 mg/kg MK-801 dose exhibited a significant reduction in the number of active nose-poke responses ($F(3, 20) = 20.8673$, $P < 0.01$), coinciding with a reduction in numbers of sucrose pellets obtained ($F(3, 20) = 23.77$, $P < 0.01$)(Fig. 4).

Effects of MK-801 on rat general activity

We did not observe any apparent impact of 0.1 mg/kg or 0.2 mg/kg MK-801 on general locomotor activity in rats ($P > 0.05$), whereas the higher 0.4 mg/kg MK-801 dose significantly increased this activity ($F(3, 20) = 22.812$, $P < 0.01$)(Fig. 5).

Discussion

The results of this report clearly demonstrate that in self-administration studies propofol is capable of mediating reinforcement, consistent with past results[6–8]. We found that lower doses of MK-801 (0.1–0.2 mg/kg) were able to increase propofol self-administration infusion numbers in a dose-dependent fashion in rats without impacting general locomotor activity, consistent with similar previous results. For example, MK-801 has been shown to reduce the reward effect associated with cocaine[23, 24], and in studies of cocaine self-administration via a progressive-ratio schedule, MK-801 was shown to increase the self-administration breaking point[32]. NMDA receptor antagonists have been found to be less reliable as reinforcing agents than are stimulants such as cocaine[33]. We additionally found that MK-801 at these dose levels did not impact locomoter activity or sucrose-self administration in rats, with our results thus indicating that 0.2 mg/kg MK-801 increases propofol reinforcement.

For the highest MK-801 dose used in this study (0.4 mg/kg), the increase in number of propfol infusions over control was lower than for the two lesser MK-801 doses (Fig. 1B). This is consistent with previous results indicating that at lower doses MK-801 is capable of lowering the reward, threshold for brain stimulation, thereby influencing self-administration, whereas higher doses (0.3 mg/kg) are capable of disrupting operant performance [34], consistent with the observed impact on sucrose self-administration in the present study (Fig. 4P < 0.01). Higher doses of MK-801 may be inducing continuously increasing effects on brain electric energy, leading to stronger behavioral effects[35], which can lead to increased ataxia in rats[36]. Consistent with this, we observed no impact of lower MK-801 doses on rat general locomotion, whereas the higher 0.4 mg/kg MK-801 dose led ataxia and increased hovering in animals in the present study (Fig. 5P < 0.01).

Multiple mechanisms have the potential to explain the ability of MK-801 to increase propofol rewarding. MK-801 is able to potently bind to the NMDA binding site in a non-competitive manner [37]. As such, MK-801 is able to block NMDA receptor signaling, thereby reducing transduction through glutamatergic nerves. MK-801 has also been shown to enhance the effects of propofol via increasing DA input in the NAc. In microdialysis experiments, the systemic delivery of MK-801 (0.2–0.5 mg/kg) has indeed been shown to result in a marked increase in extracellular DA within the NAc[38]. Another hypothesis proposes that DA signaling may be a dominant mediator of drug addiction, with glutamate signaling playing a less substantial secondary role in this process. Indeed, MK-801 is only able to partially ablate the expression of c-Fos induced by cocaine, whereas the D1 receptor antagonist SCH23390 can completely abolish this induction [39]. Similarly, MK-801 can mediate partial inhibition of progressive ERK activation in the NAc and dorsal stratum of rats following acute Δ9-tetrahydrocannabino (THC) administration, while SCH23390 fully blocked this response[40]. We have previously found the D1 dopamine receptors to be linked with ERK activity in the NAc in the context of propofol self-administration[7, 8]. This suggests that NMDAR activity is likely a mediator of propofol self-administration responses, with dopamine signaling being dominant and glutamate signaling playing a secondary role in this process.

In summary, these results suggest that NMDA receptors play a role in regulating propofol self-administration. This study does have certain limitations, such as the lack of inclusion of other NMDAR

antagonists or agonists, and a lack of intracerebral microinjection experiments or measurements of ERK protein activation. As such, additional research will be needed to clarify the role of these receptors in propofol addiction.

Conclusion

These findings indicate that NMDA receptors may play a role in regulating rat self-administration of propofol.

Declarations

Abbreviations

NMDA N-methyl-D-aspartate

FR fixed ratio

GABA Gamma-aminobutyric acid

VTA ventral tegmental area

D1R Dopamine1 receptor

NAc nucleus accumbens

PFC Prefrontal cortex

I.p Intraperitoneal injection

DA Dopamine

THC Δ9-tetrahydrocannabino

Ethics approval and consent to participate

All animal protocols were approved by the Animal Care and Use Committee of Wenzhou Medical University(wydw2015-0121,Zhejiang,China).

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

BC Contribution: Design the study, conduct the study, analyse the data, and write the manuscript. XH Contribution: Conduct the study and analyze the data. DD Contribution: Design the study. HW Contribution: Design the study and write the manuscript. TZ Contribution: Design and conduct the study and write the manuscript. BW Contribution: Design the study, analyze the data. All authors read and approved the final manuscript.

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Figures

Figure 1

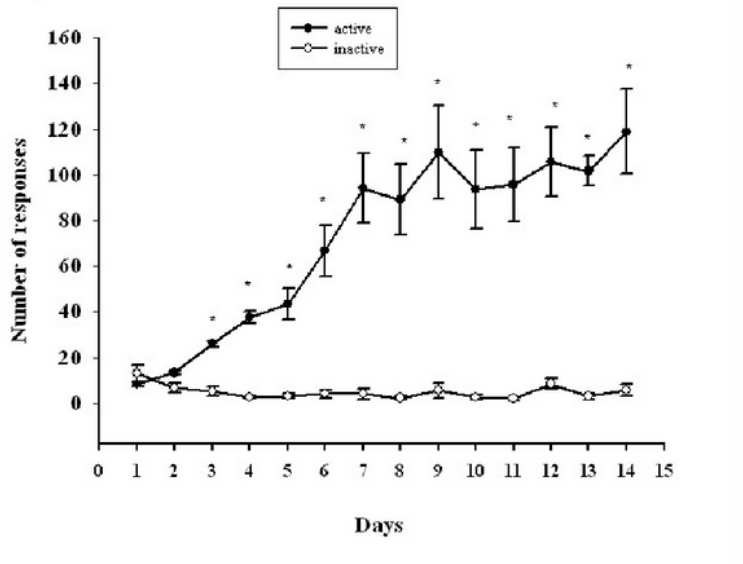

Fig1 Active and inactive nose-poke responses during propofol self-administration training. *P<0.01

Figure 1

Active and inactive nose-poke responses during propofol self-administration training. *P<0.01

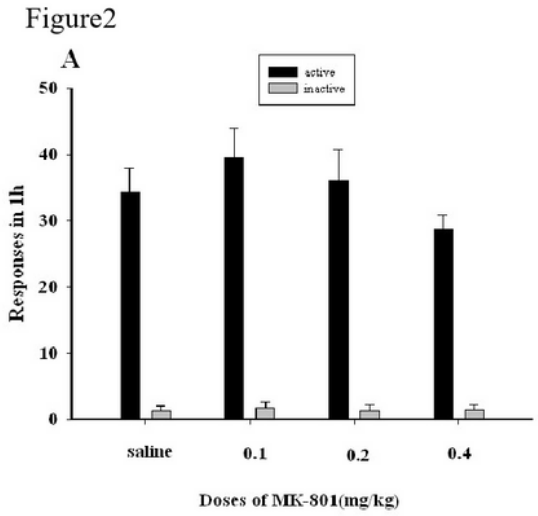

Fig2A MK-801 effects on active and inactive nose-poke responses.

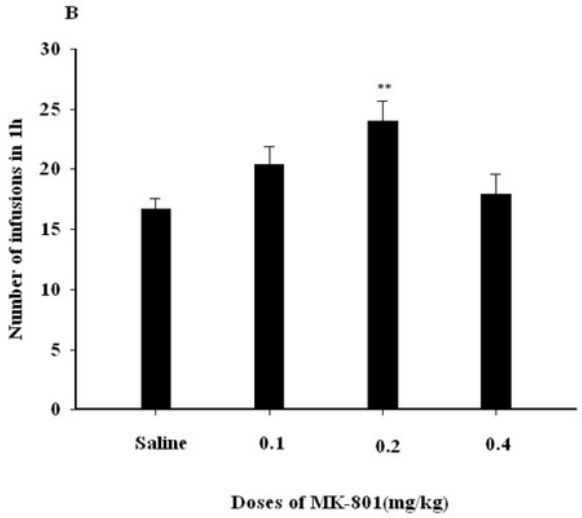

Fig2B MK-801 affects the number of propofol infusions per session.***P<0.01

Figure 2

A- MK-801 effects on active and inactive nose-poke responses. B- MK-801 affects the number of propofol infusions per session.**P<0.01

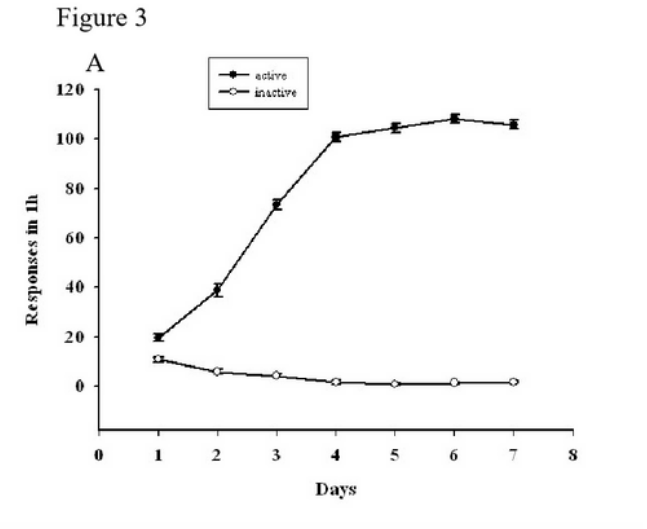

Fig3A Numbers of active and inactive nose poke during sucrose self-administration training.

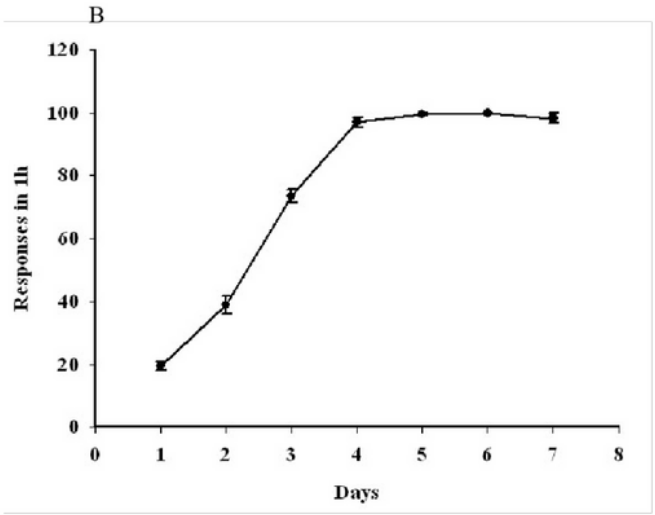

Fig3B Numbers of food pellets acquired during sucrose self-administration training.

Figure 3

A- Numbers of active and inactive nose poke during sucrose self-administration training. B- Numbers of food pellets acquired during sucrose self-administration training.

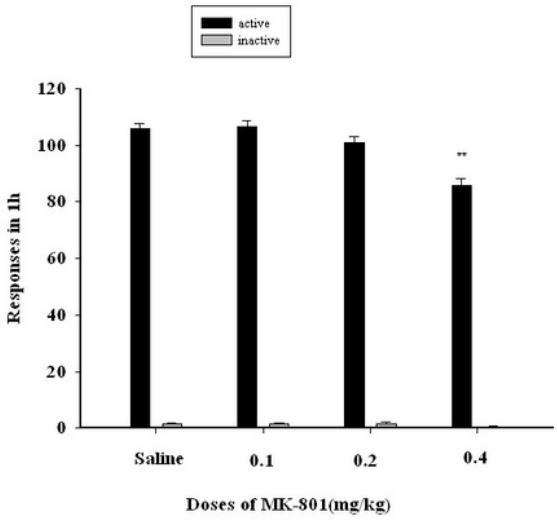

Fig4 Effects of MK-801 on sucrose self-administration.**P<0.01.

Figure 4

Effects of MK-801 on sucrose self-administration.**P<0.01.

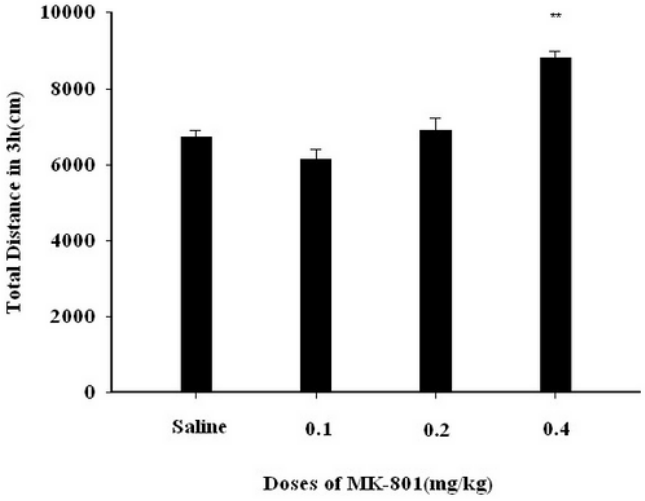

Fig5 Effects of MK-801 on general locomotor activity.**P<0.01.

Figure 5

Effects of MK-801 on general locomotor activity.**P<0.01.

Supplementary Files

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