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NMDA RECEPTORS ARE INVOLVED IN THE ANTIDEPRESSANT-LIKE EFFECTS OF CAPSAICIN FOLLOWING AMPHETAMINE WITHDRAWAL IN MALE MICE

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Abstract—Amphetamine withdrawal (AW) is accompanied by diminished pleasure and depression which plays a key role in drug relapse and addictive behaviors. There is no efficient treatment for AW-induced depression and underpinning mechanisms were not well determined. Considering both transient receptor potential cation channel, subfamily V, member 1 (TRPV1) and *N*-Methyl-D-aspartate (NMDA) receptors contribute to pathophysiology of mood and addictive disorders, in this study, we investigated the role of TRPV1 and NMDA receptors in mediating depressive-like behaviors following AW in male mice. Results revealed that administration of capsaicin, TRPV1 agonist, (100 μg/mouse, i.c.v.) and MK-801, NMDA receptor antagonist (0.005 mg/kg, i.p.) reversed AW-induced depressive-like behaviors in forced swimming test (FST) and splash test with no effect on animals' locomotion. Co-administration of sub-effective doses of MK-801 (0.001 mg/kg, i.p.) and capsaicin (10 μg/mouse, i.c.v) exerted antidepressant-like effects in behavioral tests. Capsazepine, TRPV1 antagonist, (100 μg/mouse, i.c.v) and NMDA, NMDA receptor agonist (7.5 mg/kg, i.p.) abolished the effects of capsaicin and MK-801, respectively. None of aforementioned treatments had any effect on behavior of control animals. Collectively, our findings showed that activation of TRPV1 and blockade of NMDA receptors produced antidepressant-like effects in male mice following AW, and these receptors are involved in AW-induced depressive-like behaviors. Further, we found that rapid antidepressant-like effects of capsaicin in FST and splash test are partly mediated by NMDA receptors. © 2016 Published by Elsevier Ltd on behalf of IBRO.

Key words: amphetamine withdrawal, depression, TRPV1, NMDA receptors, FST, splash test.

INTRODUCTION

Several lines of evidence indicate that withdrawal from psychostimulants induces behavioral and neurochemical alterations (Renoir et al., 2012; Che et al., 2013). Withdrawal from stimulants is accompanied by dysphoric state which contributes to drug-seeking behavior and relapse, and causes treatment failure in individuals with stimulant dependence (Koob et al., 1998; Oleson et al., 2014). Recent evidence suggests that applying animal models of psychostimulants withdrawal provided appropriate tools for understanding underlying mechanisms involved in mood disorders namely depression (Barr and Markou, 2005). Amphetamine (AMPH)-style drugs are potent psychostimulants which their acute abstinence is associated with depressive-like behaviors such as motivational impairment and behavioral despair (Cryan and Holmes, 2005). In animal studies, it has been proposed that depressive-like behaviors following AMPH withdrawal (AW) are associated with abnormal neurotransmission in the regions of the brain relevant to depression (Sulzer et al., 2005). In this regard, it has been accepted that acute phase of psychostimulant withdrawal is associated with abnormal glutamatergic neurotransmission in several brain areas that may be associated with negative affect observed in early recovery state (Kalivas and Volkow, 2005; D'Souza and Markou, 2010). Further, recent studies have shown that chronic administration of stimulants (such as AMPH) enhances hippocampal glutamatergic

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Abbreviations: AW, amphetamine withdrawal; FST, forced swimming test; MK-801, dizocilpine; NMDA, *N*-Methyl-D-aspartate; OFT, open-field test; TRPV1, transient receptor potential cation channel, subfamily V, member 1.

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activity which induces hippocampal plasticity through *N*-Methyl-D-aspartate (NMDA) receptors (D'Souza and Markou, 2010; Underhill et al., 2014). Increase in sensitivity to glutamate following AW plays a crucial role in behavioral difficulties observed after drug cessation (Kalivas and Volkow, 2005; Koltunowska et al., 2013). Evidence suggests that impairment of dopaminergic system activity contribute to difficulties with self-care and motivation following AW (Rossetti et al., 1992). It is well-established that serotonergic drugs are inefficient for treatment of depression in acute phase of AW (Zorick et al., 2011). In this context, emerging lines of research suggest that glutamatergic system can be an appropriate therapeutic target in moderating dysphoric state following AW (D'Souza and Markou 2010; Iijima et al., 2013; Fuller et al., 2015). Although it has been well documented that glutamatergic system plays an important role in AMPH-induced behavioral abnormalities, underlying mechanisms by which acute AMPH abstinence exerts its depressant effects is not clear.

Evidence indicates that transient receptor potential cation channel, subfamily V, member 1 (TRPV1) is involved in pathophysiology of mood disorders (Di Marzo et al., 2008; Terzian et al., 2009; Ho et al., 2012). In this regard, both TRPV1 agonists and antagonist have been reported to have antidepressant effects by different mechanisms including involvement of NMDA receptors (Manna and Umathe, 2012; Abdelhamid et al., 2014). Furthermore, it has been reported that TRPV1 plays a role in pathophysiology of addiction (Wescott et al., 2013; Martins et al., 2014). Expression of TRPV1 undergoes alterations following stimulant administration in the brain, (Tian et al., 2010) and also these channels have been shown to have a regulatory role in morphine-induced reward (Nguyen et al., 2014). Since both NMDA and TRPV1 receptors are implicated in behavioral abnormalities relevant to depression and addiction, their roles in mediating depressive-like behaviors following AW have remained elusive.

Considering that dysphoria following AMPH abstinence is involved in drug seeking and relapse, we aimed to investigate the effects of capsaicin, a selective TRPV1 receptor agonist, on depressive-like behaviors following AW in male mice. In this regard, we challenged the hypothesis that TRPV1 and NMDA receptors play a role in depressive-like behaviors following acute AW in male adult mice.

EXPERIMENTAL PROCEDURES

Animals

Male NMRI mice (Pasteur Institute, Tehran, Iran), weighing 25–30 g, were used. Animals were housed under standard conditions (temperature: 22 ± 2 °C, humidity: 50 ± 10%, 12-h light–dark cycle, and free access to food and water). All procedures in this study were carried out in accordance with the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals (NIH publication # 80-23) and institutional guidelines for animal care and use (Department of Pharmacology, School of Medicine, TUMS).

Stereotaxic surgery

Animals were anesthetized by a ketamine (100 mg/kg) and xylazine (10 mg/kg) subsequently submitted to a stereotaxic frame. The animals were implanted with a 22-gauge stainless-steel guide cannula placed above the right lateral cerebral ventricle (stereotaxic coordinates were: AP, −0.9 mm to the bregma; L, 1.4 mm lateral to the midline; V, −2.5 mm below the top of the skull). The cannula was fixed to the skull using one screw and dental cement. A stylet was inserted into the guide cannula to keep it open prior to injections. Implantation was performed at least five days before initiation of the chronic AMPH treatment.

Drugs

Following drugs were used: D-amphetamine sulfate and MK-801 (Sigma-Aldrich, St. Louis, MO, USA), Capsaicin (Fluka, Switzerland), Capsazepine (Tocris, UK), *N*-Methyl-D-aspartate or NMDA (Tocris, UK). Capsaicin and capsazepine were dissolved in Tween 80: DMSO: saline in 1:2:7 ratios and administered i.c.v 15 min before the examination. MK-801 and NMDA (intraperitoneally, i.p.) were dissolved in saline and administered 15 min before the test. D-amphetamine sulfate was dissolved in saline and administered for five consecutive days (i.p.) in the volume of 10-ml/kg of mouse weight.

Open-field test (OFT)

The OFT was used to evaluate the locomotion of animals in response to AW and different treatments according to the criteria described by Amiri et al. (2015a). The open-field apparatus was white opaque Plexiglas (50 cm × 50 cm × 30 cm), which was dimly illuminated. Each mouse was placed gently on the center square (30 cm × 30 cm), and behaviors were recorded by a camera for 5 min and were analyzed by Ethovision software version 8.5 (Noldus, Netherlands). The surface of the apparatus was cleaned with 70% ethanol after each experiment. The distance moved (horizontal activity) and the number of rearings (vertical activity) were evaluated.

Forced swimming test (FST)

We used FST to evaluate the immobility time of animals in response to an acute inescapable stress challenge reflecting behavioral despair (Cryan and Holmes, 2005; Haj-Mirzaian et al., 2015). In brief, mice were separately placed in an open cylinder-shaped flask (diameter: 10 cm, height: 25 cm), containing 19 cm water at 23 ± 1 °C. Mice were permitted to swim for 6 min and the immobility time was recorded throughout the last 4 min of the test. Each mouse was judged to be immobile when it ceased struggling and stayed floating motionless in the water, making only those movements necessary to keep its head above water.

Splash test

Splash test is accepted tool to evaluate the motivational and self-care difficulties as core symptoms of depression in rodents (David et al., 2009; Amiri et al., 2015b). In this test, grooming behavior of mice, which can be considered as an indirect measure of palatable solution intake, was measured. A 10% sucrose solution was squirted on the dorsal coat of animals in their home cage and mice were videotaped for 5 min. The total grooming activity time was recorded during 5 min after the sucrose vaporization. Grooming activity consists of nose/face grooming, head washing and body grooming.

Experimental design

Twenty-four hours after the last injection of AMPH (5 mg/kg) or saline, mice were divided into two groups (6–8 mice in each group): (1) AW and (2) Controls. Locomotion (in the OF), immobility time (in the FST) and grooming activity time (in the splash test) were evaluated in both groups. In order to determine the sub-effective doses of drugs, various doses of vehicle, capsaicin (10, 100, 200 and 300 μg/mouse, i.c.v), capsazepine (100 and 200 μg/mouse, i.c.v), NMDA (7.5 and 75 mg/kg, i.p.) and MK-801 (0.001, 0.005, 0.05 mg/kg, i.p) and their combinations were applied in both groups.

For investigation of possible involvement of TRPV1 channels in the antidepressant-like effects of capsaicin, we treated AW mice with sub-effective dose of capsazepine/vehicle (100 μg/mouse, 5 min prior to capsaicin injection, i.c.v) and capsaicin/vehicle (100 μg/mouse, 15 min prior to tests, i.c.v). In order to evaluate the possible involvement of NMDA receptors in antidepressant-like effects of capsaicin, we used the co-administration of sub-effective dose of capsaicin/vehicle (10 μg/mouse, 15 min prior to tests, i.c.v) and MK-801/saline (0.001 mg/kg, 45 min prior to tests, i.p.). Furthermore, we co-treated mice with NMDA/saline (7.5 mg/kg, 30 min prior to tests, i.p.) and capsaicin/vehicle (100 μg/mouse, 15 min prior to tests, i.c.v) to ensure the contribution of NMDA receptors in effects of capsaicin. Doses of each drug were chosen according to our pilot and previous studies (Manna and Umathe, 2012; Salehi-Sadaghiani et al., 2012; Haj-Mirzaian et al., 2015)

Statistics

SPSS (version 21) and GraphPad prism statistical (version 6.1) softwares were used for data analysis and figure creation. The differences in immobility time, grooming activity time and locomotor activity between animal groups were analyzed by a one-way ANOVA, followed by Tukey's post hoc test. $P < 0.05$ was considered significant in all experiments.

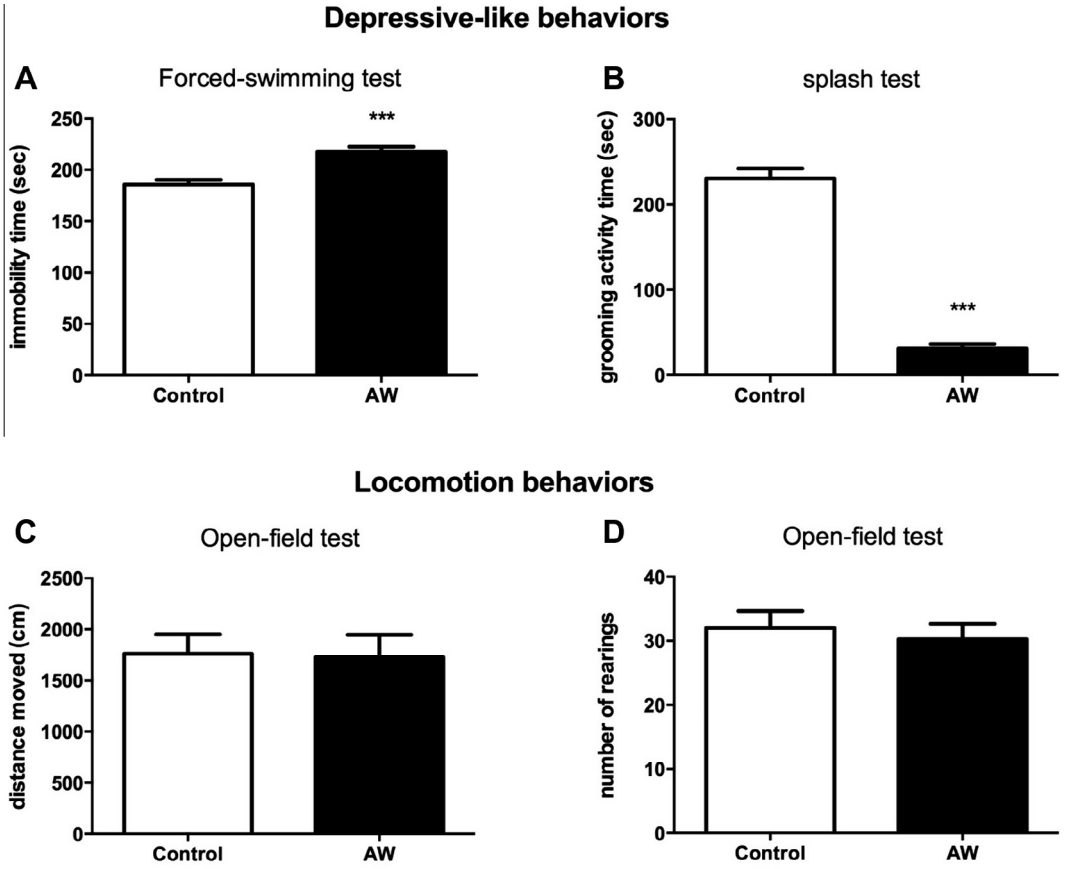

Fig. 1. Effect of amphetamine-withdrawal (AW) on depressive-like behaviors. Effect of AW, on the immobility time in the FST (A), grooming activity time in the splash test (B), total distance moved in the OF (C), and number of rearings in the OF (D). Values are expressed as mean ± S.E.M and were analyzed using *t*-test. $^{***}P < 0.001$ compared with the control group.

RESULTS

AW provoked depressive-like behaviors in mice

Helplessness and hopelessness are observed in depressed people in response to stressful conditions. Exposing depressed animals to an acute inescapable condition such as FST, results in an increase in immobility time. Fig. 1A shows that the immobility time increased in AW group when compared to the control group in the FST ($t = 4.435$, df = 12, $P < 0.001$, Fig. 1A). Motivational and self-care difficulties are considered as main symptoms of depression that have been translated in rodents by a reduction in grooming time in the splash test. Results show that acute AW caused a significant reduction in grooming activity time in the splash test ($t = 15.29$, df = 14, $P < 0.001$, Fig. 1B). In the OF, there is no significant differences in the total distance moved (horizontal activity) ($t = 0.113$, df = 14, $P > 0.05$, Fig. 1C) and number of rearings (vertical activity) ($t = 0.485$, df = 14, $P > 0.05$, Fig. 1D) between AW and control mice.

Capsaicin and not capsazepine attenuated the depressant effect of AW

We assessed the effects of various doses of capsaicin (100, 200, and 300 μg/mouse, i.c.v.) and capsazepine (100 and 200 μg/mouse, i.c.v.) on depression related behaviors (Fig. 2A, C, E, G). An ANOVA revealed that there were significant differences between the treated groups in FST ($F(6, 42) = 307.8$, $P < 0.001$, Fig. 2A) and splash test ($F(6, 48) = 2.641$, $P < 0.05$, Fig. 2C), but not in the distance moved in OF ($F(6, 49) = 0.1071$, $P > 0.05$, Fig. 2E), and number of rearings in OF ($F(6, 49) = 0.1082$, $P > 0.05$, Fig. 2G).

In the FST, Tukey's analysis showed that administration of capsaicin (200 and 300 μg/mouse) ($P < 0.001$) and capsazepine (200 μg/mouse) ($P < 0.001$) to normal mice significantly decreased the immobility time in comparison with vehicle-treated mice (Fig. 2A). Treatment with the lower doses, capsaicin 100 μg/mouse and capsazepine 100 μg/mouse, did not produce significant alterations in the immobility time of mice when compared with vehicle-treated animals ($P > 0.05$, Fig. 2A). In the splash test, Tukey's analysis showed that administration of capsaicin (200 and 300 μg/mouse) ($P > 0.05$) and capsazepine (200 μg/mouse) ($P > 0.05$) did not alter the grooming activity of control animals when compared to vehicle-treated group (Fig. 2C). Similarly, administration of the lower doses of capsaicin (100 μg/mouse) and capsazepine (100 μg/mouse) had no significant effect on grooming activity time of control groups ($P > 0.05$, Fig. 2C). In the OF, administration of the applied doses of each drugs did not alter the both total distance moved and number of rearings of control mice in comparison with vehicle-treated group ($P > 0.05$, Fig. 2E, G). Also, our results show that vehicle treatment did not affect the behaviors of normal mice in all applied behavioral tests ($P > 0.05$).

In the next step, we evaluated the effects of the sub-effective doses of each drug, on depressive-like and locomotion behaviors in the AW animals (Fig. 2B, D, F, H). An ANOVA revealed that there were significant differences between the treated groups in FST ($F(4, 30) = 5.505$, $P < 0.01$, Fig. 2B) and splash test ($F(4, 27) = 31.69$, $P < 0.001$, Fig. 2D), but not in the distance moved in OF ($F(4, 35) = 0.3727$, $P > 0.05$, Fig. 2F), and number of rearings in OF ($F(4, 35) = 0.0557$, $P > 0.05$, Fig. 2H).

Tukey's analysis shows that administration of capsaicin (100 μg/mouse, but not 10 μg/mouse) significantly reduced the duration of immobility in the AW animals when compared with the vehicle-treated group ($P < 0.01$, Fig. 2B). However, capsazepine (100 μg/mouse) did not produce any significant alterations in immobility time of mice undergoing AW in the FST ($P > 0.05$, Fig. 2B). In the splash test, tukey's analysis shows that administration of capsaicin (100 μg/mouse, but not 10 μg/mouse) enhanced the grooming activity time of AW animals when compared to vehicle-treated group ($P < 0.001$, Fig. 2D). But, capsazepine (100 μg/mouse) did not increase the grooming activity time of AW groups ($P > 0.05$, Fig. 2D). In the OF, injection of the applied doses of each drug did not change neither total distance moved nor number of rearings of AW animals when compared to the vehicle-treated groups ($P > 0.05$, Fig. 2F, H). Likewise the last part, data showed that vehicle treatment did not change the behavior of animals in all applied behavioral tests ($P > 0.05$).

Depressant effects of AW were reversed by MK-801 treatment

In order to assess the role of NMDA receptors in AW-induced depressive-like behaviors, we investigated the effects of different doses of MK-801 and NMDA. At first, we investigated the possible effect of treatments in control animals. An ANOVA shows that there were significant differences between the treated groups in FST ($F(5, 36) = 6.673$, $P < 0.001$, Fig. 3A) and splash test ($F(5, 42) = 6.749$, $P < 0.001$, Fig. 3C), but not in the distance moved in OF ($F(5, 42) = 0.065$, $P > 0.05$, Fig. 3E), and number of rearings in OF ($F(5, 42) = 0.071$, $P > 0.05$, Fig. 3G).

Tukey's analysis showed that administration of MK-801 (0.05 mg/kg, i.p.) significantly improved the mice behavior in FST ($P < 0.001$, Fig. 3A) as well as splash test ($P < 0.05$, Fig. 3C). However, administration of the lower doses of MK-801 (0.005 and 0.001 mg/kg) did not alter the immobility time and grooming activity time of control animals in comparison with saline-treated group ($P > 0.05$). An analysis revealed that administration of NMDA (7.5 and 75 mg/kg, i.p.) did not significantly increase the immobility time of control mice in the FST ($P > 0.05$, Fig. 3A). Also, administration of NMDA (7.5 and 75 mg/kg) had no effect on the grooming activity time of animals in splash test ($P > 0.05$, Fig. 3C). Moreover, MK-801 and NMDA treatments did not affect the both locomotor activities of control mice in the OF ($P > 0.05$, Fig. 3E, G).

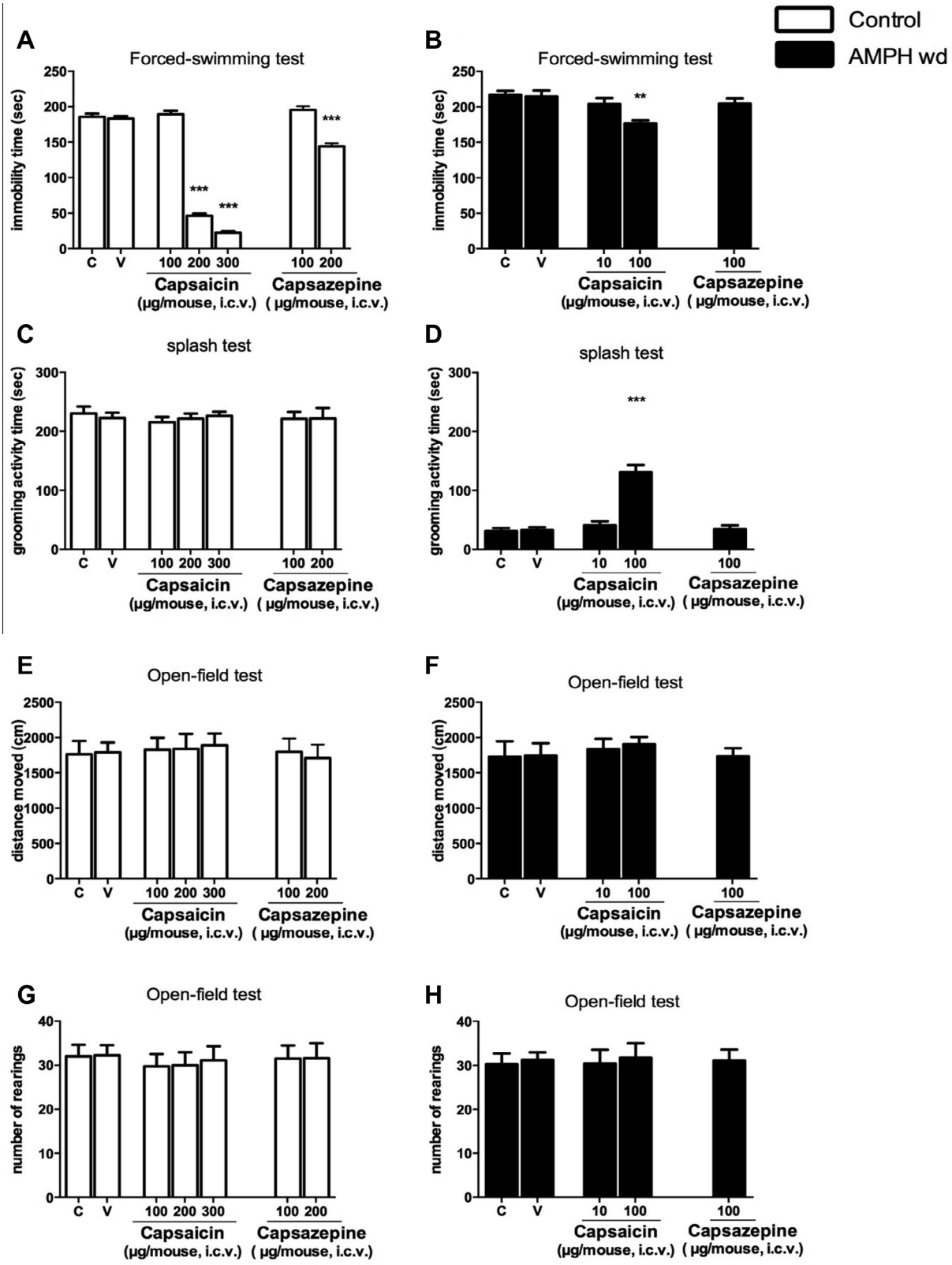

Fig. 2. Effect of capsaicin and capsazepine treatments on depressive-like behaviors. Effects of capsaicin (100, 200, and 300 μg/mouse, i.c.v.) and capsazepine (100 and 200 μg/mouse, i.c.v.) on the immobility time in the FST (A, B), grooming activity time in the splash test (C, D), total distance moved in the OF (E, F), and number of rearings in the OF (G, H) in the control and amphetamine-withdrawn (AW) animals. Values are expressed as mean ± S.E.M and were analyzed using a one-way ANOVA followed by Tukey's post hoc test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with the vehicle-treated control group (V group) in each figure.

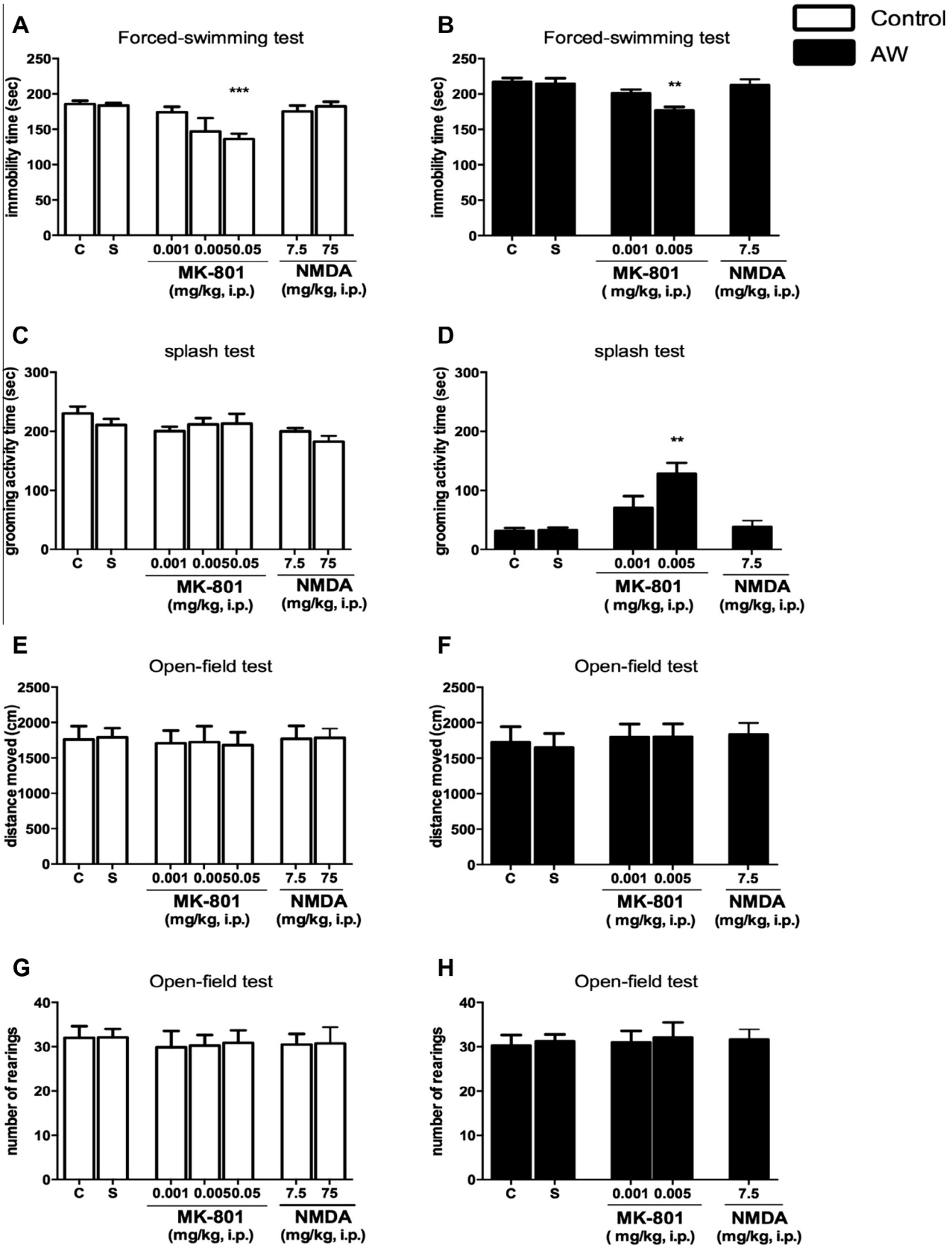

Fig. 3. Effect of MK-801 and NMDA treatments on depressive-like behaviors. Effects of MK-801 (0.001, 0.005, and 0.05 mg/kg, i.p.) and NMDA (7.5 and 75 mg/kg, i.p.) on the immobility time in the FST (A, B), grooming activity time in the splash test (C, D), total distance moved in the OF (E, F), and number of rearings in the OF (G, H) in the control and amphetamine-withdrawn (AW) animals. Values are expressed as mean ± S.E.M and were analyzed using a one-way ANOVA followed by Tukey's post hoc test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with the saline-treated control group (S group) in each figure.

Secondly, we investigated the effects of the sub-effective doses of MK-801 and NMDA, on animal behaviors in the AW groups (Fig. 3B, D, F, H). An ANOVA revealed that there were significant differences between the treated groups in FST ($F(3, 24) = 6.567$, $P < 0.01$, Fig. 3B) and splash test ($F(3, 24) = 8.648$, $P < 0.001$, Fig. 3D), but not in the distance moved in OF ($F(3, 28) = 0.2054$, $P > 0.05$, Fig. 3F), and number of rearings in OF ($F(3, 28) = 0.0368$, $P > 0.05$, Fig. 3H).

Tukey's analysis showed that administration of MK-801 (0.005 mg/kg) significantly reversed the depressant effect of AW in FST ($P < 0.01$, Fig. 3B) and splash test as well ($P < 0.01$, Fig. 3D). However, administration of the lower dose of MK-801 (0.001 mg/kg) did not alter either the immobility or grooming time of AW mice in comparison with saline-treated group ($P > 0.05$). Also, an analysis demonstrated that NMDA (7.5 mg/kg) had no effect on the immobility and grooming activity times of AW animals in the behavioral tests ($P > 0.05$, Fig. 3B, D). In the OF, administration of MK-801 and NMDA did not alter total distance moved and number of rearings of AW mice in comparison with saline-treated group ($P > 0.05$, Fig. 3F, G). It is important to note that administration of NMDA (75 mg/kg) to AW mice correlated with significant seizure-like behaviors (running and loss of writing ability) and mortality in mice (3 of 6). Thus, we only administered NMDA (7.5 mg/kg) to mice.

Capsazepine abolished the antidepressant-like effects of capsaicin in AW mice

Fig. 4 shows the effects of capsazepine and capsaicin co-treatment on the behavioral tests. An ANOVA showed that there were significant differences between all treated groups in FST ($F(7, 48) = 7.898$, $P < 0.001$, Fig. 4A) and splash test ($F(7, 50) = 69.72$, $P < 0.001$, Fig. 4B), but not in the distance moved in OF ($F(7, 56) = 0.2287$, $P > 0.05$, Fig. 4C), and number of rearings in OF ($F(7, 56) = 0.078$, $P > 0.05$, Fig. 4D).

An analysis revealed that treatment with capsazepine (100 μg/mouse) abolished the effects of capsaicin (100 μg/mouse) in the FST and splash test. There were significant differences between capsaicin (100 μg/mouse) and capsaicin (100 μg/mouse) + capsazepine (100 μg/mouse) administered groups in the both FST ($P < 0.001$, Fig. 4A) and splash test ($P < 0.01$, Fig. 4B). However, capsazepine and capsaicin injections did not affect the behavior of control mice in the FST and splash test ($P > 0.05$, Fig. 4A, B). In addition, administration of applied drugs did not alter total distance moved and number of rearings of control and AW mice in comparison with vehicle-treated group ($P > 0.05$, Fig. 4C, D).

Antidepressant-like effects of capsaicin are partly related to NMDA receptors

In order to evaluate the possible role of NMDA receptors in the antidepressant effect of TRPV1 agonist, the sub-effective doses of NMDA receptor antagonist/agonist were administered alone or in combination with capsaicin. An analysis showed that there were significant differences between all treated groups in FST ($F(7, 48) = 5.984$, $P < 0.001$, Fig. 5A) ($F(7, 48) = 6.667$, $P < 0.001$, Fig. 6A) and splash test ($F(7, 51) = 39.00$, $P < 0.001$, Fig. 5B) ($F(7, 51) = 52.78$, $P < 0.001$, Fig. 6B), but not in the distance moved in OF ($F(7, 56) = 0.1227$, $P > 0.05$, Fig. 5C) ($F(7, 56) = 0.2089$, $P > 0.05$, Fig. 6C), and number of rearings in OF ($F(7, 56) = 0.1187$, $P > 0.05$, Fig. 5D) ($F(7, 56) = 0.1074$, $P > 0.05$, Fig. 6D). Tukey's analysis showed that injection of capsaicin (10 μg/mouse), MK-801 (0.001 mg/kg), and NMDA (7.5 mg/kg) did not alter the behavior of animals in both experimental groups ($P > 0.05$).

Data showed that co-administration of MK-801 (0.001 mg/kg) with capsaicin (10 μg/mouse) significantly reduced the immobility time of AW mice when compared to vehicle-treated group in the FST ($P < 0.001$, Fig. 5A). In addition, administration of MK-801 (0.001 mg/kg) significantly augmented the antidepressant-like effect of capsaicin (10 μg/mouse) in AW animals in splash test ($P < 0.001$, Fig. 5B). Analysis showed that none of the above-mentioned treatments changed the behaviors of the control mice in the FST and splash test ($P > 0.05$). Also, MK-801 and capsaicin either alone or in combination did not change the total distance moved and number of rearings of animals in the OF ($P > 0.05$, Fig. 5C, D).

Treatment with NMDA (7.5 mg/kg) abolished the antidepressant-like effects of capsaicin (100 μg/mouse) in AW mice in the FST and splash test. There were significant differences between capsaicin (100 μg/mouse) and capsaicin (100 μg/mouse) + NMDA (7.5 mg/kg) administered groups in the FST ($P < 0.01$, Fig. 6A) and splash test ($P < 0.05$, Fig. 6B). Capsaicin and NMDA injections did not change the behaviors of control animals in the FST and splash test either alone or in combination ($P > 0.05$). Also, capsaicin and NMDA treatments did not change total distance moved and the number of rearings of both experimental groups in the OF ($P > 0.05$, Fig. 6C, D).

DISCUSSION

Results of this study have demonstrated that TRPV1 channels and NMDA receptors are involved in depressive-like behaviors following AW. We showed that antidepressant-like effects of capsaicin are partially mediated by NMDA receptors. Abuse of AMPH-like drugs is a challenging dilemma which affects large number of people. Unfortunately, no effective pharmacological treatment has been yet introduced for treatment of stimulants addiction and cognitive therapy has achieved poor results in managing the condition (Shoptaw et al., 2009; Chomchai and Chomchai, 2015). Acute AMPH abstinence correlates with severe dysphoric state that renders the drug seeking and relapses in withdrawn individuals. It has been well-established that AW induces potent depressive behaviors in both animals and humans (Barr and Markou, 2005). In agreement with previous investigations, we showed that AW mice exhib-

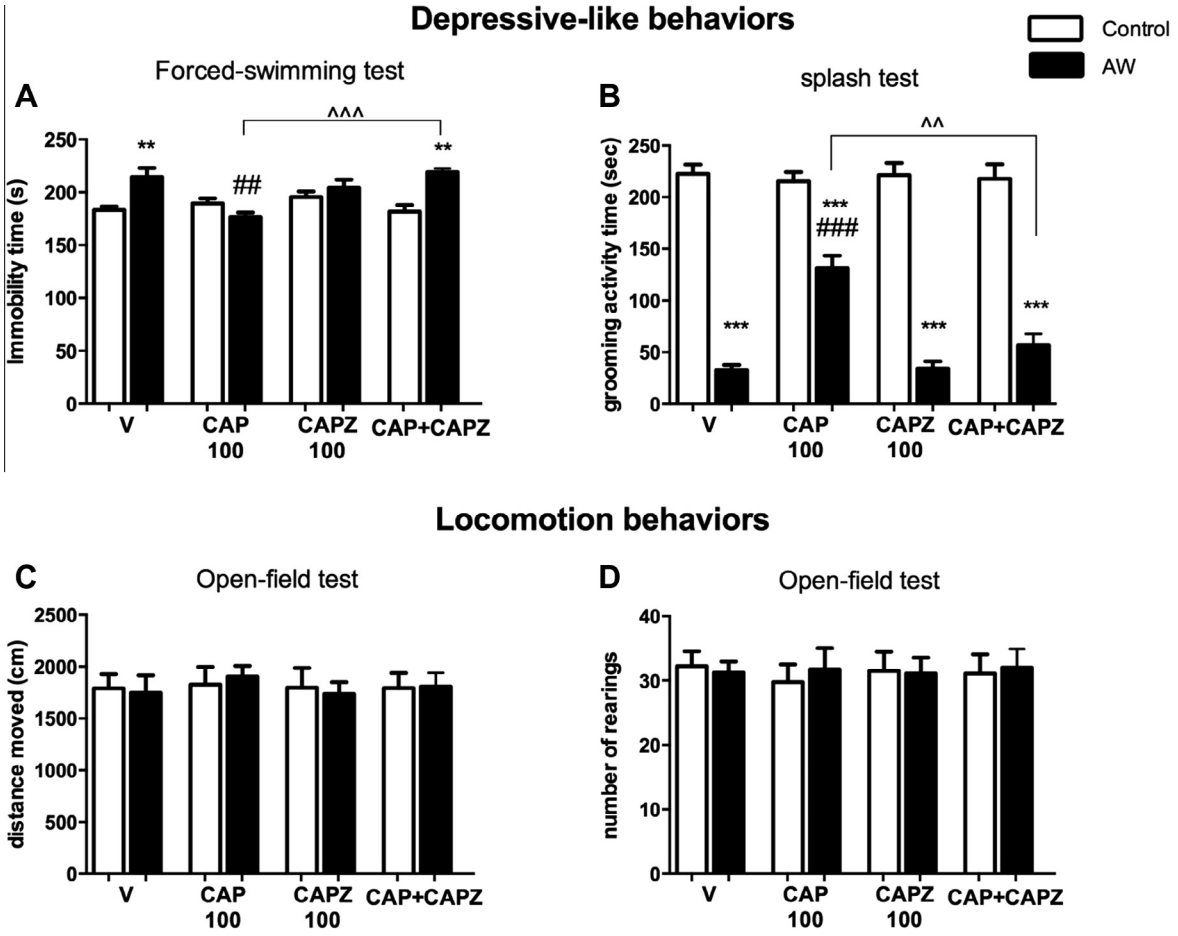

Fig. 4. Effects of capsaicin and capsazepine co-administration on depressive-like behaviors. Effects of capsaicin (100 μg/mouse, i.c.v.) and capsazepine (100 μg/mouse, i.c.v.) co-administration on the immobility time in the FST (A), grooming activity time in the splash test (B), total distance moved in the OF (C), and number of rearings in the OF (D) in the normal (control) and amphetamine-withdrawn (AW) animals. Values are expressed as mean ± S.E.M and were analyzed using a one-way ANOVA followed by Tukey's post hoc test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with the vehicle-treated control group (V group). $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ compared with the vehicle-treated withdrawn group (V group). $^{\wedge\wedge}P < 0.01$ and $^{\wedge\wedge\wedge}P < 0.001$ compared with the capsaicin (100 μg/mouse)-treated AW group.

ited depressive-like behaviors in both FST and splash test. Increase in immobility time in the FST reflects the behavioral despair and passive coping responses in rodents in response to an inescapable stressful challenge (Cryan and Holmes, 2005). Splash test has been reported as a behavioral measure of the motivation and self-care behaviors in rodents, in which poor response to the sucrose (decrease in the grooming activity time) reflects the difficulties in these behaviors (David et al., 2009; Marrocco et al., 2014).

Growing body of evidence indicates that TRPV1 channels are involved in pathophysiology of the various brain disorders such as addiction, mood and cognitive difficulties (Martins et al., 2014; Aguiar et al., 2014). These channels are widely distributed in brain structures such as limbic system and cortical areas which are critical regions of the brain involved in cognitive and behavioral processes (Cristino et al., 2006; Edwards, 2014). Our results revealed that administration of capsaicin and capsazepine dose-dependently decreased the immobility time in control mice. Also, we found that administration of sub-effective dose of capsaicin (and not capsazepine) possessed anti-depressant- like behaviors in FST and splash test without changing the locomotor activity in AW mice. Pretreatment with capsazepine reversed the effects of capsaicin suggesting that antidepressant-like effects of capsaicin are mediated by TRPV1 channels. To explain the possible underlying mechanism(s) of antidepressant-like effects of capsaicin in AW mice, recent clinical and preclinical investigations suggest that decrease in dopaminergic tone and extracellular glutamate levels are associated with depression following abstinence of AMPH-like stimulants (Kalivas and Volkow,2005; D'Souza and Markou, 2010). Evidence suggests that AW-induced motivational difficulties are related to impaired activity of dopaminergic system in mesocorticolimbic pathway (Koob, 1992; George et al., 2012; Der-Avakian and Markou, 2012). It has been shown that TRPV1 channels are expressed in dopaminergic neurons in the several regions of the brain including hippocampus and cortical areas (Cristino et al., 2006; Edwards, 2014). Activation of TRPV1 channels is known to induce depolarization in the neurons through enhancing the calcium influx (Madasu et al., 2015). In this regard, a study by

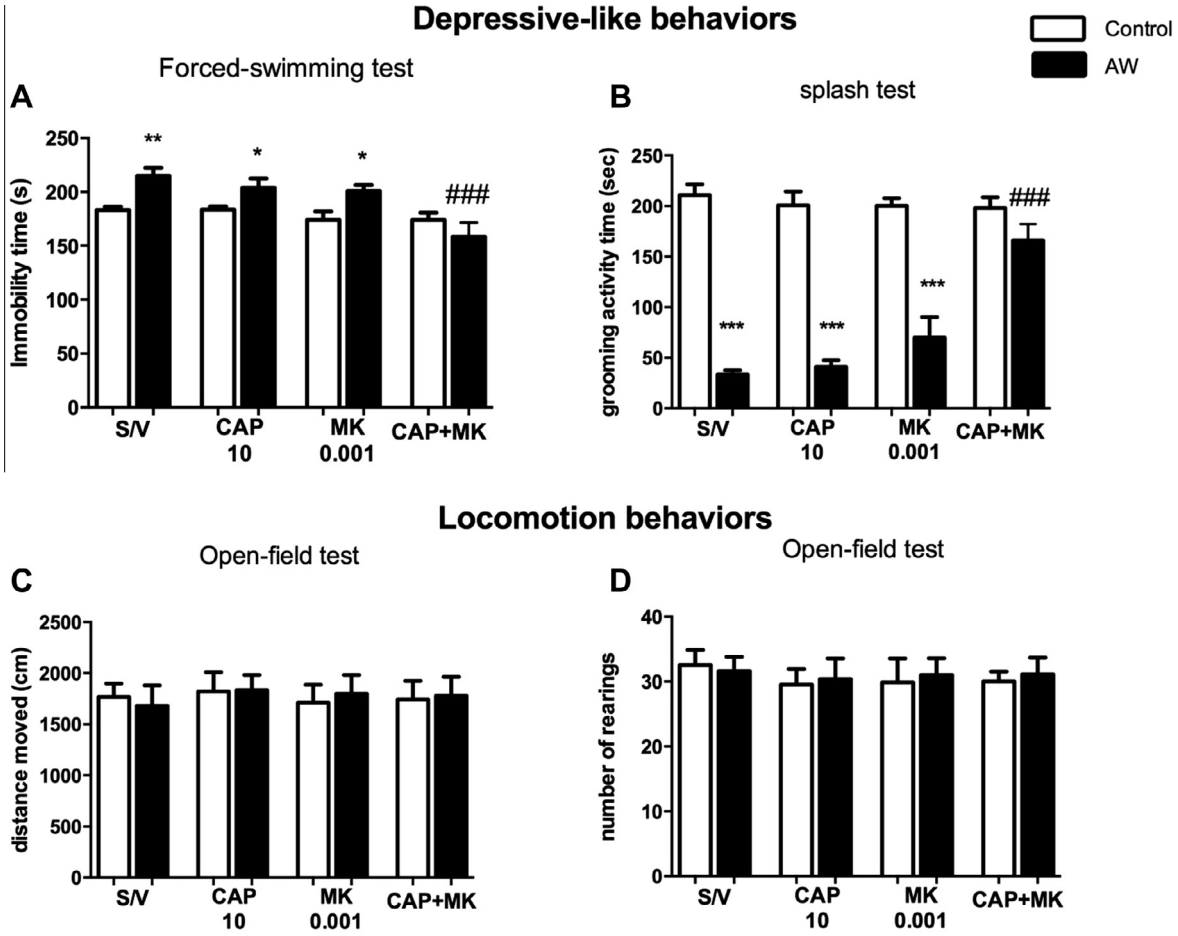

Fig. 5. Effects of capsaicin and MK-801 co-administration on depressive-like behaviors. Effects of capsaicin (10 μg/mouse, i.c.v.) and MK-801 (0.001 mg/kg, i.p.) co-administration on the immobility time in the FST (A), grooming activity time in the splash test (B), total distance moved in the OF (C), and number of rearings in the OF (D) in the normal (control) and amphetamine-withdrawn (AW) animals. Values are expressed as mean ± S.E.M and were analyzed using a one-way ANOVA followed by Tukey's post hoc test. $^{*}P < 0.01$, $^{**}P < 0.01$, and $^{***}P < 0.001$ compared with the saline/vehicle-treated normal group (control S/V group). $^{###}P < 0.001$ compared with the saline/vehicle-treated withdrawn group (AW S/V group).

Marinelli and colleagues has demonstrated that stimulation of TRPV1 channels by capsaicin increases dopaminergic tone by activation of dopamine neurons in the ventral tegmental area and nucleus accumbens (Marinelli et al., 2005). Therefore, anti-withdrawal effects of capsaicin in AW mice may be associated with its promoting effect on dopaminergic activity. It is important to note that clinical investigations for the treatment of depression during psychostimulants withdrawal indicate the efficacy of pharmacological agents that targets dopaminergic system such as amineptine (D'Souza and Markou, 2010; Russo and Nestler, 2013).

Given the critical role of the glutamatergic system in both addictive and depressive-like behaviors following stimulants withdrawal (Kalivas and Volkow, 2005; Zorumski and Izumi, 2012), we found that administration of low doses of MK-801effectively produced antidepressant-like effects in mice following AW. Considering that NMDA receptors play a critical role in pathophysiology of depression, our results showed that hyper-sensitivity of the NMDA receptors after AW plays a key role in mediation of depressive-like behaviors in animals. Our results were in line with recent studies that have demonstrated ketamine, functional and non-comparative NMDA receptor antagonist is able to attenuate the AW-induced affective-like behaviors in rodents (Koltunowska et al., 2013; Belujon et al., 2015; Fuller et al., 2015). Nevertheless, evidence indicates that administration of NMDA receptor antagonists potently enhances dopaminergic system activity in mesocorticolimbic circuits (Li et al., 2015; Cui et al., 2015). In this context, an interesting research by Bartsch and colleagues has recently revealed that hippocampal NMDA receptor antagonists enhanced dopaminergic system activity through a hippocampus-ventral tegmental area loop (Bartsch et al., 2015). Thus, MK-801 not only is able to improve dopaminergic tone, but also blocks NMDA receptors that together may account for its antidepressant-like effects in AW mice. To support this, our results showed that NMDA (7.5 mg/kg) could reverse the effects of

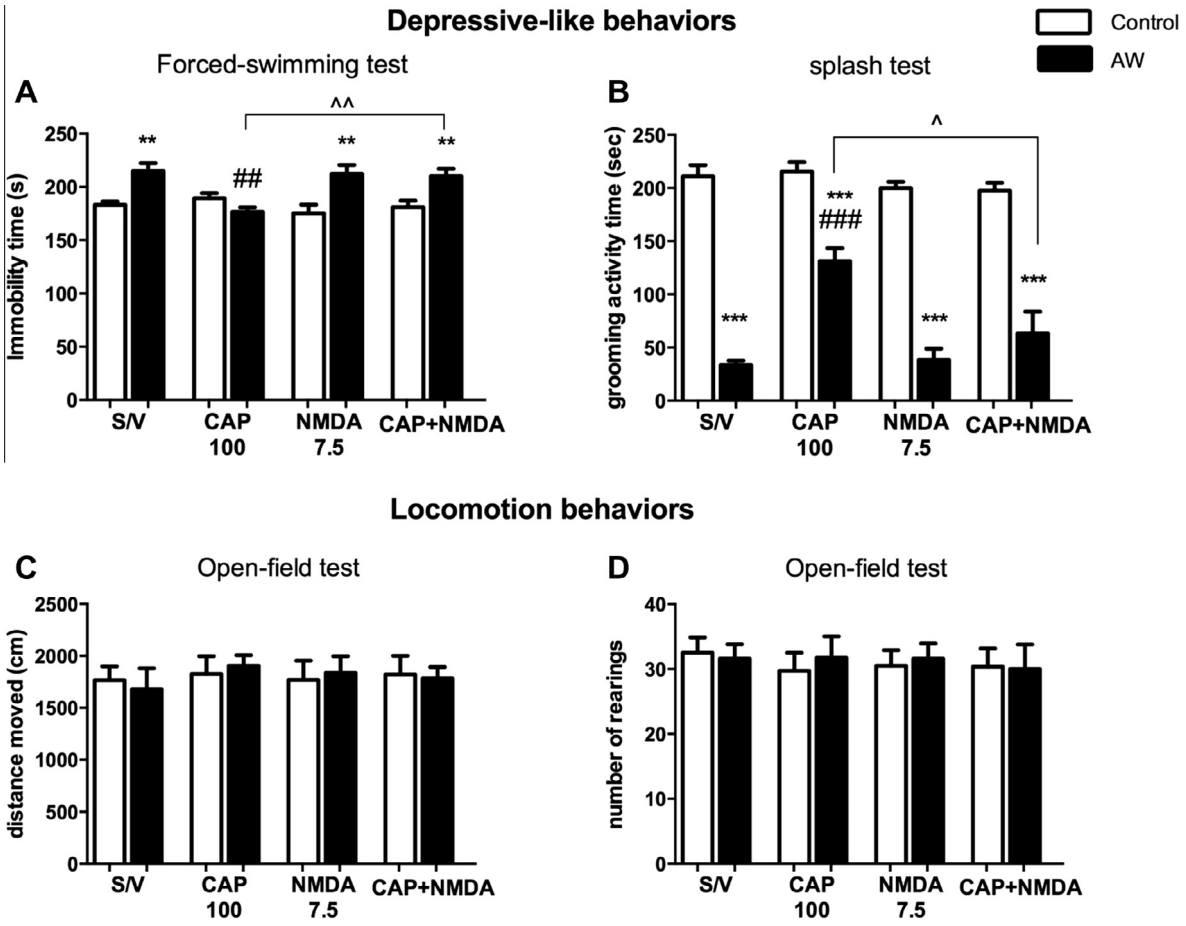

Fig. 6. Effects of capsaicin and NMDA co-administration on depressive-like behaviors. Effects of capsaicin (100 μg/mouse, i.c.v.) and NMDA (7.5 mg/kg, i.p.) co-administration on the immobility time in the FST (A), grooming activity time in the splash test (B), total distance moved in the OF (C), and number of rearings in the OF (D) in the normal (control) and amphetamine-withdrawn (AW) animals. Values are expressed as mean ± S.E.M and were analyzed using a one-way ANOVA followed by Tukey's post hoc test. $^{**}P < 0.01$ and $^{***}P < 0.001$ compared with the saline/vehicle-treated normal group (control S/V group). $^{\#\#}P < 0.01$ and $^{\#\#\#}P < 0.001$ compared with the saline/vehicle-treated withdrawn group (AW S/V group). $^{\wedge}P < 0.05$ and $^{\wedge\wedge}P < 0.01$ compared with the capsaicin (100 μg/mouse)-treated AW group.

capsaicin in behavioral tests proposing that NMDA receptors potently contribute to depressive-like behaviors following acute AW.

Furthermore, we found that unlike control animals, co-administration of MK-801 and capsaicin at sub-effective doses exerted antidepressant-like effects in AW mice without affecting locomotion. The synergistic effects of these drugs may be associated with their ability to improve the impaired dopamine neurotransmission and reward pathway. Our results were in line with previous studies that have reported i.c.v (and not peripheral) administration of capsaicin produced antidepressant-like effects in mice and NMDA receptors may mediate its effects (Hayase, 2011; Manna and Umathe 2012; Jang et al., 2013). Further, there are previously published investigations that are not consistent with our results. These studies showed that activation of the TRPV1 channels was accompanied by depressive-like behaviors in rodents (Abdelhamid et al., 2014; Navarria et al., 2014). Inconsistency between the findings about the role of TRPV1 receptors in depressive-like behaviors may be attributed to conditions (physiologic/pathophysiologic) in which the behaviors were evaluated. Also, it is important to note that those studies did not used the OFT (a necessary test to validate the results of FST) to evaluate locomotor activity in experimental rodents. Thus, increased immobility time following administration of TRPV1 agonists in their experiments may be associated with direct hypo-locomotion effects of TRPV1 activation under physiologic conditions.

On the other hand, it has been well-evident that addiction to drugs of abuse is associated with development of anxiety disorders (Lüthi and Lüscher, 2014). Evidence indicates that both TRPV1 and NMDA receptors contribute to pathophysiology of anxiety disorders (Zorumski and Izumi, 2012; Martins et al., 2014). In this regard, it has been reported that activation of TRPV1 receptors is associated with anxiogenic behaviors while; blockade of these channels produces anxiolytic effects. However, a comprehensive review by Madasu and colleagues have demonstrated that activation/blockade of TRPV1 receptors has different effects on anxiety-like behaviors regarding the site of drug injection (Madasu et al., 2015). Further, NMDA receptor antagonists have

been reported to have anxiolytic effects in both human and rodents (Barkus et al., 2010). However, a recent study by Haj-Mirzaian et al. showed that NMDA receptor antagonists (such as ketamine and MK-801) were able to attenuate depressive-like behaviors (and not anxiety-like behaviors) is socially isolated mice (Haj-Mirzaian et al., 2015). Our study also has limitations because we used only male mice in this study. In fact, our reason to use male mice was that most amphetamine addicts/abusers are men. However, evidence indicates that there are significant differences between men and women in tendency to rewarding effects of drugs of abuse (Fattore et al., 2014; Bobzean et al., 2014). In addition, we did not evaluate the role of other glutamate receptors in this work. Previous investigations have reported that AMPA receptors are also involved in pathophysiology of depression and addiction (Chourbaji et al., 2008; Fumagalli et al., 2011; Vogt et al., 2014; Chen and Chen, 2015). Similarly, meabotropic glutamate receptor (mGluR) 5 is involved in pathophysiology of both mood and addiction disorders (Osborne and Olive, 2008; Inta et al., 2013). Furthermore, mGluR7 has been suggested as a therapeutic target for treatment of psychostimulant addiction (Li and Markou, 2015).

CONCLUSION

In present study we found that both MK-801 and capsaicin are able to mitigate depressive-like behaviors following AW in male mice. Further, NMDA receptors, at least partially, play a role in anti-withdrawal effects of capsaicin. Further studies seem warranted to understand mechanisms which are involved in depressive-like behaviors following AMPH-like drugs.

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