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ORIGINAL ARTICLE

Suppression of Methamphetamine Self-Administration by Ketamine Pre-treatment Is Absent in the Methylazoxymethanol (MAM) Rat Model of Schizophrenia

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Abstract Ketamine may prove to be a potential candidate in treating the widespread drug addiction/substance abuse epidemic among patients with schizophrenia. Clinical studies have shown ketamine to reduce cocaine and heroin cravings. However, the use of ketamine remains controversial as it may exacerbate the symptoms of schizophrenia. Therefore, the aim of this study is to characterize the effects of ketamine on drug addiction in schizophrenia using the methylazoxymethanol (MAM) acetate rat model on operant IV methamphetamine (METH) self-administration. MAM was administered intraperitoneally (22 mg/kg) on gestational day 17. Locomotor activity test and later IV self-administration (IVSA) were then performed in the male offspring followed by a period of forced abstinence and relapse of METH taking. After reaching stable intakes in the relapse phase, ketamine (5 mg/kg) was administered intraperitoneally 30 min prior to the self-administration session. As documented previously, the MAM rats showed a lack of habituation in the locomotor activity test but developed stable maintenance of METH self-administration with no difference in operant behaviour to control animals. Results show that ketamine treatment significantly reduced the METH intake in the control animals but not in MAM animals. Ketamine effect on METH self-administration may be explained by increased glutamatergic signalling in the prefrontal cortex caused by the N-methyl-D-aspartate antagonism and disinhibition of GABA interneurons which was shown to be impaired in the MAM rats. This mechanism may at least partly explain the clinically proven anti-craving potential of ketamine and allow development of more specific anti-craving medications with fewer risks.

Keywords Ketamine · MAM model · Methamphetamine · Self-administration · Sprague-Dawley rats

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Introduction

Drug addiction is a serious psychosocial problem. Most of the treatment options including pharmacologic and psychologic focus on support of sustained drug abstinence by changing psychostimulant metabolism, reducing craving or balancing the reinforcing and aversive effects of the drug use (Phillips et al. 2014).

Recently, glutamatergic antagonism has been proposed to be a promising intervention in treating drug addictions. Several N-methyl-D-aspartate (NMDA) receptor antagonists such as dizocilpine, ketamine, acamprosate and memantine have shown to inhibit drug cravings in clinical studies (Olive et al. 2012; Dakwar et al. 2014a, b). Moreover, other drugs (mostly anticonvulsants, e.g. gabapentin, topiramate or lamotrigine) that also result in inhibition of glutamatergic signalling seem to possess similar effects (Olive et al. 2012). In particular, ketamine is now extensively studied for its acute antidepressant potential in both clinical (Xu et al. 2016) and preclinical studies (Scheuing et al. 2015) yielding promising results. In a clinical study, it has been shown to dose-dependently reduce cocaine craving 24 h post-infusion (Dakwar et al. 2014b). The authors claim this is due to its

mystical psychologic effects which were assessed by Hood's Mysticism Scale (Dakwar et al. 2014a). Even at high doses, ketamine seems to retain this property as it was shown to inhibit drug cravings in heroin addicts at psychedelic levels (Krupitsky et al. 2002).

Preclinical experiment on a variety of NMDA antagonists have shown to suppress conditioned place preference (CPP) in vivo despite having reinforcing properties of their own at high doses (Layer et al. 1993; Bokor and Anderson 2014; Babinska and Ruda-Kucerova 2017). Dizocilpine (MK-801) suppressed CPP in rat studies with methamphetamine (METH) (Kim and Jang 1997), cocaine (Ida et al. 1995) and morphine (Suzuki et al. 2000). Also, riluzole suppressed morphine- and amphetamine-induced CPP (Tzschentke and Schmidt 1998). Interestingly, ketamine had failed to suppress methamphetamine-induced CPP which has been observed with other NMDA antagonists (Xu et al. 2006). Furthermore, there are numerous lines of evidence showing that dizocilpine exerts a protective effect against neurochemical changes induced by methamphetamine and similar psychostimulants (Gibb et al. 1989; Lowy 1990; Weihmuller et al. 1991; Johnson et al. 1992; Muraki et al. 1992; Farfel et al. 1992).

Clinical evidence indicates that the incidence of drug abuse is higher in the population with psychiatric morbidity (Wedekind et al. 2010), including schizophrenia (Koskinen et al. 2009; Mesholam-Gately et al. 2014). Almost 50% of patients with schizophrenia suffer comorbid addiction (Lybrand and Caroff 2009). More importantly, all drug classes were shown to be abused by the patients with schizophrenia with the most common being nicotine (Chambers et al. 2001; Wing et al. 2012; Mackowick et al. 2014) and alcohol (Regier et al. 1990; Kalyoncu et al. 2005; Kerner 2015) but abuse of opiates (Kern et al. 2014), amphetamines (Grant et al. 2012) and *Cannabis* drugs (McLoughlin et al. 2014) is reported as well. Due the high incidence of substance abuse, development of effective anti-craving treatment options suitable for patients with schizophrenia is a current challenge.

Drug abuse behaviours observed in rat neurodevelopmental models of schizophrenia are highly translational to their human counterparts. These models are based on human epidemiological data that indicate prenatal or perinatal environmental insults (exposure to a toxin, malnutrition, infection, etc.) increase the risk of developing schizophrenia later in life (Micale et al. 2013; Kucerova et al. 2014). In the neonatal ventral hippocampal lesion (NVHL) model, rats were found to self-administer higher doses of cocaine, needed more days to extinguish the drug-seeking behaviour and showed higher drug- (Chambers and Self 2002) and cue-induced (Karlsson et al. 2013) reinstatements. In a methamphetamine self-administration study, NVHL rats achieved higher break points in progressive ratio paradigm confirming higher motivation whilst there was no difference in responding at fixed ratio (Brady et al. 2008). Furthermore, in adult rats, alcohol drinking was not influenced by the NVHL lesion (Berg et al. 2011) but a light alcohol exposure in adolescence was shown to enhance drinking behaviour of the NVHL rats in adulthood (Jeanblanc et al. 2014). On the other hand, nicotine appeared to possess a higher addictive potential in this model (Berg and Chambers 2008). Prenatal immune activation models were also used to model the comorbidity of schizophrenia and drug abuse. Prenatal lipopolysaccharide exposure increased alcohol intake in adult rat offspring (Liu et al. 2004). Rats prenatally treated with polyinosinic/polycytidylic acid (polyI:C) were also reported to show enhanced amphetamine-induced reinstatement of CPP (Richtand et al. 2012).

Another neurodevelopmental model of schizophrenia induced by prenatal treatment with DNA-alkylating mitotoxin methylazoxymethanol (MAM) acetate (Lodge and Grace 2009) was also used to study schizophrenia addiction comorbidity. The MAM-treated animals are characterized by a maximal activation of mesolimbic dopaminergic pathway and increased number of activated dopaminergic neurons. Consequently, these characteristics seem to have led to the higher behavioural response to amphetamine challenge doses (Lodge and Grace 2009, 2012). Despite the proven increased dopaminergic responsiveness, the influence of the MAM phenotype on addictive behaviour was not confirmed in cocaine (Featherstone et al. 2009) and METH self-administration studies (Ruda-Kucerova et al. 2017). Interestingly, MAM females were found to consume more alcohol than MAM males whilst no difference were observed between genders in the control groups (Ruda-Kucerova et al. 2017). However, these studies evaluated mostly absolute drug intake in the MAM model whilst other variables such as motivation to obtain the drug in an extinction paradigm or pre-exposure in adolescence were not studied yet.

Although ketamine has a promising potential in addiction treatment (Dakwar et al. 2014a; b), its application may be problematic in patients with schizophrenia. It has been consistently shown to exacerbate symptoms of the schizophrenia at sub-anaesthetic doses in humans (Lahti et al. 2001; Hu et al. 2015). In addition, NMDA antagonists have been successfully used in vivo to model schizophrenia-like phenotype (Lipska and Weinberger 2000).

Therefore, a better understanding of ketamine effect on drug-seeking behaviour in schizophrenia would be of great importance. The current study aims to assess the effects of ketamine at low doses on operant IV methamphetamine self-administration between MAM-exposed and control male rats. This neurodevelopmental model was selected because the rats were shown to react differentially to glutamatergic manipulations due to altered glutamate signalling. Specifically, this model was shown to have attenuated extracellular release of glutamate in medial prefrontal cortex and increased locomotor response after a dizocilpine challenge (Lena et al. 2007). Similarly, MAM rats show higher locomotion after low-dose ketamine challenge (Phillips et al. 2012). In this study, we

opted for IV self-administration paradigm as CPP failed to show ketamine-induced suppression of methamphetamine-seeking behaviour (Xu et al. 2006).

Material and Methods

Animals

Timely mated female albino Sprague-Dawley rats were purchased from Charles River (Germany) at gestational day 13 and housed individually. As previously described (D'Addario et al. 2017; Ruda-Kucerova et al. 2017), methylazoxymethanol (MAM) acetate or saline was administered intraperitoneally on gestational day (GD) 17. The average surviving litter size was $n = 9.6$ in control and $n = 11.5$ in MAM-treated mothers. The average proportions of male and female offspring were for 52% of males and 48% of females. No cross-fostering was used, the mothers were regularly weighted and no differences were observed between control and MAM-treated mothers. The offspring were weaned on the postnatal day (PND) 22 and housed in groups of five. At the age of 9 weeks, when the self-administration protocol was initiated, rats were individually housed and the study lasted for another 9 weeks, i.e. at the end, the rats were 18 weeks old. Twenty male offspring were used in the beginning of this study. Specifically, 10 vehicle rats from four different litters and 10 MAM rats from five different litters were used. The final numbers in the IV self-administration study were lower due to surgery or catheter patency. There were $n = 7$ male vehicle (M VEH) and $n = 5$ male MAM (M MAM) included in all analyses. Environmental conditions during the whole study were constant: relative humidity 50–60%, temperature 23 ± 1 °C, inverted 12-h light-dark cycle (7 a.m. to 7 p.m. darkness). Food and water were available ad libitum. All procedures were performed in accordance with EU Directive no. 2010/63/EU and approved by the Animal Care Committee of the Faculty of Medicine, Masaryk University, Czech Republic, and Czech Governmental Animal Care Committee, in compliance with Czech Animal Protection Act No. 246/1992.

Drugs and Treatments

Ketamine solution was prepared by diluting a ready-made solution (NARKAMON inj. ad us. vet., Bioveta Inc., Czech Republic, ketamine hydrochloride 100 mg/ml) by saline to obtain a concentration of 5 mg/kg ketamine in 1 ml of solution. Ketamine was administered intraperitoneally (IP) 30 min before the IVSA session. Saline was injected to all animals several days before ketamine as vehicle pair-wise control.

Methylazoxymethanol acetate (MAM; Midwest Research Institute, Kansas City, USA) was dissolved in saline and administered intraperitoneally at dose 22 mg/kg in 1 ml/kg volume on gestational day (GD) 17. Saline was injected to the control group as vehicle.

Methamphetamine (METH, Sigma Chemical, Co., St. Louis, MO, USA) available in the operant cage for IV self-administration was 0.08 mg/kg per infusion with the maximum number of infusions obtainable in 1 session set to 50 as previously described and validated (Kucerova et al. 2009, 2012; Amchova et al. 2014; Ruda-Kucerova et al. 2015).

Locomotor Activity Test

Before starting the IVSA study, basal behavioural profile was assessed in all animals. In a brightly lit room, rats were individually tested for locomotor activity using the Actitrack system (Panlab, Spain) as previously described (Pistovcakova et al. 2008; Ruda-Kucerova et al. 2015, 2017). Each plexiglass arena (45 × 45 × 30 cm) was surrounded by two frames equipped with photocells located one above another at 2 and 12 cm over the cage floor. Animals were placed in the centre of arena and the spontaneous locomotor activity was tracked for 10 min. At the end of the session, animals were returned to their home cage and arenas were wiped with 1% acetic acid to remove potential olfactory cues.

IVSA Protocol

Animals were deeply anaesthetised with IP injection of 50 mg/kg ketamine (NARKAMON inj. ad us. vet., Bioveta Inc., Czech Republic, ketamine hydrochloride 100 mg/ml) plus 8 mg/kg xylazine (ROMETAR inj. ad us. vet., Bioveta Inc., Czech Republic, xylazine hydrochloride 20 mg/ml. The selection of ketamine for general anaesthesia may be questionable, but there are valid studies evaluating exposure to low-dose ketamine whilst using for anaesthesia the same or analogous drug—tiletamine (Li et al. 2016; Mutti et al. 2016). This approach is, however, a potential limitation of the study.

Under aseptic conditions, a permanent intracardiac silastic catheter was implanted through the external jugular vein to the right atrium. The outer part of the catheter exited the skin in the midscapular area. After surgery, a 1-week recovery was allowed. The catheters were flushed daily by 17 mg/kg enrofloxacine (ENROXIL MAX 10%, KRKA s.r.o., Czech Republic, enrofloxacine 100 mg/ml) solution followed by 0.1 ml of a heparinized (1%) sterile saline solution to prevent infection and occlusion of the catheter. IVSA was conducted as previously described (Kucerova et al. 2009, 2012; Amchova et al. 2014; Ruda-Kucerova et al. 2015) in the same operant boxes (Coulbourn Instruments, USA) using nose-poke operandi under an FR-1. Nose-poking in the active hole led to the activation of the infusion pump and administration of an infusion followed by a 10-s time-out, when nose poking was recorded but not rewarded. The cage was illuminated by a house light which was flashing when administering infusion

and off during the time-out period. IVSA sessions lasted 90 min and took place 7 days/week between 8 a.m. and 3 p.m. during the dark period of the inverted light-dark cycle. After 14 days of METH intake, the maintenance phase was terminated and rats were kept in their home cages for the 14 days of the forced abstinence period. After completing the abstinence period, the animals were introduced again to the IVSA boxes to re-establish drug-taking behaviour for 5 days. When self-administration behaviour was stable for 3 days, an IP injection of saline was administered to assess the effect of injection on the METH intake. After reaching the stable intake again (at least 1 day after saline test if no effect was recorded) a 5 mg/kg IP ketamine dose was administered before the session.

Statistical Data Analysis

Primary data were summarized using arithmetic mean and standard error of the mean (±SEM) estimate. All data were tested by Kolmogorov-Smirnov test of normality and analysed accordingly. Locomotor data were analysed by repeated measures ANOVA (factor: MAM model, repeating factor: minute), the habituation score was evaluated by the *t* test. For comparison of METH IVSA variables in maintenance and relapse phases of the study, repeated measures ANOVA was used (factor: MAM model, repeating factor: day). To test potential effect of ketamine/saline treatment on the METH taking behaviour, Kruskal-Wallis ANOVA or two-way ANOVA (factors: treatment and MAM model) with Bonferroni post hoc test were used depending on the outcome of the normality test. The analyses were calculated using Statistica 13.2 (StatSoft, USA). A value $p < 0.05$ was recognized as boundary of statistical significance in all applied tests.

Results

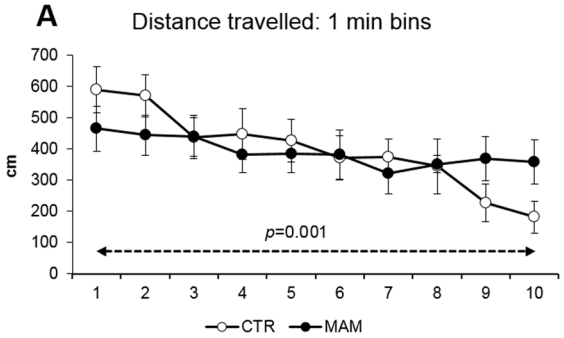
Basal Locomotor Characteristics

Before starting the IV self-administration protocol, basal locomotor and exploratory activity was assessed in all groups to exclude the possibility that these characteristics would lead to different drug-taking behaviour. Figure 1 illustrates the results on total horizontal activity in 1-min bins (Fig. 1a) and habituation process (Fig. 1b). Repeated measures ANOVA (factor: MAM model, repeated factor: minute) has revealed a significant effect of minute: $F_{(1,9)} = 10.490$, $p = 0.000$ and minute ×model interaction: $F_{(9,90)} = 3.514$, $p = 0.001$. However, Bonferroni post hoc test did not identify a significant difference between the groups at any minute of measurement. Furthermore, important difference was proven in habituation calculated by subtracting the locomotion in minute 1 from the score in minute 10. This number shows decrease in locomotion over time, i.e. habituation to the novel arena. This evaluation showed a highly significant difference between MAM and control animals (*t* test, $p = 0.0003$) showing that MAM animals did not habituate to the novel environment. Control rats decreased their locomotion over 10 min of the test approximately four times more than MAM-treated animals.

Characteristics of Maintenance and Relapse of METH IVSA

The METH-taking behaviour during the last 5 days of maintenance period (14 days in total) and five relapse sessions after forced abstinence was assessed in terms of mean number of nose pokes, infusions self-administered per session and by the mean METH dose per session in milligrams per kilogram. The data were analysed separately for the maintenance and relapse periods. As shown on Fig. 2, during the MAINTENANCE phase, (days 1–14) there was no important difference between the groups in the active nose-poking (Fig. 2a), number of infusions (Fig. 2b) or dose self-administered (Fig. 2c), tested by repeated measures ANOVA (factor: MAM model, repeated factor: day). Specifically, in the comparison of active nose-poking ANOVA showed following results: effect of MAM model $F_{(1,11)} = 0.396$, $p = 0.542$; significant effect of day $F_{(18,198)} = 1.866$, $p = 0.039$ (Bonferroni post hoc test, n.s.) and effect of MAM model × day interaction $F_{(13,143)} = 1.587$, $p = 0.095$. The results of the numbers of infusions analysis: effect of MAM model $F_{(1,11)} = 0.536$, $p = 0.480$; significant effect of day $F_{(13,143)} = 1.856$, $p = 0.041$ (Boferroni post hoc test, n.s.) and effect of MAM model × day interaction $F_{(13,143)} = 0.950$, $p = 0.504$. Lastly, the results of the METH dose analysis: effect of MAM model $F_{(1,11)} = 0.595$, $p = 0.457$, significant effect of day $F_{(13,143)} = 1.950$, $p = 0.029$ (Bonferroni post hoc test, n.s.), and effect of MAM model × day interaction $F_{(13,143)} = 1.061$, $p = 0.340$. The significant effect of day shows the successful training process in the operant task which was expected in both groups; however, the post hoc test did not reveal any differences between specific days.

Analogous analysis of the RELAPSE phase (days 31–35) showed similar results. Nose-poking behaviour: effect of MAM model $F_{(1,11)} = 1.438$, $p = 0.256$; effect of day $F_{(4,44)} = 0.857$, $p = 0.497$ and effect of MAM model × day interaction $F_{(4,44)} = 1.364$, $p = 0.262$. The results of the numbers of infusions analysis: effect of MAM model $F_{(1,11)} = 1.165$, $p = 0.304$; significant effect of day $F_{(4,44)} = 5.256$, $p = 0.002$ (Boferroni post hoc test, n.s.) and



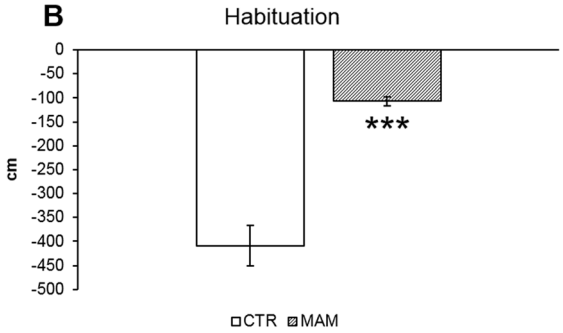
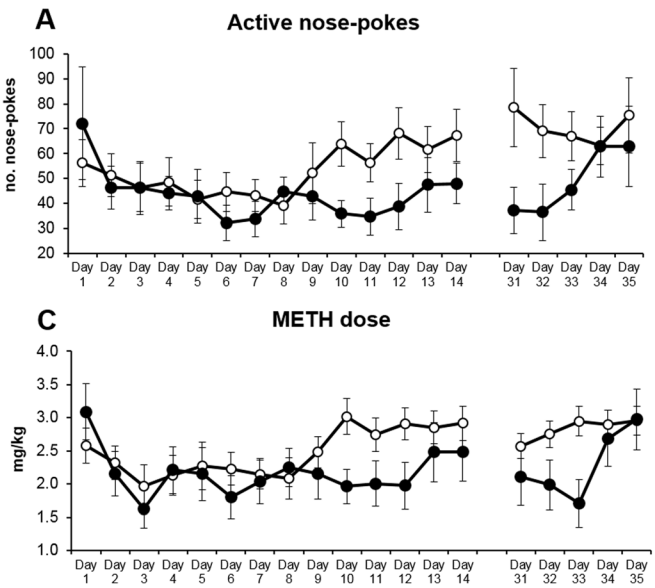


Fig. 1 MAM animals show low locomotor habituation in novel activity cage. **a** Distance travelled (in centimetres) in 1-min bins. Repeated measures ANOVA revealed a significant MAM model × minute interaction (p = 0.001). **b** Summarizes the habituation process (calculated by subtracting the locomotion in minute 1 from the score in minute 10). The data show animals in the control group have reduced their locomotor activity by approximately 400 cm whilst the MAM animals only by roughly 100 cm (***t test, p = 0.0003). All data are shown as means (±SEM)

significant effect of MAM model × day interaction $F_{(4,44)}$ = 3.037, p = 0.027 (Boferroni post hoc test, n.s.). Lastly, the results of the METH dose analysis: effect of MAM model $F_{(1,11)}$ = 1.263, p = 0.285; significant effect of day $F_{(4,44)}$ = 4.245, p = 0.005 (Bonferroni post hoc test, n.s.) and significant effect of MAM model × day interaction $F_{(4,44)}$ = 2.880, p = 0.033 (Bonferroni pos -hoc test, n.s.). The significant effect of day and MAM model × day interaction indicated certain delay in reaching the maintenance level of operant responding which can be attributed mainly to the MAM group but no significant effect of the MAM model was actually demonstrated. However, the post hoc test did not reveal any differences between specific days. The relapse values are also converted to a percentage of the maintenance scores in all the measures (D) and this conversion did not detect any changes either: t test, nose poking p = 0.985, number of infusions p = 0.926 and METH dose p = 0.764.

Acute Ketamine Pre-treatment Effect on METH IVSA

After reaching stable self-administration behaviour for 3 days, an IP injection of saline was administered to assess the effect of injection on the METH intake. After reaching the stable intake again, an IP ketamine dose was administered before the session. The results are depicted on Fig. 3 in terms of number of active nose-pokes (Fig. 3a), number of infusions (Fig. 3b) and METH dose self-administered in milligrams per kilogram (Fig. 3c). Kruskal-Wallis ANOVA revealed significant effect in the number of nose-pokes: $H(3)$ = 7.995, p = 0.046; however, multiple comparison of the groups



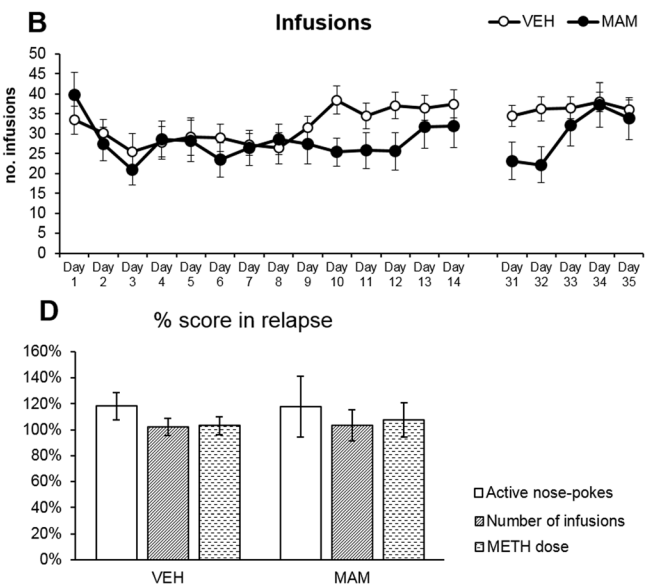


Fig. 2 Comparison of drug-taking behaviours in maintenance and relapse phases. The graphs show mean (±SEM) values of IVSA parameters during 14 days of maintenance and 5 days of relapse in MAM and control animals: active drug-paired nose-pokes (**a**), number of infusions (**b**) and METH dose self-administered (**c**). **d** Conversion to percent: relapse values/maintenance values × 100. There was no difference between maintenance and relapse in either group (MAM or control) which would suggest differences between the groups

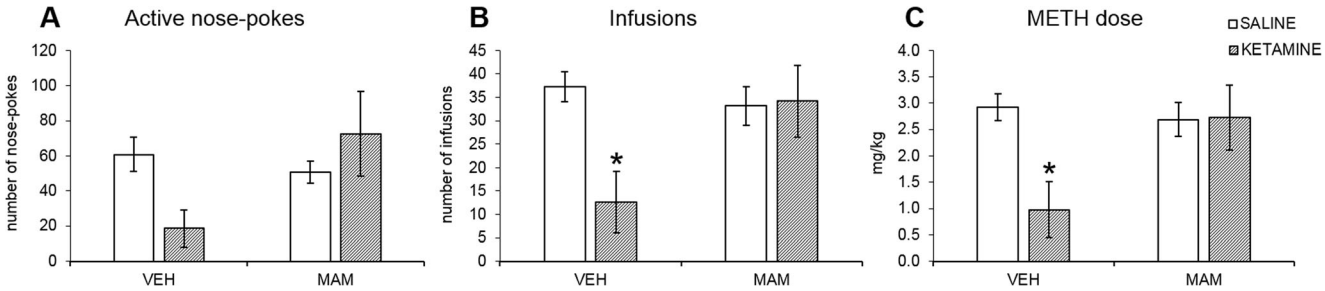


Fig. 3 Acute ketamine effect on METH IVSA. The graphs indicate mean (±SEM) values of IVSA parameters after saline (vehicle) or ketamine IP injection in control and MAM rats. Kruskal-Wallis ANOVA revealed significant effect in the number of active nose-pokes (**a**); however, multiple comparison of the groups rendered only $p = 0.078$ for VEH-SAL vs. VEH-KET (not marked in the graph) and no effect of treatment in the MAM rats. In analysis of the number of infusions (**b**), Kruskal-Wallis ANOVA with multiple comparison of the groups identified a significant effect of ketamine in the control group: $*p = 0.026$. Lastly, METH dose data (**c**) were analysed by two-way ANOVA with Bonferroni post-hoc test ($*p = 0.022$)

rendered only $p = 0.078$ for VEH-SAL vs. VEH-KET. In analysis of the number of infusions, Kruskal-Wallis ANOVA also revealed a significant effect: $H(3) = 9.741$, $p = 0.021$. Furthermore, multiple comparison of the groups identified a significant effect of ketamine in the control group: $p = 0.026$. METH dose data were normally distributed and analysed by two-way ANOVA which detected an almost significant effect of treatment: $F_{(1,20)} = 4.325$, $p = 0.0506$, as well as a significant interaction of model × treatment: $F_{(1,20)} = 4.701$, $p = 0.0424$. No effect was detected in case of the model: $F_{(1,20)} = 2.719$, $p = 0.115$. Bonferroni post hoc test confirmed the effect of treatment ($p = 0.023$) and in the analysis of the interaction, detected a significant difference between VEH-SAL vs. VEH-KET ($p = 0.022$).

To provide a better insight into the specific reaction of animals on ketamine dose, the self-administration patterns after vehicle and ketamine dose of individual animals are summarized on Figs. 4 and 5 for control and MAM animals, respectively. Interestingly, in the control group, there are three types or reactions to the drug. Four animals extinguished the operant behaviour almost entirely, two experienced a delayed onset and one did not react. In MAM animals, one showed suppression, two did not respond and two increased the operant behaviour.

Discussion

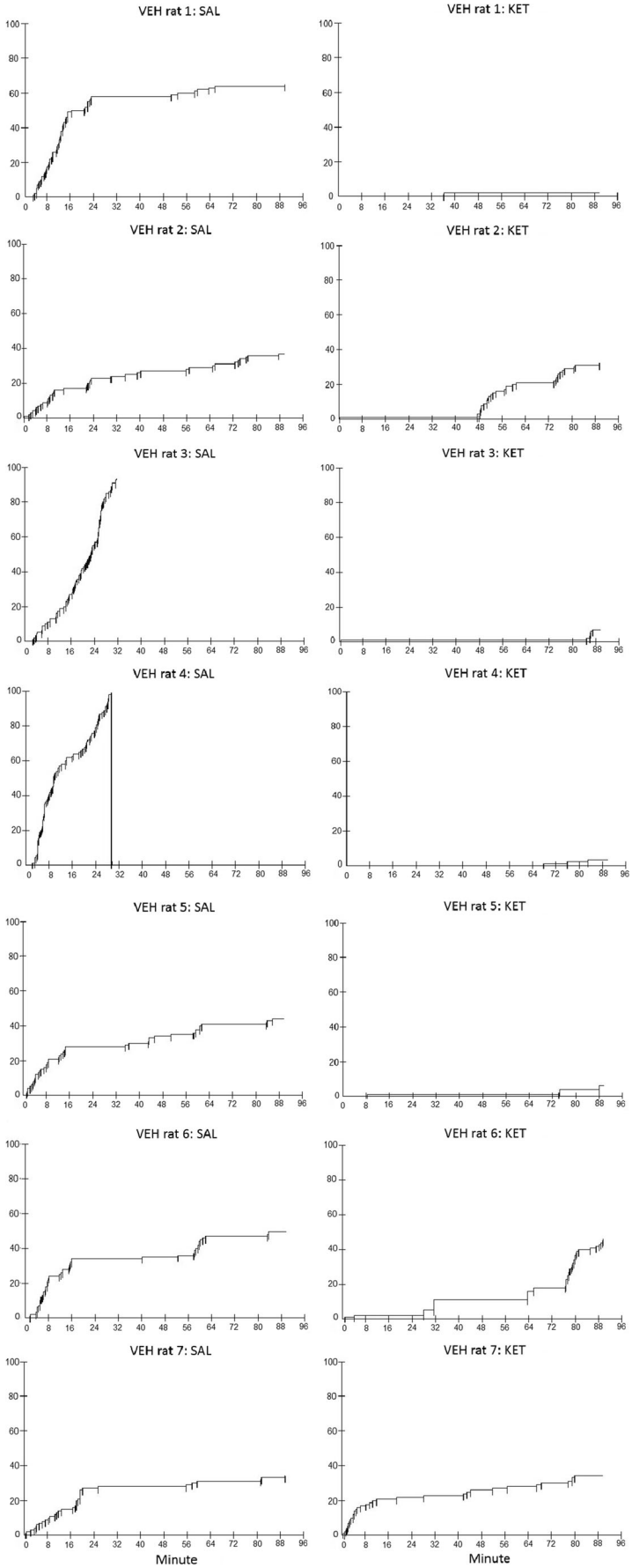
Psychostimulant Self-Administration in the MAM Model

In this study, we used the well-validated neurodevelopmental model of schizophrenia induced by prenatal (GD 17) treatment with methylazoxymethanol (MAM) acetate. The schizophrenia-like phenotype was apparent by the lack of habituation and a trend to hyperactivity in novel environment as previously described (Lodge and Grace 2007; Le Pen et al. 2011). The spontaneous hyperlocomotion (resulting in slower habituation process) is a marker of psychomotor agitation considered as one of the hallmarks of the schizophrenia-like phenotype which may be interpreted as a positive-like symptom (Young et al. 2010).

As expected, both control and MAM rats developed stable maintenance of METH self-administration with no differences in operant behaviour between the groups as shown earlier (Ruda-Kucerova et al. 2017) with METH and in cocaine (Featherstone et al. 2009). This result can be supported by the fact that amphetamine challenge dose increases dopaminergic (DA) release in both medial prefrontal cortex (PFC) and nucleus accumbens (NAc) shell in MAM and control rats alike (Flagstad et al. 2004). This suggests equivalent rewarding effect of moderate psychostimulant exposure as the dose used in the study was 2 mg/kg, similar to what was spontaneously self-administered.

Furthermore, the relapse stage of the study showed the same extent of drug intake in both control and MAM animals indicating a simple continuation in the stable drug self-administration. Relapse phase of this study was conducted under the same conditions as the maintenance phase, i.e. fixed ratio 1 schedule of reinforcement. This setting shows rather consummator behaviour than the extent of appetitive behaviour, i.e. motivation to obtain the drug as progressive schedules would do (Roberts et al. 2013) or escalation of drug taking as prolonged session approach showing loss of control over the drug intake (Kitamura et al. 2006). Therefore, it seems that consummator behaviour is unaffected in the MAM model but we cannot rule out potential differences in METH-driven

Fig. 4 Self-administration patterns of individual control animals after ▶ vehicle and ketamine treatment. The figure shows temporal responding patterns of the IVSA session after saline and later ketamine treatment. The *line* indicates the increasing cumulative record of nose-poking whilst the *vertical bars* indicate the flashing light as a cue for infusion delivery. The caption of each figure refers to the specific number of animal. The saline treatment is on the left and ketamine on the right side. The IVSA patterns of control animals show almost total suppression of operant behaviour in four rats (numbers 1, 4, 5, and 6); well visible delay to begin self-administration behaviour (numbers 2 and 6) and no effect in the rat 7)


VEH rat 1: SAL
VEH rat 1: KET
VEH rat 2: SAL
VEH rat 2: KET
VEH rat 3: SAL
VEH rat 3: KET
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VEH rat 4: KET
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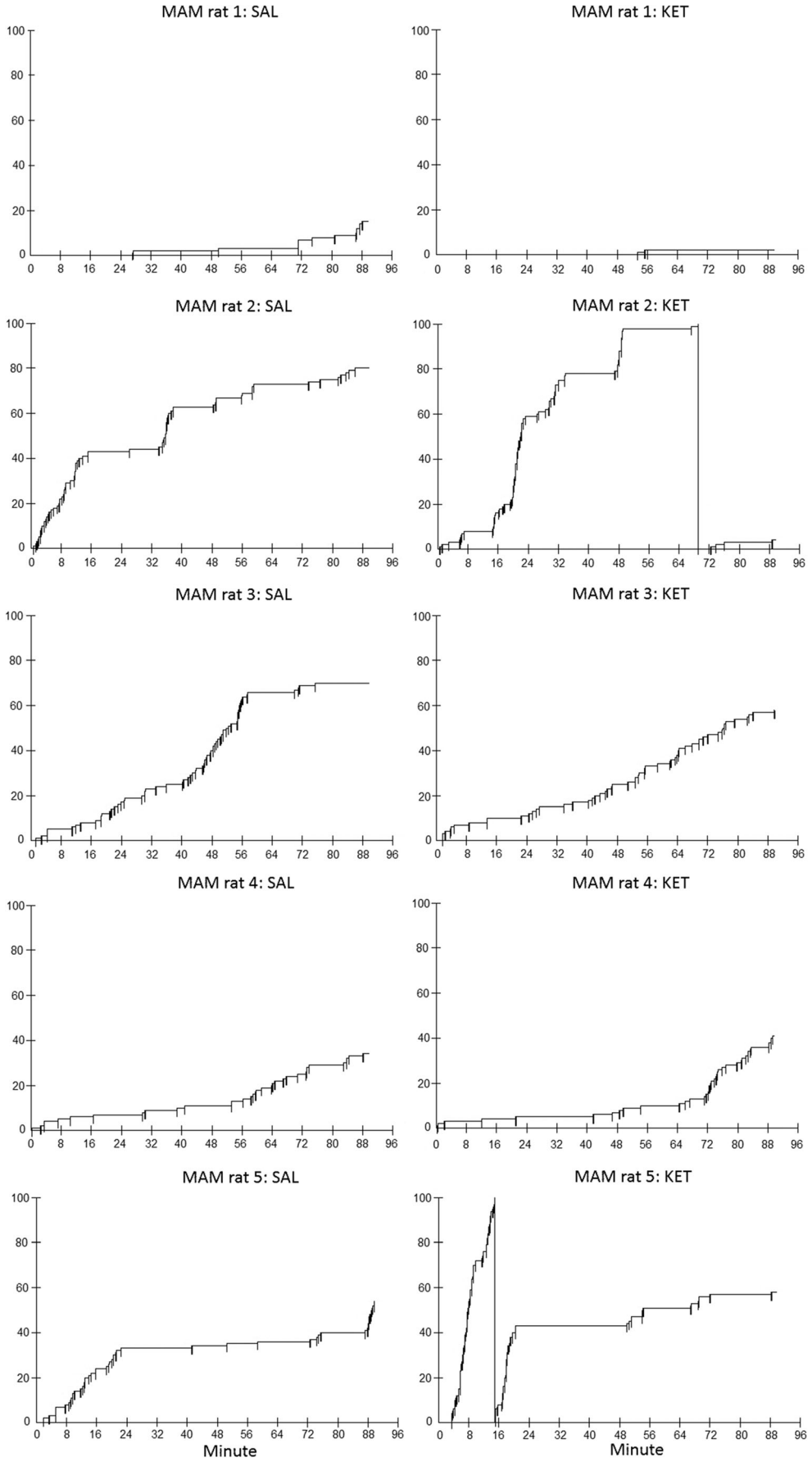
MAM rat 1: SAL
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MAM rat 4: SAL
MAM rat 4: KET
MAM rat 5: SAL
MAM rat 5: KET
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◀ **Fig. 5** Self-administration patterns of individual MAM animals after vehicle and ketamine treatment. The figure shows temporal responding patterns of the IVSA session after saline and later ketamine treatment. The *line* indicates the increasing cumulative record of nose-poking whilst the *vertical bars* indicate the flashing light as a cue for infusion delivery. The caption of each figure refers to the specific number of animal. The saline treatment is on the *left* and ketamine on the *right* side. In the MAM animals only rat 1 showed a decrease after ketamine dose whilst all other animals either did not respond at all or even increased the operant responding (rat 5)

appetitive behaviours of the MAM rats which were not assessed yet.

Potential Mechanisms of Ketamine-Induced Suppression of METH Self-Administration

The most important finding of this study was that low-dose ketamine effectively suppressed METH IV self-administration in control rats. This is consistent with clinical reports showing that ketamine is able to effectively decrease cocaine (Dakwar et al. 2014a, b) and heroin (Krupitsky et al. 2002) craving whilst an earlier study using a CPP paradigm did not detect this effect (Xu et al. 2006).

An explanation of the operant behaviour suppression in the control rats could lie in the acute effect of ketamine on METH withdrawal symptoms including increased NMDA transmission in the NAc as shown in preclinical studies with alcohol (Davidson et al. 1995; Dahchour et al. 1998). Another possible explanation could be ketamine's effect to induce BDNF levels in METH withdrawal phases. METH withdrawal has also been characterised by development of depressive-like state with lowered BDNF levels (Koob and Volkow 2016). Decrease of BDNF may be a universal effect of drug withdrawal as this was found after d-amphetamine repeated administration (Angelucci et al. 2007) or morphine self-administration study in rats (Lee et al. 2016) as well as in male patients abstaining from alcohol (Heberlein et al. 2016). A study exploring the neurochemical effects of d-amphetamine discontinuation in Sprague-Dawley rats suppressed BDNF release in several brain regions and this dysregulation was restored by 10 mg/kg dose of ketamine (Fuller et al. 2016). Moreover, this notion is further supported by a recent study showing that a micro-infusion of BDNF into prelimbic cortex (a part of prefrontal cortex) suppresses cocaine seeking in a relapse session in rats (Go et al. 2016).

Although ketamine has multiple proposed molecular targets, its anti-addiction properties are believed to derive mainly from its ability to non-competitively antagonize NMDA receptors. Ketamine exerts an acute enhancing effect on BDNF signalling (Lepack et al. 2014) and its NMDA antagonistic mechanism may also suppress potential behavioural sensitization and inhibit the drug-associated memories (Landa et al. 2014). Acute sub-anaesthetic doses of ketamine is believed to initiate neuroplastic changes, increase neuronal connectivity and synaptogenesis in PFC due to disinhibited glutamate release (Miller et al. 2016; Abdallah et al. 2016). Acute ketamine (3 mg/kg), as soon as 30-min post-infusion, induce significant decrease in immobility in FST in wild-type but not in BDNF knockout mice. This effect was abolished by administration of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and kainate receptor antagonist NBQX. At this early time point (30-min post-infusion), enhanced BDNF expression was also already present (Autry et al. 2011).

Current evidence suggests that rapid antidepressant effect of ketamine is mediated by upregulation of BDNF followed by activation of tropomyosin receptor kinase B (TrkB) (Bjorkholm and Monteggia 2016). However, the matter is inconclusive. A comprehensive study in mice combined subchronic METH exposure and following chronic treatment with TrkB ligands showing that METH dosing over 5 days lead to depressive-like behaviours and increased BDNF expression in NAc. TrkB antagonist reduced this phenomena, blocked expression of behavioural sensitization (locomotion), suppressed METH-induced (1 mg/kg) DA release in NAc shell and normalized dendritic changes without influence on BDNF levels (Ren et al. 2015). A different report indicates that ketamine has a similar acute antidepressant-like behavioural effects as TrkB antagonist as shown in a model of depression induced by social defeat where both substances also increased BDNF in PFC (Zhang et al. 2015). This contradiction suggests that other mechanism than TrkB regulation in the PFC is responsible for the rapid antidepressant effect. On the other hand, ketamine alone increased DA release in NAc shell at both low (Mathe et al. 1998; Marcus et al. 2001) and high doses (Masuzawa et al. 2003). Furthermore, MRI spectroscopy showed ketamine-induced hyperglutamatergic activity in the PFC in rats (Kim et al. 2011).

Recently, more attention has been diverted to the AMPA agonistic property of ketamine. AMPA-mediated responses were identified as soon as after 30 min after administration of 10 mg/kg of ketamine (El Iskandrani et al. 2015), i.e. the same dose and timing used in this study. More importantly, the antidepressant-like effects of ketamine were also blocked by NBQX administered both systemically or via a microinjection into the mPFC (Fukumoto et al. 2016). Another study also suggested that the sustained antidepressant effect of ketamine is due to enhancement of AMPA-mediated transmission as a mechanism responsible for sustained antidepressant effect of ketamine (Koike and Chaki 2014). Furthermore, low doses of AMPA alone or in combination with ketamine were also shown to exert antidepressant-like effects (Akinfiresoye and Tizabi 2013). Therefore, it seems that the suppressing effect of acute ketamine on METH IVSA found in this study may be also explained by increased glutamatergic signalling in the PFC presumably via AMPA agonistic properties. Notably, kainate receptors may play a similar role as we proposed for

AMPA receptors but their exact role have not been elucidated since mixed AMPA-kainate antagonists (like NBQX) are often used. Recently, intra-prelimbic cortical infusion of BDNF was shown to suppress operant cocaine seeking in rats which was abolished when gluN2A or gluN2B antagonist was infused before BDNF (Go et al. 2016). This evidence further supports our hypothesis that ketamine-induced enhancement of glutamatergic signalling in the PFC may be the mechanism responsible for the anti-craving effect. However, the matter is complicated and the exact mechanism needs to be identified.

Lack of Ketamine Effect on METH Self-Administration in the MAM Rats

Interestingly, ketamine's inhibition on drug craving was completely absent in the MAM rats indicating a disrupted/impaired neurochemical pathway in this model in which ketamine would normally act upon. MAM rats showed a higher locomotor response to 10 mg/kg to ketamine than control rats which is considered as positive-like symptomatology confirming the schizophrenia-like phenotype (Phillips et al. 2012). Therefore, a different effect of ketamine on METH self-administration behaviour can be expected as well. Similarly as seen in drug-naïve patients with schizophrenia (Hu et al. 2015), MAM rats seem to have impaired PFC functions (hypofrontality) shown by morphological, functional, metabolic and behavioural alterations (Kaneko et al. 2016). This could explain their unresponsiveness to ketamine, which induces glutamatergic signalling in the PFC. In accordance, MAM rats were also shown to have attenuated extracellular release of glutamate in medial PFC but not in the NAc shell after a dizocilpine challenge compared to control rats and at the same time increased locomotion (Lena et al. 2007). This is also in accordance with the lack of METH self-administration suppressing effect found in the control rats in this study, i.e. abolished AMPA agonistic effect in the PFC. The NMDA antagonistic effect of ketamine which leads glutamate release in the PFC in healthy brain may fail in the MAM model. Direct AMPA agonistic manipulation might provide positive data on the METH self-administration suppression. Furthermore, we have detected an increased expression of BDNF in several brain regions including PFC and NAc in the MAM model (data in preparation) which represents a possibility of altered neurochemical response to acute ketamine.

Conclusion

It seems that ketamine effectively blocks potential depressive-like symptoms following METH withdrawal leading to suppression of spontaneous METH intake whilst this mechanism fails in the MAM model. This effect may be explained by increased glutamatergic and BDNF signalling in the PFC; however, this study did not provide direct evidence on which would prove this mechanism. The lack of effect in the MAM rats can be explained by their impaired prefrontal glutamatergic signalling. Therefore, increased glutamatergic and BDNF signalling in the PFC may at least partly explain the clinically proven anti-craving potential of ketamine and further research could allow development of more specific anti-craving medications with less risks.

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Compliance with Ethical Standards

Conflict of Interest None.

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