Behavioural Brain Research 348 (2018) 211–218

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Effects of methamphetamine exposure on anxiety-like behavior in the open field test, corticosterone, and hippocampal tyrosine hydroxylase in adolescent and adult mice

Katelyn H. Struntz, Jessica A. Siegel*

Department of Psychology, University of St. Thomas, 2115 Summit Ave, Saint Paul, MN, 55105, USA

ARTICLE INFO

Keywords:
Methamphetamine
Corticosterone
Adolescence
Anxiety
Tyrosine hydroxylase
Mice

ABSTRACT

Methamphetamine (MA) is a psychomotor stimulant drug that can alter behavior, the stress response system, and the dopaminergic system. The effects of MA can be modulated by age, however relatively little research has examined the acute effects of MA in adolescents and how the effects compare to those found in adults. The hippocampal dopamine system is altered by MA exposure and can modulate anxiety-like behavior, but the effects of MA on the hippocampal dopamine system have not been well studied, especially in adolescent animals. In order to assess potential age differences in the effects of MA exposure, this research examined the effects of acute MA exposure on locomotor and anxiety-like behavior in the open field test, plasma corticosterone levels, and hippocampal total tyrosine hydroxylase and phosphorylated tyrosine hydroxylase levels in adolescent and adult male C57BL/6 J mice. Tyrosine hydroxylase is the rate limiting enzyme in the synthesis of dopamine and was used as a marker of the hippocampal dopaminergic system. Mice were exposed to saline or 4 mg/kg MA and locomotor and anxiety-like behavior were measured in the open field test. Serum and brains were collected immediately after testing and plasma corticosterone and hippocampal total tyrosine hydroxylase and phosphorylated tyrosine hydroxylase levels measured. MA-exposed mice showed increased locomotor activity and anxiety-like behavior in the open field test compared with saline controls, regardless of age. There was no effect of MA on plasma corticosterone levels or hippocampal total tyrosine hydroxylase or phosphorylated tyrosine hydroxylase levels in either adolescent or adult mice. These data suggest that acute MA exposure during adolescence and adulthood increases locomotor activity and anxiety-like behavior but does not alter plasma corticosterone levels or hippocampal total tyrosine hydroxylase or phosphorylated tyrosine hydroxylase levels, and that these effects are not modulated by age.

1. Introduction

Methamphetamine (MA) is a psychomotor stimulant drug that alters multiple neurotransmitter systems, including the dopamine (DA) system [1]. MA is a widely used illicit drug, and rates of MA use among adolescents increased in the early 2000s [2,3]. Adolescent MA users show increased levels of anxiety and impaired executive function compared to non-drug using adolescents [4,5] and increased levels of depression compared to adolescents using other drugs of abuse [6]. Adult MA users also show high levels of anxiety and other psychiatric symptoms [7], and reductions in hippocampal volumes compared to controls [8]. MA also acutely increases feelings of anxiety in healthy non-drug using adults [9]. As the adolescent brain is still developing, MA may have different behavioral and neurobiological effects in adolescents compared to adults. Therefore, it is important to investigate potential differences in the effects of MA exposure between adolescents and adults.

Research in human MA users shows greater gray and white matter alterations in adolescent MA users compared to adult MA users [10]. Preclinical research has also examined the age-dependent effects of MA and studies in rodents show acute MA exposure affects adolescents and adults differently. For example, while both adolescent and adult mice show MA-induced increases in locomotor activity, the magnitude of this increase is lower in adolescent rodents compared to adult rodents [11–14]. Adolescent rats show lower MA-induced increases in locomotor activity over 5 consecutive days of MA exposure compared to adult rats [14]. Studies have also examined the effects of MA on anxiety-like behavior in rodents. Studies examining the effects of acute MA exposure on anxiety-like behavior in adult rodents have produced conflicting results. For example, acute MA exposure decreases anxiety-

* Corresponding author at: 2115 Summit Ave, JRC LL56, Saint Paul, MN 55105, USA.
E-mail addresses: stru6260@stthomas.edu (K.H. Struntz), jessica.siegel@stthomas.edu (J.A. Siegel).

https://doi.org/10.1016/j.bbr.2018.04.019
Received 24 February 2018; Received in revised form 9 April 2018; Accepted 14 April 2018
Available online 20 April 2018
0166-4328/

like behavior in adult rats in the open field test [15,16] and the elevated plus maze [15,17,18], but acute MA exposure has also been shown to increase anxiety-like behavior in the elevated plus maze [19]. Relatively little research has examined the effects of acute MA exposure in adolescent rodents. Previous research from our lab shows that acute MA exposure increases anxiety-like behavior in the open field test in adolescent mice [20]. However more research is needed to understand how the effects of acute MA exposure may differ between adolescents and adults. The goal of the current study was to replicate previous research examining the effects of acute MA exposure in adolescent mice [20] and include a direct comparison with the adult age group. In order to better understand how acute MA exposure alters anxiety-like behavior and how these effects may differ between adolescents and adults, the current study assessed the effects of acute MA exposure on anxiety-like behavior in the open field in both adolescent and adult mice.

MA's effects on the hypothalamic pituitary (HPA) axis and the stress response system may be one mechanism by which MA can alter anxiety-like behavior. Adolescent MA users show increased cortisol levels following a social stressor compared to non-using controls [4]. In contrast, abstinent adult MA users have lower cortisol levels compared to non-using controls [21]. In rodents, acute MA exposure increases corticosterone levels in neonates [22–25] and adults [26–28], but not in adolescents [20]. Further research is needed to understand age differences in the effects of MA on the HPA axis.

MA-induced changes in anxiety-like behavior may also be due to MA's effects on the DA system [1] in various brain regions, including the hippocampus. It is well established that MA increases DA release from the ventral tegmental area (VTA) and alters the striatal DA system [29]. The hippocampus receives DA projections from the VTA and substantia nigra (SN) [30], two regions of the brain reward pathway that are directly affected by MA [29]. However, little research has examined the effects of MA on the hippocampal DA system and potential age differences in the effects of MA on the hippocampus. Although the hippocampus is not commonly implicated in MA abuse behaviors, recent evidence shows its involvement in the response to MA. For example, MA infusions directly into the hippocampus result in increased MA seeking behavior and self-administration, and these responses are blocked by DA D_1/D_5 receptor antagonists in the hippocampus [31]. There is evidence in humans that MA use affects the hippocampus [8] and MA induces long-term reductions in DA transporter levels in the hippocampus in rats [32]. The hippocampal DA system also modulates anxiety-like behavior [33]. Lesions of the hippocampus can increase anxiety-like behavior and studies have shown that DA receptors in the hippocampus are involved in anxiety-like behavior (for a review, see [33]). Additionally, the hippocampus interacts with the HPA axis and can inhibit further activation of the HPA axis and regulate the stress response [34]. Thus, MA's effects on anxiety-like behavior may be, in part, modulated by its actions on the HPA axis and the DA system in the hippocampus, and more research is warranted to better understand the effects of MA on the hippocampal DA system. Tyrosine hydroxylase (TH) is the rate limiting enzyme in the synthesis of DA [35], and the phosphorylated form of TH (pTH) is the activated form of the enzyme [35]. Phosphorylation of TH stimulates production of DA [36,37], and levels of TH and pTH can be used as markers of the DA system. Psychomotor stimulant drugs have been shown to decrease pTH levels in the caudate and the nucleus accumbens in rats 15 min following drug exposure, suggesting this modification of the TH enzyme occurs quickly following psychomotor stimulant exposure [38]. As little research has examined the effects of MA on the hippocampal DA system, we assessed the effects of acute MA exposure on total TH and pTH levels in the hippocampus of adolescent and adult mice.

To the best of our knowledge, no study has directly compared the effects of acute MA exposure on anxiety-like behavior in adolescent and adult mice or examined the effects of acute MA exposure on the hippocampal DA system in adolescent mice, and how these effects may differ from the effects in adult mice. Previous work from our lab shows increased anxiety-like behavior in adolescent mice following acute MA exposure [20], but it remains unclear if this effect is age-dependent and differs from the effects of MA in adults. Therefore, in the current study, we examined the effects of acute MA exposure on locomotor activity and anxiety-like behavior, plasma corticosterone levels, and hippocampal levels of TH and pTH in adolescent and adult mice. We hypothesized that acute MA exposure would increase locomotor activity, increase anxiety-like behavior, increase corticosterone levels, and decrease hippocampal TH and pTH levels to a greater degree in adult mice compared to adolescent mice.

2. Material and methods

2.1. Mice

Eighteen adolescent and 18 adult male C57BL/6 J mice from The Jackson Laboratory (Bar Harbor, ME, USA) were used. Mice arrived in our colony on postnatal day (PND) 24 for adolescent mice and PND 90 for adult mice. Mice were housed according to age with 2 mice per cage in standard mouse cages with bedding and nesting material under a 12-hour light/dark cycle (light on at 09:00). Mice had ad libitum access to food and water. In order to habituate the mice to handling and injections, all mice received intraperitoneal (IP) injections of 0.9% sterile saline (0.1 mL) 3 days a week for 2 consecutive weeks from PND 30–41 for adolescent mice and from PND 96-107 for adult mice (Fig. 1). All procedures and protocols were approved by the University of St. Thomas Institutional Animal Care and Use Committee (IACUC).

2.2. Open Field testing

The open field test was performed on either PND 42 or PND 43 for adolescent mice and on either PND 108 or PND 109 for adult mice (Fig. 1). Locomotor activity and anxiety-like behavior were measured in the open field test [39]. Testing was conducted under bright light (530 lux) and with background white noise (55 dB). Mice were tested in 2 consecutive 20-minute trials. Trial 1 was used to assess baseline behavior and trial 2 assessed behavior following treatment exposure. Consecutive trials to establish baseline behavior and behavioral

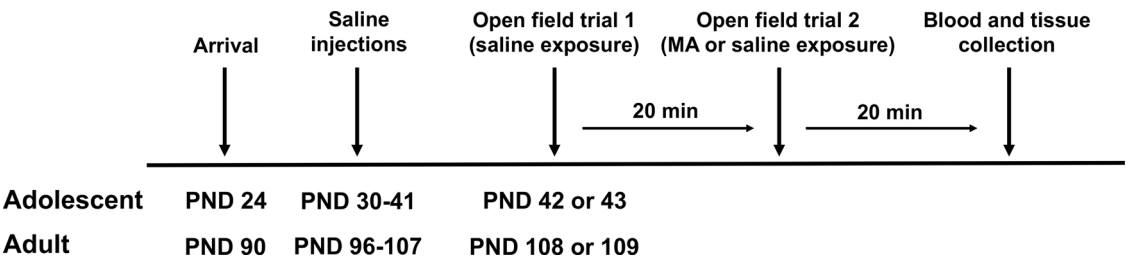

Fig. 1. Timeline of experiment. For open field testing, mice were injected with saline immediately prior to trial 1 (20 min). Following trial 1, mice were removed from the open field arenas, injected with either saline or 4 mg/kg MA, and then immediately placed back in the open field arenas for trial 2 (20 min). Blood and tissue collection occurred immediately after trial 2 was completed. MA = methamphetamine.

changes following MA exposure have been used in previous studies to examine the age-dependent effect of MA exposure [14]. In addition, one goal of this study was to directly replicate previous research examining the effects of adolescent MA exposure, and thus we used the same open field testing paradigm [20]. The open field arenas were 40 × 40 cm arenas with clear Plexiglas walls. The center of the arenas was defined as the inner 20 × 20 cm area [40,41] and the corners of the arenas were defined as the 10 × 10 cm squares in each corner of the arena. For the first 20-minute trial (trial 1), all mice received IP injections of 0.9% sterile saline (0.1 mL) and were immediately placed in the center of the open field arena. Following baseline open field testing in trial 1, mice were removed from the arenas and received an IP injection of either 0.9% sterile saline (0.1 mL, $n = 9$ per age group) or 4 mg/kg (d)-MA hydrochloride (Sigma Aldrich, St. Louis, MO) dissolved in 0.9% sterile saline (0.1 mL, $n = 9$ per age group). This dose was used to replicate previous research from our lab [20] and based on previous research showing 4 mg/kg MA increases locomotor activity to a greater degree than 1 mg/kg or 2 mg/kg MA in adolescent C57BL6/J mice [42] and increases DA levels in the brain reward pathway [43]. Treatments were counterbalanced between the mice in each cage, age groups, and the days of testing. Mice were immediately placed back in the center of the open field arena for another 20-minute trial (trial 2) following treatment exposure. Anymaze Video Tracking program (Stoelting Co., Wood Dale, IL) was used to record and measure total distance moved, the percent time spent in the center of the open field arena, the percent distance moved in the center of the open field arena, and the percent time spent in the corners of the arena in each trial. Percent time in the center and percent distance moved in the center of the arena were used as measures of anxiety-like behavior [39,40,44,45]. In addition, we examined the percent of time the mice spent in the corners of the arena as an additional measure of anxiety-like behavior [46]. Arenas were cleaned with 70% isopropyl alcohol between trials.

2.3. Corticosterone ELISA

Immediately after open field testing, mice were euthanized via cervical dislocation and decapitation. Serum was collected and stored at −80 °C until use. Plasma corticosterone levels were measured in 6 mice per treatment group using a competitive ELISA kit according to the manufacturer's instructions (Abcam, Cambridge, MA) and the absorbance was measured at 450 nm using a spectrophotometer.

2.4. Total tyrosine hydroxylase and phosphorylated tyrosine hydroxylase western blotting

Immediately after open field testing, mice were euthanized via cervical dislocation and decapitation, brains were extracted and flash frozen in liquid nitrogen, and brains were stored at −80 °C until use. Lysis buffer (150 nM NaCl, 0.1% Triton X-100, 50 mM Trish HCl, SigmaFast protease inhibitor (Sigma Aldrich, St. Louis, MO)) was added to dissected hippocampi from 5–6 mice per treatment group. Samples were homogenized twice for 30 s each (OMNI Bead Ruptor, OMNI International, Inc., Kennesaw, GA), and placed on a shaker for 30 min on ice. Samples were centrifuged at 12,000 RPM for 20 min at 4 °C. The supernatant was analyzed by BCA assay to assess protein levels (ThermoFisher, Waltham, MA). 20 µg of each sample was mixed with Laemmli sample buffer with 10% mercaptoethanol (Bio-Rad, Hercules, CA), boiled for 10 min, and loaded on a graded 4–20% precast polyacrylamide gel (Bio-Rad, Hercules, CA). Proteins were separated by SDS-PAGE at 100 V for 90 min before proteins were transferred to nitrocellulose membranes at 4 °C overnight at 10 mA. Membranes were blocked at room temperature with 5% nonfat dry milk in phosphate buffered saline (PBS) with 0.2% triton X-100 (PBS-T). Membranes were washed with PBS-T and incubated in rabbit anti-TH primary antibody in 5% nonfat dry milk (1:2000 concentration; Millipore, Burlington, MA), rabbit anti-pTH (phosphor Ser40) primary antibody in 5% nonfat dry milk (1:1000 concentration; GeneTex, Irvine, CA), or rabbit anti-beta actin primary antibody in 5% nonfat dry milk (1:5000 concentration; Abcam, Cambridge, MA) overnight at 4 °C. Membranes were washed and then incubated in biotinylated goat anti-rabbit secondary antibody in 5% nonfat dry milk (1:5000 concentration; Vector Laboratories, Burlingame, CA) for 2 h at room temperature. Membranes were washed with PBS-T and incubated in avidin-biotin complex (ABC Elite Kit, Vector Laboratories, Burlingame, CA) for 1 h at room temperature. Labeling was visualized by incubating membranes in nickel-enhanced 3,3′-diaminobenzidine (DAB; 2% v/v 5 mg/mL DAB, 0.1% v/v 3% H_2O_2, 0.25% nickel ammonium sulfate in PBS) for 15 min at room temperature and membranes were washed with PBS. Images of the protein bands were converted to black and white, bands were traced, and the greyscale binary mean intensity (0 = black and 255 = white) within the trace was quantified using NIS-Elements Software (Nikon, Tokyo, Japan).

2.5. Data analysis

The effects of trial (trial 1 and trial 2, repeated measure), treatment (saline or MA), and age (adult or adolescent) on total distance moved, percent time spent in center, percent distance moved in the center, and percent time spent in the corners of the open field were assessed using a repeated measure analysis of variance (ANOVA). Significant interactions were explored with univariate ANOVA tests. Distance moved in the open field test was also assessed in 5-min blocks for each trial using a 4-way repeated measure ANOVA, with block and trial as the repeated measures and treatment and age as the between-subjects factors. Significant interactions were further explored in each trial separately until the analysis reached its simplest terms. Greenhouse-Geisser correction for the violation of the assumption of sphericity was used for repeated measures ANOVAs. The effects of treatment and age on plasma corticosterone levels, hippocampal total TH levels, and hippocampal pTH levels were assessed using 2-way ANOVAs. All statistical analyses were conducted using SPSS software (IBM, Armonk, NY). A significance level of $p < 0.05$ was used.

3. Results

3.1. Open field testing

Repeated measures ANOVA was used to assess distance moved in the open field in 5 min blocks across trial 1 and trial 2. When the assumption of sphericity was violated, a Greenhouse-Geisser correction was used for all repeated measures ANOVAs. The analysis showed a significant 3-way block x trial x treatment interaction (F (1.91, 61.39) = 27.2, $p < 0.01$). To explore this interaction, we assessed distance moved in 5 min blocks for each trial separately. For trial 1, there was a significant main effect of block (F (2.40, 81.48) = 43.88, $p < 0.01$). There was no main effect of treatment or interaction between treatment and block. Post-hoc comparisons showed that all mice moved a greater distance during the first block (0–5 min) compared to all other blocks, and all mice moved a greater distance during the second block (5–10 min) compared to the third (10–15 min) and fourth blocks (15–20 min; Fig. 2a). For trial 2, there was a significant block x treatment interaction (F (1.86, 63.23) = 25.04, $p < 0.01$). Thus, we explored the effect of block in each treatment group separately. There was a main effect of block on distance moved for the saline-exposed mice (F (3, 51) = 3.19, $p = 0.03$). Post-hoc comparisons showed that saline-exposed mice moved a greater distance during the first block (0–5 min) compared to the fourth block (15-20 min). There was also a main effect of block on distance moved for the MA-exposed mice (F (1.78, 30.30) = 22.97, $p < 0.01$). Post-hoc comparisons showed that MA-exposed mice moved a greater distance during the third (10–15 min) and fourth blocks (15–20 min) compared to the first (0–5 min) and second blocks (5–10 min), and MA-exposed mice moved

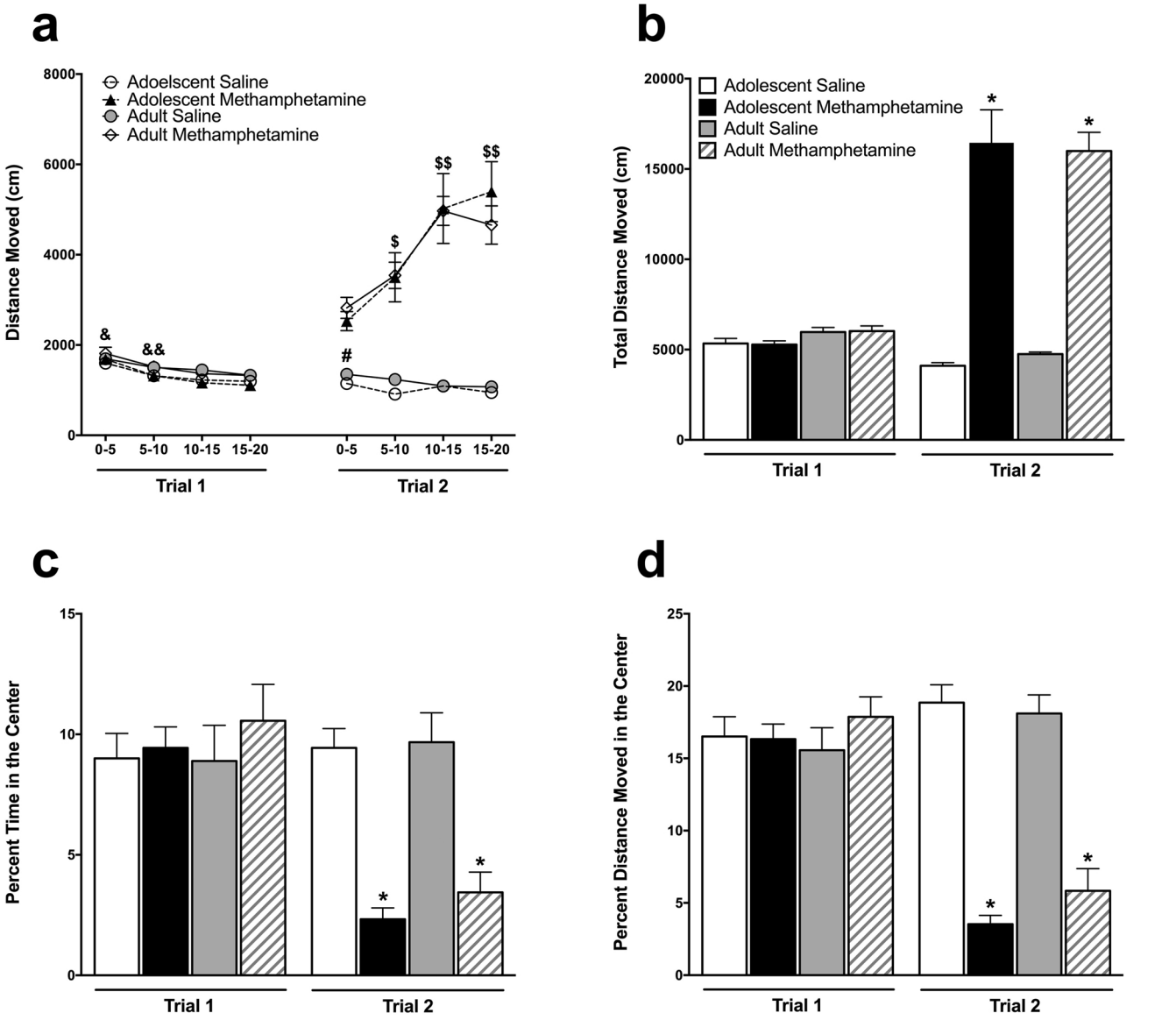

Fig. 2. Behavior in the open field test. All mice received injections of saline immediately prior to trial 1, and mice received injections of either saline or 4 mg/kg methamphetamine immediately prior to trial 2. a) Distance moved in 5-min blocks in trial 1 and trial 2 of the open field test. In trial 1, all mice moved a greater distance during the 0–5 min block compared to all other blocks, and all mice moved a greater distance during the 5–10 min block compared to the 10–15 min and 15–20 min blocks. For trial 2, saline mice moved a greater distance during the 0–5 min block compared to the 15–20 min block. Methamphetamine mice moved a greater distance during the 5–10 min block compared to the 0–5 min block and moved a greater distance during the 10–15 min and 15–20 min blocks compared to the 0–5 min and 5–10 min blocks. b) Total distance moved in the open field test in trial 1 and trial 2. Methamphetamine mice moved a greater total distance in trial 2 compared with saline mice, regardless of age. c) Percent time spent in the center of the open field arena in trial 1 and trial 2. Methamphetamine mice spent a lower percent of time in the center of the open field arena in trial 2 compared with saline mice, regardless of age. d) Percent distance moved in the center of the open field arena in trial 1 and trial 2. $N = 9$ mice per group. Methamphetamine mice showed a lower percent distance moved in the center of the arena during trial 2 compared with saline mice, regardless of age. $^{\&}$0–5 min block higher than all other blocks for all mice, $p < 0.05$. $^{\&\&}$5–10 min block higher than 10–15 min and 15–20 min blocks for all mice, $p < 0.05$. $^{\#}$0–5 min block higher than 15–20 min block in the saline mice, $p < 0.05$. $^{\$}$5–10 min block higher than 0–5 min block in the methamphetamine mice, $p < 0.05$. $^{\$\$}$10–15 min and 15–20 min blocks higher than 0–5 min and 5–10 min blocks in methamphetamine mice, $p < 0.05$. *Methamphetamine mice significantly different from saline mice for both adolescents and adults, $p < 0.05$.

a greater distance during the second block (5–10 min) compared to the first block (0–5 min; Fig. 2a).

Repeated measures ANOVA was used to assess the effect of trial, treatment, and age on total distance moved in the open field test. There was a significant trial x treatment interaction (F (1, 32) = 137.40, $p < 0.01$). One-way ANOVAs were used to explore the effect of treatment in each trial separately. There was no main effect of treatment in trial 1 (F (1, 34) = 0.001, $p = 0.985$). There was a main effect of treatment in trial 2 (F (1, 34) = 131.76, $p < 0.01$), with MA-exposed mice moving a greater total distance than saline-exposed mice, regardless of age (Fig. 2b). There was no main effect of age (F (1, 32) = 0.458, $p = 0.50$) or any interactions with age on total distance moved in the open field test.

Repeated measures ANOVA was used to assess the effect of trial, treatment, and age on the percent time spent in the center of the open field arena. There was a significant trial x treatment interaction (F (1, 32) = 49.13, $p < 0.01$). One-way ANOVAs were used to explore the effect of treatment in each trial separately. There was no main effect of treatment in trial 1 (F (1, 34) = 0.86, $p = 0.36$). There was a main effect of treatment in trial 2 (F (1, 34) = 60.12, $p < 0.01$), with MA-

exposed mice showing lower percent time spent in the center of the arena compared with saline-exposed mice (Fig. 2c). There was no main effect of age (F (1, 32) = 0.45, p = 0.51) or any interactions with age on percent time in the center of the open field arena.

For percent distance moved in the center of the open field arena, there was a significant trial x treatment interaction (F (1, 32) = 133.26, p < 0.01). One-way ANOVAs were used to explore the effect of treatment in each trial separately. There was no main effect of treatment in trial 1 (F (1, 34) = 0.65, p = 0.43). There was a main effect of treatment in trial 2 (F (1, 34) = 128.25, p < 0.01), with MA-exposed mice showing lower percent distance moved in the center of the arena compared with saline-exposed mice (Fig. 2d). There was no main effect of age (F (1, 32) = 0.23, p = 6.33) or any interactions with age on percent distance moved in the center of the open field arena.

Repeated measures ANOVA was used to assess the effect of trial, treatment, and age on the percent time spent in the corners of the open field arena. There was a significant trial x treatment interaction (F (1, 32) = 8.50, p < 0.01). One-way ANOVAs were used to explore the effect of treatment in each trial separately. There was no main effect of treatment in trial 1 (F (1, 34) = 0.003, p = 0.96). There was a main effect of treatment in trial 2 (F (1, 34) = 7.85, p < 0.01), with MA-exposed mice (5.30 ± 0.27%) showing a higher percent time spent in the corners of the arena compared with saline-exposed mice (4.37 ± 0.19%). There was no main effect of age (F (1, 32) = 1.04, p = 0.32) or any interactions with age on percent time in the center of the open field arena.

3.2. Plasma corticosterone levels

There was no main effect of treatment (F (1, 20) = 1.18, p = 0.29) or age (F (1, 20) = 0.70, p = 0.80), nor an interaction between treatment and age, on plasma corticosterone levels (Table 1).

3.3. Total tyrosine hydroxylase and phosphorylated tyrosine hydroxylase levels

There was no main effect of treatment (F (1, 17) = 0.002, p = 0.97) or age (F (1, 17) = 1.04, p = 0.32), nor an interaction between treatment and age, on hippocampal total TH levels (Fig. 3a). There was no main effect of treatment (F (1, 20) = 0.15, p = 0.71) or age (F (1, 20) = 1.73, p = 0.20), nor an interaction between treatment and age, on hippocampal pTH levels (Fig. 3b).

4. Discussion

The aim of the current study was to examine potential age differences between adolescent and adult mice in the acute effects of MA exposure on behavior in the open field test, plasma corticosterone levels, and hippocampal total TH and pTH levels. We found that MA exposure increased locomotor activity and anxiety-like behavior in the open field compared with saline controls, but MA exposure did not alter corticosterone levels or hippocampal TH or pTH levels immediately following open field testing. The effects of MA did not differ between adolescent and adult mice.

MA increased locomotor activity in both adolescent and adult mice.

Table 1
Plasma corticosterone concentrations.

Age	Treatment	Plasma corticosterone concentrations (ug/mL)
Adolescent	Saline	97.52 ± 6.63
Adolescent	Methamphetamine	105.46 ± 6.67
Adult	Saline	96.70 ± 7.29
Adult	Methamphetamine	103.75 ± 5.11

Note: All measures shown as group means ± SEM.
N = 6 mice per group.

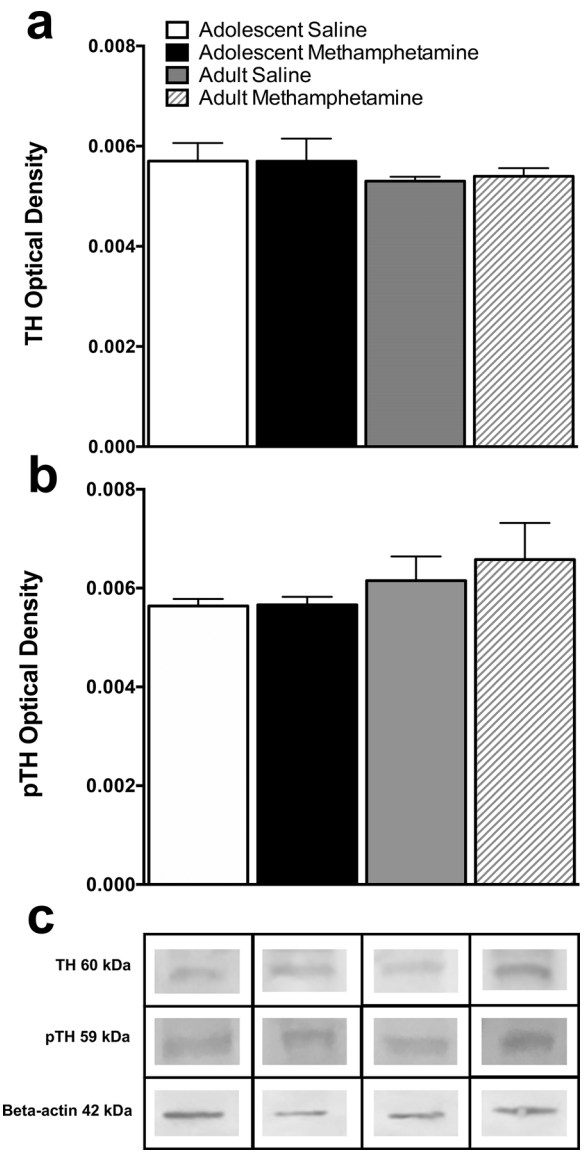

Fig. 3. Western blot analysis of total TH and pTH in the hippocampus of saline- and methamphetamine-exposed adolescent and adult mice. a) Optical density for total hippocampal TH levels. There was no effect of treatment or age on hippocampal TH levels. b) Optical density for hippocampal pTH levels. There was no effect of treatment or age on hippocampal pTH levels. c) Representative blot images for total TH, pTH, and beta-actin control. Optical density was calculated by taking the inverse of the greyscale binary mean intensity. Data presented as mean ± SEM optical density. N = 5–6 hippocampi per group.

This finding is consistent with a plethora of previous research showing MA increases locomotor activity (for a review, see [47]). Interestingly, we did not find any age differences in the effects of MA on locomotor activity. This is in contrast to other studies showing adolescent rodents are resistant to amphetamine- and MA-induced increases in locomotor activity compared to adult rodents [11–14]. However, locomotor activity was measured for longer durations in previous studies, and age differences in the effects of acute MA exposure do not appear until after 20 min post-exposure. For example, adolescent and adult mice showed similar MA-induced increases in locomotor activity for the first 45 min following exposure, followed by a decrease in locomotor activity between 45–90 minutes in adolescents but not in adults [11]. Thus, it is possible that in the current study we might have seen age differences in locomotor activity if behavior had been measured beyond 20 min after MA exposure. The goal of this study was to directly replicate previous

research examining the effects of MA in adolescent mice in 20-minute open field trials [20], and thus we aimed to keep this methodology similar. However, future research is warranted to examine age differences in the effects of MA beyond this 20-minute time period. Adolescent and adult mice show similar concentrations of MA in the blood and brain 15 min after an injection [42], potentially contributing to similar levels of locomotor activity in the first 15–20 min following MA exposure.

MA increased anxiety-like behavior in both adolescent and adult mice compared to saline controls. In the open field test, MA-exposed mice spent less time and moved less distance in the center of the open field arenas and spent more time in the corners of the open field arenas compared to saline-exposed mice. This increase in anxiety models what is seen in human adolescent [4] and adult MA users [7] and adult non-drug users following acute MA exposure [9]. This finding also replicates our previous research showing acute MA-induced increases in anxiety-like behavior in the open field test in adolescent mice [20]. While relatively little research has examined the acute effects of MA in adolescents, more research has examined the long-term effects of adolescent MA exposure (for a review, see [48]). For example, adolescent MA exposure causes long-term increases in depression-like behavior [41], reductions in anxiety-like behavior in the open field test [49], increases in anxiety-like behavior in the elevated plus maze [50], and impairments in spatial and sequential learning [51], reversal learning and visual discrimination [52], working memory [53], and reference memory [50]. The effects of adolescent MA exposure depend on the age of exposure as well as when behavior is measured. Taken together with our data on the acute effects of MA in adolescents, these findings give cause for concern about the effects of MA use that initiates in adolescence and more research is warranted to examine the consequences of adolescent MA exposure.

Our finding of increased anxiety-like behavior in the adult MA-exposed mice contradicts previous research showing MA exposure decreases anxiety-like behavior in adult rats in the open field test [15,16]. However, these studies in adult rats used lower doses of MA (1 mg/kg and 2 mg/kg) and MA injections occurred 20 min [16] or 30 min [15] before behavior was measured in the open field, which is in contrast to our study where injections occurred immediately prior to testing and a higher dose of MA (4 mg/kg) was used. It is possible that these differences account for different effects of MA on anxiety-like behavior in the open field test in adults. To the best of our knowledge, this is the first study to directly compare the effects of acute MA exposure on anxiety-like behavior in adolescent and adult rodents, and the findings suggest that there are no age differences in the effects of acute MA exposure on anxiety-like behavior in the open field test.

The dose of MA used in the current study was chosen to replicate previous research from our lab [20], as one primary goal of this study was to directly replicate this previous research and include the adult age group. Furthermore, the dose of 4 mg/kg MA was used based on previous research showing 4 mg/kg MA increases locomotor activity to a greater degree than 1 mg/kg or 2 mg/kg MA in adolescent C57BL6/J mice [11,42] and increases DA levels in the brain reward pathway [43]. However, lower doses of MA are often used to assess the effects of MA on locomotor activity and anxiety-like behavior in rodents [14,15]. Further research is warranted to examine and compare the effects of lower doses of MA on behavior in the open field test in adolescent and adult mice. Furthermore, the dose of 4 mg/kg MA could have induced stereotypy behaviors in the mice in the current study, which are repetitive and compulsive behaviors, such as continuous sniffing, circling, head bobbing, and mouthing [54]. Higher doses of MA can induce stereotypy behaviors and may have affected the results from the open field test. This again suggests that further research is warranted to examine the effects of acute MA exposure on open field behavior in adolescent and adult mice with lower doses of MA. Although stereotypy was not measured in the current study, we have evidence to suggest minimal stereotypy was induced by MA exposure. Previous research has shown that only 30% of mice show stereotypy behavior following 5 mg/kg MA and stereotypy behavior doesn't begin until 20 min following MA exposure in adult mice [55]. The increase in locomotor activity in the MA-exposed mice suggests that the animals were not engaged in stereotypy behaviors because stereotypy behaviors typically occur after an initial locomotor activation phase [56] and engagement in stereotypy behaviors generally results in reduced locomotor activity [42,57]. However, we cannot be sure that the higher dose of 4 mg/kg MA did not induce some stereotypy behaviors and influence behavior in the open field test, and this should be measured in future studies.

There are various aspects of anxiety-like behavior in rodents and multiple tests that can be used to assess this behavior, including the open field test and the elevated plus maze [39]. Measurements of social interaction and ultrasonic vocalizations can also be used to assess an anxiety response in rodents [58]. The effects of psychomotor stimulant drugs have been examined in various anxiety models, with inconsistent findings. For example, acute MA exposure decreases anxiety-like behavior in rodents in the open field test [15,16,59], while in the elevated plus maze acute MA exposure has been shown to either decrease [15,17,18] or increase [19,60] anxiety-like behavior. Schutova et al. (2010) showed acute MA exposure in adult rats decreases anxiety-like behavior in the open field test but has no effect on anxiety-like behavior in the elevated plus maze [59]. Both amphetamine and MA decrease social interaction behaviors, which is interpreted as increased anxiety-like behavior [61–63]. Amphetamine reduces ultrasonic vocalizations during a social interaction test in adolescent rats [64] but induces long-term increases in vocalizations in adult rats [65]. Finally, Slamberova et al. (2015) showed acute MA exposure did not alter anxiety-like behavior in the open field test nor alter ultrasonic vocalizations, but it did reduce social interactions behavior in rats [58]. These findings highlight that the effects of psychomotor stimulant exposure on anxiety-like behavior are potentially dependent on what test is used and what aspect of anxiety is assessed. The current study only examined behavior in the open field test, and further research is needed to compare these effects to other measures of anxiety in adolescent and adult mice.

There were no differences in plasma corticosterone levels immediately following open field testing between saline- and MA-exposed mice in either the adolescent or adult age groups. This finding replicates previous research showing MA does not alter plasma corticosterone levels in adolescent mice [27]. However, we did not replicate previous research showing acute MA exposure increases plasma corticosterone levels in adult rodents. In adult rats, much higher doses of MA were used (4 × 10 mg/kg injections) prior to corticosterone analysis [26,27], suggesting if we had used a higher dose of MA we may have found increases in corticosterone levels in the current study. In contrast, adult mice show increases in plasma corticosterone levels 30 min following a 1 mg/kg dose of MA [28]. Adult mice also show a prolonged HPA axis response following acute MA exposure [28], suggesting future studies should examine corticosterone levels up to 120 min following exposure and open field testing. It is possible that the stress of the open field test immediately prior to blood collection in the current study could have masked potential effects of MA on plasma corticosterone levels, altering corticosterone levels significantly in both MA- and saline-exposed mice. Interestingly, adult humans show no immediate changes in salivary cortisol levels following acute MA exposure [66], suggesting the effect of acute MA exposure on the HPA axis is not straightforward and requires further research. Future research should directly compare the effects of MA exposure on plasma corticosterone levels in adolescent and adult mice without prior behavioral testing to mitigate any potential effects of the behavioral testing on corticosterone levels.

The mechanism of MA-induced increases in anxiety-like behavior remains unclear. It is possible that MA-induced changes in the HPA axis are linked to MA-induced changes in anxiety-like behavior, as increases in corticosterone are associated with increases in anxiety-like behavior in the open field test [67]. However, in our study, MA caused increases in anxiety-like behavior in the absence of an effect on corticosterone

levels in adolescent and adult mice. Exploratory correlational analyses showed no statistically significant correlation between plasma corticosterone levels and percent time spent in center or percent distance moved in the center of the open field during trial 2 (data not shown). MA alters many other systems that are involved in anxiety-like behavior [1], including the DA, serotonin, and norepinephrine systems (for a review, see [34]), and thus changes in these systems may underlie MA's effects on anxiety-like behavior.

There were no differences in hippocampal total TH or pTH levels between saline- and MA-exposed mice in either the adolescent or adult age groups immediately following open field testing. TH and pTH levels were measured immediately following open field trial 2 testing, which was 20 min following MA or saline exposure. It is reasonable to expect that levels of pTH would potentially change by this time point, as DA levels are immediately affected by MA exposure [43]. TH activity is reduced by negative feedback from DA, and phosphorylation of TH reduces the ability of DA to modulate TH activity. Previous studies show that pTH levels are affected 15 min following cocaine exposure in the caudate and nucleus accumbens in rats [38] and 15 min following haloperidol exposure in the striatum in mice 15 [68]. However, we did not find any effects of MA exposure on total TH or pTH levels in the hippocampus 20 min following MA exposure. While the DA system can modulate anxiety-like behavior [33], our findings suggest that acute MA exposure does not alter pTH or total TH levels in the hippocampus, and thus changes in the synthesis of DA in the hippocampus might not contribute to MA-induced changes in anxiety-like behavior. Previous research shows that MA decreases D_1 DA receptors and increases DA reuptake transporters in the hippocampus of adult mice 6 weeks following MA exposure, but there were no effects of MA on the levels of hippocampal TH [53]. MA exposure also causes long-term decreases in hippocampal DA levels in rats [69]. It is possible that TH and pTH levels in the striatum are affected by acute MA exposure in adolescents and adults, and further research is warranted to assess this possibility and any potential age differences in these effects. Studies have shown that adolescent rats are resistant to the long-term MA-induced decreases in total TH levels in the striatum compared to adult rats [70]. The DA system goes through developmental changes during adolescence. Compared to adult rodents, adolescent rodents have lower total TH levels in the nucleus accumbens and medial prefrontal cortex [12], increased levels of functionally active dopamine transporters [71], and increased expression of DA D_1 and D_2 receptors in the striatum and nucleus accumbens [72]. Age differences in the DA system may account for some of the age differences in the locomotor response to MA found in previous studies [11–14]. However, the current findings suggest that acute MA exposure does not alter hippocampal TH or pTH levels and a lack of a difference in this effect between adolescent and adult mice mirrors a lack of an age difference in the effects of acute MA exposure on behavior in the current study.

In summary, the findings of this study show that acute MA exposure increases locomotor activity and anxiety-like behavior in adolescent and adult male mice, but does not alter plasma corticosterone levels, total hippocampal TH levels, or hippocampal pTH levels. Importantly, there were no age differences in the behavioral effects of MA, suggesting that immediately following acute MA exposure, MA does not affect adolescents and adults differently.

Conflicts of interest

The authors have no conflicts of interest to report.

Acknowledgements

This work was supported by a Faculty Startup Grant and a Faculty Research Grant from the University of St. Thomas. We thank Jestine Weiss and Hayley Ortman for their help with the behavioral experiments and the ELISA experiments. We thank Dr. Sarah Heimovics and Dr. Jenne Westberry for their help with western blot experiments.

References

[1] D. Sulzer, M.S. Sonders, N.W. Poulsen, A. Galli, Mechanisms of neurotransmitter release by amphetamines: a review, Prog. Neurobiol. 75 (2005) 406–433.
[2] R. Gonzales, A. Ang, M.J. McCann, R.A. Rawson, An emerging problem: methamphetamine abuse among treatment seeking youth, Subst. Abus. 29 (2008) 71–80.
[3] R.A. Rawson, R. Gonzales, M. McCann, W. Ling, Use of methamphetamine by young people: is there reason for concern? Addiction 102 (2007) 1021–1022.
[4] G. King, D. Alicata, C. Cloak, L. Chang, Psychiatric symptoms and HPA axis function in adolescent methamphetamine users, J. Neuroimmune Pharmacol. 5 (2010) 582–591.
[5] G. King, D. Alicata, C. Cloak, L. Chang, Neuropsychological deficits in adolescent methamphetamine abusers, Psychopharmacol. (Berl.) 212 (2010) 243–249.
[6] R.A. Rawson, R. Gonzales, J.L. Obert, M.J. McCann, P. Brethen, Methamphetamine use among treatment-seeking adolescents in Southern California: participant characteristics and treatment response, J. Subst. Abuse Treat. 29 (2005) 67–74.
[7] J.E. Zweben, J.B. Cohen, D. Christian, G.P. Galloway, M. Salinardi, D. Parent, M. Iguchi, Psychiatric symptoms in methamphetamine users, Am. J. Addict. 13 (2004) 181–190.
[8] P.M. Thompson, K.M. Hayashi, S.L. Simon, J.A. Geaga, M.S. Hong, Y. Sui, J.Y. Lee, A.W. Toga, W. Ling, E.D. London, Structural abnormalities in the brains of human subjects who use methamphetamine, J. Neurosci. 24 (2004) 6028–6036.
[9] S.D. Comer, C.L. Hart, A.S. Ward, M. Haney, R.W. Foltin, M.W. Fischman, Effects of repeated oral methamphetamine administration in humans, Psychopharmacol. (Berl.) 155 (2001) 397–404.
[10] I.K. Lyoo, S. Yoon, T.S. Kim, S.M. Lim, Y. Choi, J.E. Kim, J. Hwang, H.S. Jeong, H.B. Cho, Y.A. Chung, P.F. Renshaw, Predisposition to and effects of methamphetamine use on the adolescent brain, Mol. Psychiatry 20 (2015) 1516–1524.
[11] J.A. Zombeck, A.D. Lewicki, K. Patel, T. Gupta, J.S. Rhodes, Patterns of neural activity associated with differential acute locomotor stimulation to cocaine and methamphetamine in adolescent versus adult male C57BL/6J mice, Neuroscience 165 (2010) 1087–1099.
[12] I.Z. Mathews, P. Waters, C.M. McCormick, Changes in hyporesponsiveness to acute amphetamine and age differences in tyrosine hydroxylase immunoreactivity in the brain over adolescence in male and female rats, Dev. Psychobiol. 51 (2009) 417–428.
[13] W. Adriani, G. Laviola, A unique hormonal and behavioral hyporesponsivity to both forced novelty and d-amphetamine in periadolescent mice, Neuropharmacology 39 (2000) 334–346.
[14] E. Zakharova, G. Leoni, I. Kichko, S. Izenwasser, Differential effects of methamphetamine and cocaine on conditioned place preference and locomotor activity in adult and adolescent male rats, Behav. Brain Res. 198 (2009) 45–50.
[15] B. Schutova, L. Hruba, M. Pometlova, R. Slamberova, Impact of prenatal and acute methamphetamine exposure on behaviour of adult male rats, Prague Med. Rep. 110 (2009) 67–78.
[16] C.E. Herbert, R.N. Hughes, A comparison of 1-benzylpiperazine and methamphetamine in their acute effects on anxiety-related behavior of hooded rats, Pharmacol. Biochem. Behav. 92 (2009) 243–250.
[17] R. Tamaki, M. Yoshikawa, T. Shinomiya, A. Hashimoto, M. Kawaguchi, D.W. Byrne, H. Kobayashi, Acute administration of methamphetamine decreases the mRNA expression of diazepam binding inhibitor in rat brain, Tokai J. Exp. Clin. Med. 33 (2008) 51–56.
[18] K.K. Szumlinski, R.E. Haskew, M.Y. Balogun, I.M. Maisonneuve, S.D. Glick, Iboga compounds reverse the behavioural disinhibiting and corticosterone effects of acute methamphetamine: implications for their antiaddictive properties, Pharmacol. Biochem Behav. 69 (2001) 485–491.
[19] M. Pometlova, K. Nohejlova-Deykun, R. Slamberova, Anxiogenic effect of low-dose methamphetamine in the test of elevated plus-maze, Prague Med. Rep. 113 (2012) 223–230.
[20] M.A. Rud, T.N. Do, J.A. Siegel, Effects of early adolescent methamphetamine exposure on anxiety-like behavior and corticosterone levels in mice, Neurosci. Lett. 633 (2016) 257–261.
[21] S.X. Li, S.Y. Yan, Y.P. Bao, Z. Lian, Z. Qu, Y.P. Wu, Z.M. Liu, Depression and alterations in hypothalamic-pituitary-adrenal and hypothalamic-pituitary-thyroid axis function in male abstinent methamphetamine abusers, Hum. Psychopharmacol. 28 (2013) 477–483.
[22] C.E. Grace, T.L. Schaefer, N.R. Herring, M.R. Skelton, A.E. McCrea, C.V. Vorhees, M.T. Williams, (+)-Methamphetamine increases corticosterone in plasma and BDNF in brain more than forced swim or isolation in neonatal rats, Synapse 62 (2008) 110–121.
[23] M.T. Williams, S.L. Inman-Wood, L.L. Morford, A.E. McCrea, A.M. Ruttle, M.S. Moran, S.L. Rock, C.V. Vorhees, Preweaning treatment with methamphetamine induces increases in both corticosterone and ACTH in rats, Neurotoxicol. Teratol. 22 (2000) 751–759.
[24] S.F. Acevedo, T. Pfankuch, P. van Meer, J. Raber, Role of histamine in short- and long-term effects of methamphetamine on the developing mouse brain, J. Neurochem. 107 (2008) 976–986.
[25] D.G. Zuloaga, J.A. Siegel, S.F. Acevedo, M. Agam, J. Raber, Developmental methamphetamine exposure results in short- and long-term alterations in hypothalamic-pituitary-adrenal-axis-associated proteins, Dev. Neurosci. 35 (2013) 338–346.
[26] A.A. Braun, N.R. Herring, T.L. Schaefer, A.M. Hemmerle, J.W. Dickerson, K.B. Seroogy, C.V. Vorhees, M.T. Williams, Neurotoxic (+)-methamphetamine

treatment in rats increases brain-derived neurotrophic factor and tropomyosin receptor kinase b expression in multiple brain regions, Neuroscience 184 (2011) 164–171.
[27] N.R. Herring, T.L. Schaefer, P.H. Tang, M.R. Skelton, J.P. Lucot, G.A. Gudelsky, C.V. Vorhees, M.T. Williams, Comparison of time-dependent effects of (+)-methamphetamine or forced swim on monoamines, corticosterone, glucose, creatine, and creatinine in rats, BMC Neurosci. 9 (2008) 1–15.
[28] D.G. Zuloaga, L.A. Johnson, M. Agam, J. Raber, Sex differences in activation of the hypothalamic-pituitary-adrenal axis by methamphetamine, J. Neurochem 129 (2014) 495–508.
[29] D. Sulzer, How addictive drugs disrupt presynaptic dopamine neurotransmission, Neuron 69 (2011) 628–649.
[30] A. Gasbarri, C. Verney, R. Innocenzi, E. Campana, C. Pacitti, Mesolimbic dopaminergic neurons innervating the hippocampal formation in the rat: a combined retrograde tracing and immunohistochemical study, Brain Res. 668 (1994) 71–79.
[31] U.M. Ricoy, J.L. Martinez Jr, Local hippocampal methamphetamine-induced reinforcement, Front. Behav. Neurosci. 3 (2009) 47.
[32] B.D. Armstrong, K.K. Noguchi, The neurotoxic effects of 3,4-methylenedioxymethamphetamine (MDMA) and methamphetamine on serotonin, dopamine, and gaba-ergic terminals: an in-vitro autoradiographic study in rats, Neurotoxicology 25 (2004) 905–914.
[33] M.R. Zarrindast, F. Khakpai, The modulatory role of dopamine in anxiety-like behavior, Arch. Iran Med. 18 (2015) 591–603.
[34] G.A. Carrasco, L.D. Van de Kar, Neuroendocrine pharmacology of stress, Eur. J. Pharmacol. 463 (2003) 235–272.
[35] S.C. Daubner, T. Le, S. Wang, Tyrosine hydroxylase and regulation of dopamine synthesis, Arch. Biochem. Biophys. 508 (2011) 1–12.
[36] N. Lindgren, Z.Q. Xu, M. Lindskog, M. Herrera-Marschitz, M. Goiny, J. Haycock, M. Goldstein, T. Hokfelt, G. Fisone, Regulation of tyrosine hydroxylase activity and phosphorylation at Ser(19) and Ser(40) via activation of glutamate NMDA receptors in rat striatum, J. Neurochem. 74 (2000) 2470–2477.
[37] J. Harada, J.W. Wu, M. Haycock, Goldstein, Regulation of L-DOPA biosynthesis by site-specific phosphorylation of tyrosine hydroxylase in AtT-20 cells expressing wild-type and serine 40-substituted enzyme, J. Neurochem. 67 (1996) 629–635.
[38] J.P. Jedynak, S.F. Ali, J.W. Haycock, B.T. Hope, Acute administration of cocaine regulates the phosphorylation of serine-19, -31 and -40 in tyrosine hydroxylase, J. Neurochem. 82 (2002) 382–388.
[39] Y. Clement, F. Calatayud, C. Belzung, Genetic basis of anxiety-like behaviour: a critical review, Brain Res. Bull. 57 (2002) 57–71.
[40] Q. Wang, Y. Long, A. Hang, G.Y. Zan, X.H. Shu, Y.J. Wang, J.G. Liu, The anxiolytic- and antidepressant-like effects of ATPM-ET, a novel kappa agonist and mu partial agonist, in mice, Psychopharmacol. (Berl.) 233 (2016) 2411–2418.
[41] L. Joca, D.G. Zuloaga, J. Raber, J.A. Siegel, Long-term effects of early adolescent methamphetamine exposure on depression-like behavior and the hypothalamic vasopressin system in mice, Dev. Neurosci. 36 (2014) 108–118.
[42] J.A. Zombeck, T. Gupta, J.S. Rhodes, Evaluation of a pharmacokinetic hypothesis for reduced locomotor stimulation from methamphetamine and cocaine in adolescent versus adult male C57BL/6J mice, Psychopharmacol. (Berl.) 201 (2009) 589–599.
[43] L.K. Dobbs, G.P. Mark, Comparison of systemic and local methamphetamine treatment on acetylcholine and dopamine levels in the ventral tegmental area in the mouse, Neuroscience 156 (2008) 700–711.
[44] J. Li, Q.T. Liu, Y. Chen, J. Liu, J.L. Shi, Y. Liu, J.Y. Guo, involvement of 5-HT1A receptors in the anxiolytic-like effects of quercitrin and evidence of the involvement of the monoaminergic system, Neuropharmacology 62 (2012) 474–484.
[45] E. Huang, M. Ngo, S. Yee, L. Held, K. Norman, A.M. Scremin, O. Scremin, Repeated blast exposure alters open field behavior recorded under low illumination, Brain Res. 1529 (2013) 125–133.
[46] J.A. Bouwknecht, F. Spiga, D.R. Staub, M.W. Hale, A. Shekhar, C.A. Lowry, Differential effects of exposure to low-light or high-light open-field on anxiety-related behaviors: relationship to c-Fos expression in serotonergic and non-serotonergic neurons in the dorsal raphe nucleus, Brain Res. Bull. 72 (2007) 32–43.
[47] M.P. Caligiuri, C. Buitenhuys, Do preclinical findings of methamphetamine-induced motor abnormalities translate to an observable clinical phenotype? Neuropsychopharmacology 30 (2005) 2125–2134.
[48] J.M. Buck, J.A. Siegel, The effects of adolescent methamphetamine exposure, Front. Neurosci. 9 (2015) 151.
[49] J.M. Buck, A.S. Morris, S.J. Weber, J. Raber, J.A. Siegel, Effects of adolescent methamphetamine and nicotine exposure on behavioral performance and MAP-2 immunoreactivity in the nucleus accumbens of adolescent mice, Behav. Brain Res. 323 (2017) 78–85.
[50] D. Loxton, J.J. Canales, Long-term cognitive, emotional and neurogenic alterations induced by alcohol and methamphetamine exposure in adolescent rats, Prog. Neuropsychopharmacol. Biol. Psychiatry 74 (2017) 1–8.
[51] C.V. Vorhees, T.M. Reed, L.L. Morford, M. Fukumura, S.L. Wood, C.A. Brown, M.R. Skelton, A.E. McCrea, S.L. Rock, M.T. Williams, Periadolescent rats (P41-50) exhibit increased susceptibility to d-methamphetamine-induced long-term spatial and sequential learning deficits compared to juvenile (p21-30 or p31-40) or adult rats (p51-60), Neurotoxicol. Teratol. 27 (2005) 117–134.
[52] T. Ye, H. Pozos, T.J. Phillips, A. Izquierdo, Long-term effects of exposure to methamphetamine in adolescent rats, Drug. Alcohol. Depend. 138 (2014) 17–23.
[53] S.H. Braren, D. Drapala, I.K. Tulloch, P.A. Serrano, Methamphetamine-induced short-term increase and long-term decrease in spatial working memory affects protein kinase M zeta (PKMzeta), dopamine, and glutamate receptors, Front. Behav. Neurosci. 8 (2014) 438.
[54] T. Tatsuta, N. Kitanaka, J. Kitanaka, Y. Morita, M. Takemura, Lobeline attenuates methamphetamine-induced stereotypy in adolescent mice, Neurochem. Res. 31 (2006) 1359–1369.
[55] J. Kitanaka, N. Kitanaka, F.S. Hall, G.R. Uhl, H. Asano, R. Chatani, S. Hayata, H. Yokoyama, K.I. Tanaka, N. Nishiyama, M. Takemura, Pretreatment with nomifensine or nomifensine analogue 4-phenyl-1,2,3,4-tetrahydroisoquinoline augments methamphetamine-induced stereotypical behavior in mice, Brain Res. 1439 (2012) 15–26.
[56] G.V. Rebec, T.R. Bashore, Critical issues in assessing the behavioral effects of amphetamine, Neurosci. Biobehav. Rev. 8 (1984) 153–159.
[57] J.M. Caster, Q.D. Walker, C.M. Kuhn, Enhanced behavioral response to repeated-dose cocaine in adolescent rats, Psychopharmacol. (Berl.) 183 (2005) 218–225.
[58] R. Slamberova, M. Pometlova, E. Macuchova, K. Nohejlova, A. Stuchlik, K. Vales, Do the effects of prenatal exposure and acute treatment of methamphetamine on anxiety vary depending on the animal model used? Behav. Brain Res. 292 (2015) 361–369.
[59] B. Schutova, L. Hruba, M. Pometlova, R. Rokyta, R. Slamberova, Responsiveness to methamphetamine in adulthood is altered by prenatal exposure in rats, Physiol. Behav. 99 (2010) 381–387.
[60] T. Hayase, Y. Yamamoto, K. Yamamoto, Persistent anxiogenic effects of a single or repeated doses of cocaine and methamphetamine: interactions with endogenous cannabinoid receptor ligands, Behav. Pharmacol. 16 (2005) 395–404.
[61] K.J. Clemens, P.S. Van Nieuwenhuyzen, K.M. Li, J.L. Cornish, G.E. Hunt, I.S. McGregor, MDMA ("ecstasy"), methamphetamine and their combination: long-term changes in social interaction and neurochemistry in the rat, Psychopharmacol. (Berl.) 173 (2004) 318–325.
[62] R. Slamberova, A. Mikulecka, M. Pometlova, B. Schutova, L. Hruba, K. Deykun, The effect of methamphetamine on social interaction of adult male rats, Behav. Brain Res. 214 (2010) 423–427.
[63] R. Slamberova, A. Mikulecka, M. Pometlova, B. Schutova, L. Hruba, K. Deykun, Sex differences in social interaction of methamphetamine-treated rats, Behav. Pharmacol. 22 (2011) 617–633.
[64] A. Manduca, P. Campolongo, M. Palmery, L.J. Vanderschuren, V. Cuomo, V. Trezza, Social play behavior, ultrasonic vocalizations and their modulation by morphine and amphetamine in wistar and sprague-dawley rats, Psychopharmacol. (Berl.) 231 (2014) 1661–1673.
[65] N. Simola, L. Frau, A. Plumitallo, M. Morelli, Direct and long-lasting effects elicited by repeated drug administration on 50-kHz ultrasonic vocalizations are regulated differently: implications for the study of the affective properties of drugs of abuse, Int. J. Neuropsychopharmacol. 17 (2014) 429–441.
[66] A. Soderpalm, L. Nikolayev, H. de Wit, Effects of stress on responses to methamphetamine in humans, Psychopharmacol. (Berl.) 170 (2003) 188–199.
[67] D. Hestermann, Y. Temel, A. Blokland, L.W. Lim, Acute serotonergic treatment changes the relation between anxiety and HPA-axis functioning and periaqueductal gray activation, Behav. Brain Res. 273 (2014) 155–165.
[68] K. Hakansson, L. Pozzi, A. Usiello, J. Haycock, E. Borrelli, G. Fisone, Regulation of striatal tyrosine hydroxylase phosphorylation by acute and chronic haloperidol, Eur. J. Neurosci. 20 (2004) 1108–1112.
[69] P. Melo, A. Magalhaes, C.J. Alves, M.A. Tavares, L. de Sousa, T. Summavielle, P. Moradas-Ferreira, Methamphetamine mimics the neurochemical profile of aging in rats and impairs recognition memory, Neurotoxicology 33 (2012) 491–499.
[70] J.M. Kokoshka, A.E. Fleckenstein, D.G. Wilkins, G.R. Hanson, Age-dependent differential responses of monoaminergic systems to high doses of methamphetamine, J. Neurochem. 75 (2000) 2095–2102.
[71] T.J. Volz, S.J. Farnsworth, S.D. Rowley, G.R. Hanson, A.E. Fleckenstein, Age-dependent differences in dopamine transporter and vesicular monoamine transporter-2 function and their implications for methamphetamine neurotoxicity, Synapse 63 (2009) 147–151.
[72] M.H. Teicher, S.L. Andersen, J.C. Hostetter Jr, Evidence for dopamine receptor pruning between adolescence and adulthood in striatum but not nucleus accumbens, Brain Res. Dev. Brain Res. 89 (1995) 167–172.