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Sex- and Histamine-Dependent Long-Term Cognitive Effects of Methamphetamine Exposure

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As prenatal methamphetamine (MA) exposure results in long-term hippocampus-dependent cognitive deficits, the increased MA use in women of childbearing age is of great concern. As mice are most commonly used in genetic models, we started to study the potential effects of neonatal MA exposure in female and male mice on brain function 3 months later. As histamine (HA) might mediate some effects of MA in adulthood, we also tested whether in neonates HA might mediate the long-term effects of MA using HA H_3 receptor agonists and antagonists. Stimulation of HA H_3 receptors by H_3 agonists inhibits HA synthesis and release, whereas inhibition of H_3 receptors by H_3 receptor antagonists increases HA release. MA (5 mg/kg), the H_3 receptor antagonist thioperamide (5 mg/kg), and the H_3 receptor agonist immepip (5 mg/kg) alone or in the presence of MA (5 mg/kg) were administered once daily from postnatal days 11 to 20 and the mice were tested at 3 months of age. Here we show that in mice exposure to MA early in life causes sex-dependent impairments in object recognition, spatial learning, and memory in the water maze, and pre-pulse inhibition in adulthood. HA mediates these impairments. Increasing HA release mimicked, whereas inhibiting HA release blocked the long-term detrimental MA effects. This model could be used to determine the role of genetic and environmental factors in MA-dependent cognitive impairments and to develop therapeutic strategies to inhibit them.
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INTRODUCTION

In humans, cognitive effects of *in utero* methamphetamine (MA) exposure during the first year of life, such as impairments in hippocampus-dependent visual recognition memory, are well studied (Oro and Dixon, 1987; Little *et al*, 1988; Dixon and Bejar, 1989; Struthers and Hansen, 1992; Hansen *et al*, 1993; Anglin *et al*, 2000). However, relatively little is known about the potential long-term effects of *in utero* MA exposure. Some evidence suggests that prenatal MA exposure may result in long-term cognitive deficits (Cernerud *et al*, 1996), including impairments in hippocampus-dependent spatial learning and memory (Chang *et al*, 2004), and reduced volumes of several brain structures, including the hippocampus (Chang *et al*, 2004). Therefore, the rise in MA use among women of childbearing age is of great concern (Marwick, 2000).

Rodent models allow controlled assessments of the potential effects of prenatal MA on cognitive function later in life. To study potential long-term effects of MA on the developing hippocampus, neonatal rodents can be used to model the human third trimester, as granule cells of the dentate gyrus of the hippocampus are developing in humans and rodents in these respective time periods (Bayer *et al*, 1993; Rice and Barone, 2000). Previously, neonatal rats have been used as an animal model of prenatal MA exposure. Williams, Vorhees, and their colleagues have shown in rats, injections of MA during post-natal days (P) 11–20, but not from P1 to P10 (Williams *et al*, 2003a), lead to impairments in spatial learning and memory in the water maze and in sensorimotor gating ability (pre-pulse inhibition (PPI)) 2 months later (Vorhees *et al*, 1994, 1996; Rice and Barone, 2000; Williams *et al*, 2003b, 2004). Although there were overall sex differences in some cognitive measures, only relative subtle sex-dependent effects of MA were reported (Vorhees *et al*, 1994, 1996; Cappon *et al*, 1997; Rice and Barone, 2000; Williams *et al*, 2003b, 2004). As mice are most commonly used in genetic models, we started to study the potential effects of neonatal MA exposure in female and male mice on brain function 3 months later. As

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histamine (HA) might mediate some effects of MA in adulthood (Ito *et al*, 1997; Munzar *et al*, 1998, 2004; Morisset *et al*, 2000; Mori *et al*, 2002; Dai *et al*, 2004; Ito, 2004), we also tested whether in neonates HA might mediate the long-term effects of MA. Endogenous release of HA in the brain is mainly regulated by HA receptors. Stimulation of H_3 receptors by H_3 agonists inhibits HA synthesis and release, whereas inhibition of H_3 receptors by H_3 receptor antagonists increases HA release (Jansen *et al*, 1998; Rizk *et al*, 2004). Therefore, we assessed whether H_3 receptor blockade would mimic MA exposure and whether H_3 receptor stimulation would antagonize the effects of MA.

MATERIALS AND METHODS

Animals

C57BL/6J mice from Jackson Laboratories were bred for all the experiments. Litter sizes of 6–10 pups were injected using a mixed treatment design. Every litter had 2–4 MA-injected pups per litter. The mice were kept on 12:12 h light–dark schedule (lights on at 0600 hours) with chow (PicoLab Rodent Diet 20, #5053; PMI Nutrition International, St Louis, MO) and water given *ad libitum*. All litters were provided soft food during the injection period and the 2 weeks after weaning to maintain stable weight gain.

Injections

Thioperamide (THIO) (5 mg/kg) and Immepip (IM) (5 mg/kg) were synthesized by Dr de Esch and (+)-MA hydrochloride (5 mg/kg) was obtained from the Research Triangle Institute (Research Triangle Park, NC) through the National Institute of Drug Abuse drug supply program. All compounds were diluted with 0.9% sodium chloride (saline (SA)) to the appropriate concentrations and a volume between 0.05 and 0.10 μl was injected subcutaneously. Injections were administered once daily, between 0800 and 1000 hours, from P11 to P20. To adjust for weight gain, each pup was weighed daily.

Behavioral Testing

Litters born within a 2-week period were combined into four cohorts. Animals were housed singly beginning 48 h before the first behavioral test. Eight to 10 pups per treatment and sex were weaned at P21 and behaviorally tested at 3 months of age. The sequence of the behavioral tests was: open field, elevated zero maze, and elevated plus maze (week 1), novel location and novel object recognition (week 2), water maze (week 3), and rotorod and PrePulse Inhibition (PPI) (week 4). All procedures conformed to the standards of the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Animal Care and Use Committee of the Oregon Health and Science University. The open field, elevated zero maze, and novel location and novel object recognition tests were performed as described (Benice *et al*, 2006).

Elevated Plus Maze

The elevated plus maze consisted of two open arms and two closed arms equipped with infrared photocells interfaced with a computer (Hamilton-Kinder, Poway, CA). Active times, distance moved, and rest times were recorded for a single 10-min session. Recorded beam brakes were used to calculate path lengths and percent time spent in the open arms of the maze.

Water Maze

In the water maze, the mice were first trained to locate a platform clearly marked by a beacon (nonspatial training, days 1 and 2), and then to locate a platform beneath opaque (white nontoxic chalk) water (spatial training, days 3–5) using the available spatial cues in the room. There were two daily sessions 3.5 h apart, each consisting of three 60 s trials (with 10–15 min intertrial intervals). Mice that failed to find the platform within 60 s were led to the platform by the experimenter and allowed to stay on the platform for 3 s. During the visible platform training, the platform was moved to a different quadrant of the pool for each session. For the hidden platform training, the platform location was kept constant for each group. Mice from each sex and treatment were assigned to four groups using a randomized block design (quadrant was the blocking factor) in order to avoid any potential quadrant bias. The swimming patterns of the mice were recorded with the Noldus Ethovision video tracking system set at 6 samples/s.

To assess spatial memory retention, a 60 s probe trial with the platform removed from the pool was performed 1 h after the hidden platform training trial. The time spent swimming in the target quadrant (where the platform was located during hidden platform training), and in the three nontarget quadrants (right, left, and opposite quadrants) was measured.

Rotorod

Sensorimotor function was assessed using a rotorod. The rod had a diameter of 7 cm and was placed horizontally 64 cm above the floor of the chamber (Hamilton-Kinder, Poway, CA). After a 1-min adaptation period, the rod was accelerated by 5 r.p.m. every 15 s, and the length of time the mice remained on the rod (fall latency) was recorded. The mice were tested in three consecutive trials for 3 days.

Acoustic Startle

Acoustic startle was tested in Hamilton-Kinder (Poway, CA) startle chambers. After a 5-min acclimation, the baseline response was measured. Acoustic pulses were given, increasing from 80 to 120 db using increments of 2 db within a 500 ms window and the maximum force in Newtons (N) was measured.

PrePulse Inhibition

For the PPI, each mouse was tested in one session consisting of two series of acoustic stimuli followed by a testing phase. In the first series, after a 5-min acclimation period, mice were exposed to three, 40-ms acoustic stimuli (110 db). The testing phase consisted of 20 ms prepulses (65–85 db) followed by a 50 ms delay and a 40 ms acoustic stimulus (110 db). The amplitudes of the startle responses were

recorded. In the second series, mice were exposed to three, 40-ms acoustic stimuli (120 db). The testing phase consisted of 20 ms prepulses (65–85 db) followed by a 50 ms delay and a 40 ms acoustic stimulus (120 db). The amplitudes of the startle responses were again recorded. Random intertrial intervals (15–30 s) were used between all trials. These conditions were selected based on the reported optimal conditions for measuring PPI in C57BL/6 mice (Plappert *et al*, 2004). For each individual mouse, the baseline response was used as correction by subtracting an average of six no-stimulation responses, three after the initial acclimation period and three after the test phase in the second series. PPI was assessed by comparing the startle response to the acoustic stimuli following prepulse to the initial response using the following formula: % response $= 100 \times ((S-PS)/S))$, where S is the mean startle amplitude without prepulses and PS is the mean startle response following the prepulse condition. Response (100%) means that there was no effect of prepulse on the startle response (Plappert *et al*, 2004).

Statistical Analyses

Untransformed (raw) data were analyzed with the JMP3.1 statistical software package (SAS Institute Inc., Cary, NC). Following initial multimeasures or two-way ANOVAs, the data were analyzed using the Dunnett's or Tukey–Kramer *post hoc* tests. Only two-tailed tests were used. In addition to effects of sex and treatment, interactions between effects of sex and treatment were also assessed. A probability value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Neonatal Injections, Lethality, and Weight Gain

From P11 to P20, neonatal mice were injected daily with MA (5 mg/kg), the HA H_3 receptor (H_3R) antagonist THIO (5 mg/kg), the HA H_3R agonist IM (5 mg/kg), IM (5 mg/kg) in the presence of MA (5 mg/kg) (IM/MA), or SA. The daily dose of 5 mg/kg was selected as preliminary studies showed that a daily 40, 20, or 10 mg/kg doses used in rats to show cognitive deficits (Vorhees *et al*, 1994, 1996; Rice and Barone, 2000; Williams *et al*, 2003b) leads to 100% lethality in mice. In a recent study, lower doses of MA also showed cognitive effects, but in a less consistent manner (Cappon *et al*, 1997). The once daily 5 mg/kg dose still resulted in 15% lethality in the mice, similar to the 20% lethality reported using four daily injections of 10 mg/kg in rats (Vorhees *et al*, 1994, 1996; Rice and Barone, 2000; Williams *et al*, 2003b, 2004), consistent with the significant increase in spontaneous abortions following *in utero* exposure to MA in humans (Smith *et al*, 2003). Similar lethality was observed following neonatal MA exposure in the presence of IM. None of the other treatments caused any lethality. There were no effects of treatment on average weight gain of the mouse pups (Table 1a), in contrast to what has been reported in rats (Smith and Dring, 1970; Vorhees *et al*, 1994, 1996; Cappon *et al*, 1997; Rice and Barone, 2000; Williams *et al*, 2003b, 2004). Differences in MA metabolism between mice and rats (Smith and Dring, 1970; Won *et al*, 2001) likely underlie these species differences. In some aspects, mice metabolize MA more similar to humans than rats do. Humans, rats, and mice all metabolize MA to *p*-hydroxymethamphetamines (Smith and Dring, 1970). Similar to humans, mice also metabolize MA to amphetamine and other metabolites using oxidative deamination and excreting benzoic acid as the major metabolite (Smith and Dring, 1970). In contrast, rats mainly metabolize amphetamine using aromatic hydroxylation and have livers containing a heat labile factor, which inhibits the amphetamine-deaminating enzyme (Smith and Dring, 1970).

Explorative Behavior, Measures of Anxiety, and Sensorimotor Function

As alterations in exploratory behavior and anxiety can affect performance in cognitive tests, we first assessed exploratory behavior and measures of anxiety in the open field, the elevated plus maze, and the elevated zero maze (Rizk *et al*, 2004). Percent time spent in the center of the open-field enclosure was used as a measure of anxiety-like behavior. None of the treatments altered the distance moved or measures of anxiety in the open field (Table 1b). Similarly, none of the treatments altered measures of anxiety in the elevated plus or elevated zero maze (Table 1c and d). The rotorod was used to evaluate sensorimotor function. There were also no effects of any treatment on rotorod performance (Table 1e). These data show that neonatal MA or THIO exposure in mice does not affect explorative behavior, measures of anxiety, or sensorimotor function.

Novel Location and Novel Object Recognition

Next, the mice were tested in complex novel location and novel object recognition tests (Rizk *et al*, 2004). All groups habituated to the objects and spent less time exploring the three objects in trial 2 than trial 1 ($p < 0.05$). The MA females spent more time exploring the objects in the first three trials compared to SA females, but there were no group differences in time spent exploring the objects in trial 4 or 5.

The novel location recognition test assesses the ability of mice to recognize a novel spatial arrangement of familiar objects and is sensitive to hippocampal damage (Save *et al*, 1992). When a familiar object was moved to a novel location, SA-treated female and male mice spent more time exploring the object in the novel than familiar location (Figure 1a). In contrast, MA- and THIO-treated females showed impairments in novel location recognition and did not spend significantly more time exploring the object in the novel location (Figure 1a). In females, coadministration of the H3 receptor agonist IM prevented this MA-induced deficit in novel location recognition. In contrast to females, all male groups showed novel location recognition, indicating that females might be more susceptible to the effects of MA on novel location recognition.

The novel object recognition test assesses the ability to recognize a novel object in the environment (nonspatial) and is unaffected by hippocampal lesions (Ennaceur *et al*, 1997). When a familiar object was replaced by a novel one, both MA- and THIO-treated females and males ($p < 0.01$) spent significantly less time exploring it than SA-treated mice (Figure 1b) and did not explore the novel object more than the two familiar objects (Figure 1c). In females and

Table 1 Weight, Open-Field, Elevated Zero Maze, Elevated Plus Maze, and Rotorod Performance of Neonatally Treated Mice

Treatment	Sex	Weight gain (g) (P20–P11)	Weight (g) P90	Sex	Weight gain (g) (P20–P11)	Weight (g) P90
(a) Weight[a]						
SA	F	1.8±0.3	24.5±0.7	M	1.9±0.3	24.3±0.9
MA	F	2.0±0.3	22.2±0.8	M	2.1±0.4	24.4±0.9
THIO	F	2.4±0.2	23.2±1.4	M	2.6±0.4	25.4±0.8
IM	F	2.2±0.2	22.2±0.4	M	2.2±0.2	27.7±0.2
IM±MA	F	1.5±0.3	22.6±0.6	M	1.9±0.4	27.2±0.5
Treatment	**Sex**	**Distance (cm)**	**% Time in center**	**Sex**	**Distance (cm)**	**% Time in center**
(b) Open field[b]						
SA	F	5739±150	15.8±1.8	M	5282±204	13.2±1.7
MA	F	5790±266	15.7±1.5	M	5054±216	12.4±1.6
THIO	F	5935±246	12.8±1.6	M	5569±212	10.1±1.0
IM	F	5758±253	17.0±2.5	M	5758±253	13.0±2.5
IM±MA	F	5460±170	14.6±1.8	M	4957±186	12.4±1.8
Treatment	**Sex**	**Distance (cm)**	**% Time in open area**	**Sex**	**Distance (cm)**	**% Time in open area**
(c) Zero maze						
SA	F	2681±124	21.6±3.3	M	2665±260	17.8±3.4
MA	F	2666±267	18.3±2.5	M	2559±158	18.3±2.5
THIO	F	2599±116	18.7±2.4	M	2834±109	18.0±1.9
IM	F	2741±144	19.8±2.2	M	2741±144	19.9±1.5
IM±MA	F	2312±86	20.4±2.5	M	2366±229	19.1±2.5
Treatment	**Sex**	**Distance (cm)**	**% Time in open arm**	**Sex**	**Distance (cm)**	**% Time in open arm**
(d) Plus maze						
SA	F	3353±110	33.6±3.5	M	3353±173	29.7±2.4
MA	F	3271±200	32.4±4.9	M	3287±144	33.1±3.4
THIO	F	3177±151	39.3±4.4	M	3472±155	32.4±2.7
IM	F	3126±110	31.5±3.2	M	3303±88	29.9±2.0
IM±MA	F	2972±130	31.8±2.9	M	3078±257	30.0±2.8
Treatment	**Sex**	**Average fall latency (sec)**		**Sex**	**Average fall latency (sec)**	
(e) Rotorod						
SA	F	51.06±4.65		M	49.08±2.73	
MA	F	54.69±2.46		M	51.04±2.08	
THIO	F	53.14±5.36		M	54.71±2.46	
IM	F	46.29±1.32		M	46.29±1.32	
IM±MA	F	47.29±2.77		M	47.66±3.21	

All measures shown are averages±SEM.
$n=8$–10 mice per treatment and sex.
[a]A two-way ANOVA indicated that at P90 females weighed less than males ($p<0.001$).
[b]A two-way ANOVA indicated that in the open field females moved more than males ($p<0.01$).

males, coadministration of the H_3 receptor agonist IM prevented these MA-induced deficits in novel object recognition. The fact that neonatal H3 receptor blockade mimicked and neonatal H_3 receptor stimulation antagonized the detrimental effects of neonatal administration of MA on novel location and novel object recognition in adulthood supports a role for histaminergic neurotransmission in the long-term effects of MA on object recognition.

Spatial Learning and Memory in the Water Maze

Next, a modified Morris water maze was used to assess spatial learning and memory (Morris, 1981). During the

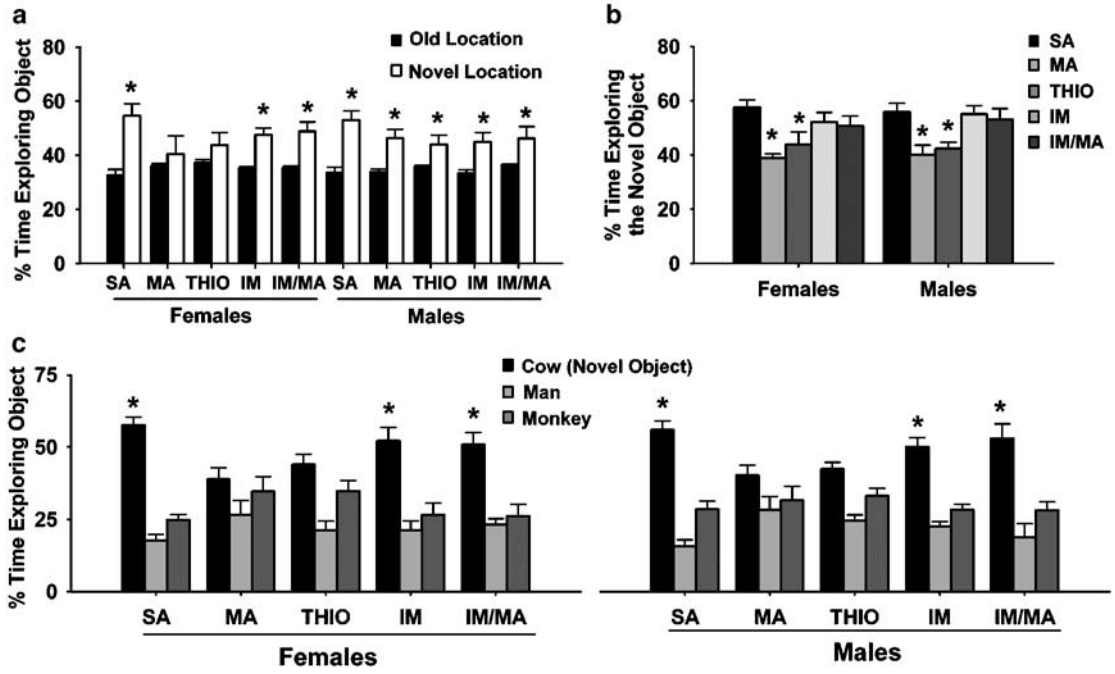

Figure 1 Novel location and novel object recognition in adulthood following neonatal treatments. (a) Novel location recognition. The % time the mice spent exploring the monkey in the familiar location in trial 3 (old location) and in the novel location in trial 4 (novel location) is shown. MA- and THIO-treated females did not spend more time exploring the object in the novel location. These MA-induced deficits were not seen when IM was co-administered. *$p<0.05$ *vs* % time exploring the object in the familiar location by analysis of variance (ANOVA). (b) Novel object recognition. The % time the mice spent exploring the novel object in trial 5 is shown. *$p<0.05$ *vs* the % time sex-matched saline-treated mice spent exploring the novel object. (c) Both female and male mice exposed to MA or THIO as neonates did not spend more time exploring the novel object than the two familiar objects. These MA-induced deficits were not seen when IM was coadministered. *$p<0.05$ *vs* any other object, Dunnett's test. $n=8$–10 mice per treatment and sex. Data shown are means ± SEM.

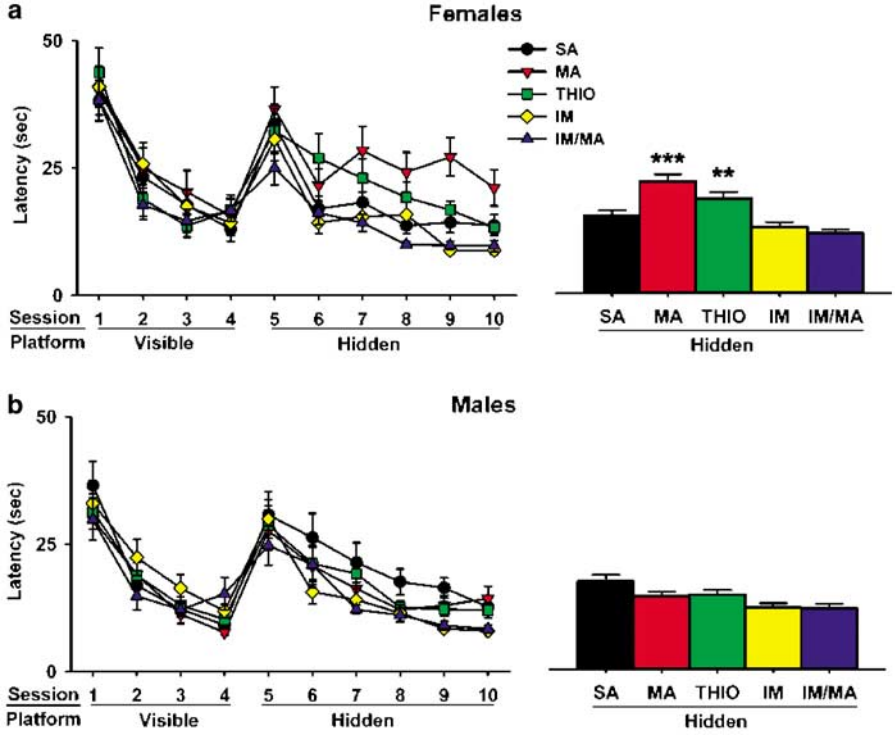

Figure 2 Water maze acquisition in adulthood following neonatal treatments. Following neonatal MA or THIO exposure, female (a), but not male (b), mice show impairments in their ability to locate the hidden platform. These MA-induced deficits were not seen when IM was coadministered. **$p<0.01$ and ***$p<0.001$ *vs* sex-matched saline-treated mice by repeated-measures ANOVA. $n=8$–10 mice per treatment and sex.

sessions with the visible platform, all treatment groups of female (Figure 2a) and male (Figure 2b) mice performed equally well in the time required to reach the platform (latency). The latency measure could be used as the swim speeds during the visible sessions were similar in all groups (female groups: SA, 15.98 ± 0.33 cm/s; MA, 15.86 ± 0.35 cm/s; THIO, 16.05 ± 0.39 cm/s; IM, 15.83 ± 0.49 cm/s, and IM/MA, 16.13 ± 0.30 cm/s; male groups: SA, 15.98 ± 0.37 cm/s; MA, 15.98 ± 0.38 cm/s; THIO, 15.59 ± 0.34 cm/s; IM, 15.62 ± 0.35 cm/s, and IM/MA, 15.59 ± 0.30 cm/s). In females, compared to neonatal SA treatment, neonatal MA and to a lesser extent THIO treatment caused impairments in ability to locate the hidden platform (Figure 2a). Strikingly, female mice treated as neonates with MA in the presence of IM did not show impairments in locating the hidden platform (Figure 2a). In contrast to females, neonatal MA or THIO treatment did not impair the ability of male mice during the hidden water maze sessions (Figure 2b).

The probe trial was designed to examine the extent of spatial discrimination learning (spatial bias) 1 h following the last session of hidden platform training. In the probe trial, SA-treated females spent more time in the target quadrant than in any other quadrant ($p < 0.05$), indicating spatial memory retention (Figure 3a and b). However, MA-treated females (Figure 3c) failed to show preferential searching in the target quadrant during the probe trial compared to all other groups (Figure 3a and b). These MA-induced impairments in spatial memory retention in the probe trial were not seen in female mice treated as neonates with MA in the presence of IM. In contrast to MA-treated females, THIO-treated females did show spatial memory retention in the probe trial, which might relate to the more robust impairments in performance during the hidden sessions of the water maze in MA- than THIO-treated females (Figure 2a). A higher dose of THIO might have caused impairments in the hidden sessions and probe trial of the water maze comparable to those seen following MA treatment. In contrast to females, MA treatment did not impair spatial memory retention of males (Figure 3a). Together with the novel location recognition data (Figure 2a), our data indicate that females might be more susceptible to the detrimental effects of neonatal MA exposure on hippocampal-dependent learning and memory in adulthood and that these effects involve histaminergic neurotransmission.

PrePulse Inhibition

PPI can be used to assess sensorimotor gating and is measured by the change in startle response following a prepulse. As potential differences in hearing sensitivity could influence PPI, the acoustic startle threshold was assessed first. There were no effects of sex or treatment on acoustic startle threshold (Figure 4a). For assessments of PPI, each mouse was tested in one session consisting of two series of acoustic stimuli followed by a testing phase. All conditions were selected based on the reported optimal conditions for measuring PPI in C57BL/6 mice (Plappert *et al*, 2004). Compared to SA-treated mice, there was a reduction in PPI following a postpulse of 120 db in MA-treated female mice and following a postpulse of 110 or 120 db in MA-treated male mice. The fact that MA reduced PPI following a postpulse of 110 db in males, but not females might relate to the lower PPI in female than male mice following neonatal SA treatment (floor effect). In both females and males, THIO mimicked and coadministration of IM prevented the effects of MA on PPI. These data support that histaminergic neurotransmission is also involved in the long-term effects of neonatal MA exposure on PPI deficits in adulthood.

In summary, here we show that neonatal MA exposure causes sex-dependent effects on cognitive function in adulthood. Although at a dose of 5 mg/kg male mice were less sensitive to the effects of neonatal MA exposure on hippocampus-dependent novel location recognition and

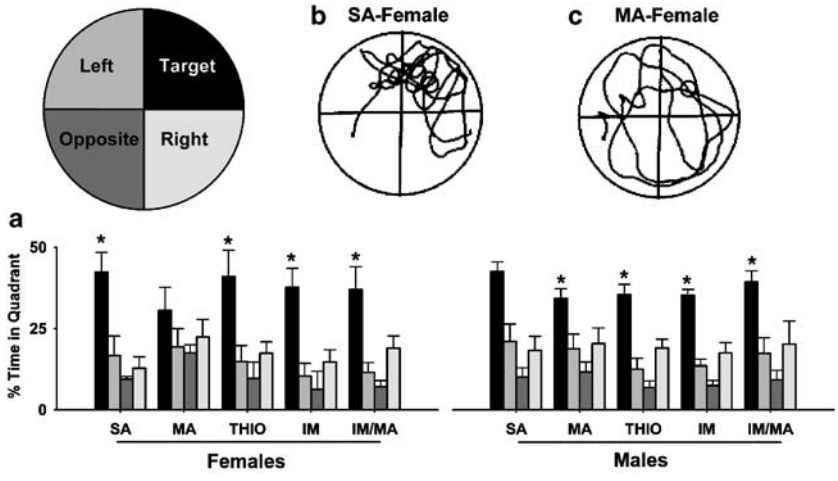

Figure 3 Spatial memory retention in the water maze probe trial in adulthood following neonatal treatments. Following neonatal MA administration, female, but not male, mice did not search more time in the target quadrant than any other quadrant in the water maze probe trial. These MA-induced deficits were not seen when IM was coadministered. *$p < 0.05$ *vs* any other quadrant, Dunnett's test. In (b) and (c), a representative searching pattern in the probe trial of a female mouse neonatally injected with SA or MA is shown. The lines define the quadrants used to divide the tank. The drop location designated by a square is located in the opposite quadrant from the target quadrant. In (a), the probe trial performance of all the mice is shown. $n = 8$–10 mice per compound(s) and sex.

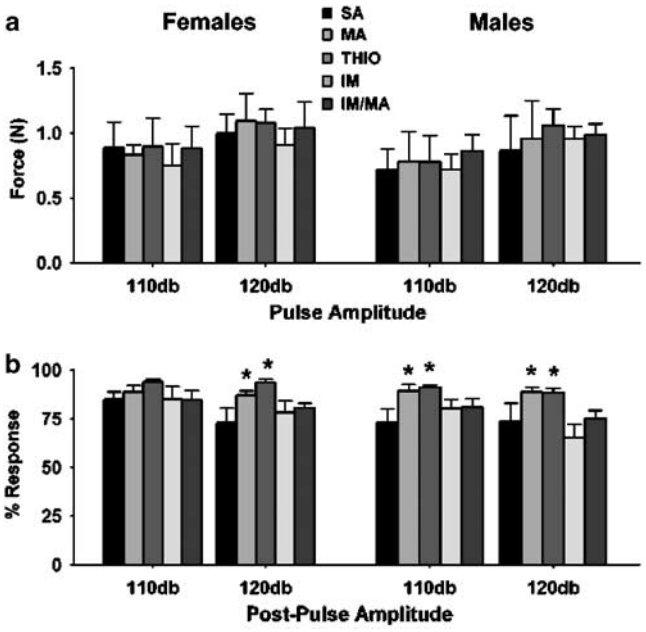

Figure 4 PPI in adulthood following neonatal treatments. (a) The average acoustic startles response to pulse alone revealed no effects of sex or treatment. (b) Prepulse inhibition. Compared to neonatal SA treatment, neonatal MA or THIO treatment impaired PPI in male mice at 110 or 120 db and in female mice at 120 db. These MA-induced deficits were not seen when IM was coadministered. $*p < 0.05$ *vs* sex-matched SA-treated mice. $n = 8$–10 mice per treatment and sex.

spatial learning and memory in the water maze in adulthood, they might show profound impairments at higher doses of MA. Sex differences in susceptibility to MA-induced hippocampal-dependent cognitive deficits might not be limited to the hippocampus. In rats, neonatal exposure to MA leads to sex-dependent changes in norpinephrine and dopamine levels in the caudate putamen and nucleus accumbens (Gomez-Da-Silva *et al*, 2004), which may contribute to the sex-dependent cognitive impairments. The ability of IM to block the effects of MA supports a role for histaminergic neurotransmission in the detrimental long-term cognitive effects of MA. As neonatal MA and MA in the presence of IM, but not THIO, caused hyperactivity in the pups, whereas neonatal MA or THIO caused behavioral alterations in adulthood, hyperactivity does not seem required or sufficient to cause the behavioral alterations in adulthood. Future studies with the neonatal mouse model are warranted to determine the potential role of genetic and environmental factors in the long-term detrimental effects of MA exposure during development and to develop potential therapeutic strategies to inhibit or even prevent these effects.

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