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Histamine-dependent behavioral response to methamphetamine in 12-month-old male mice

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Abstract

Methamphetamine (MA) use is a growing problem across the United States. Effects of MA include hyperactivity and increased anxiety. Using a mouse model system, we examined behavioral performance in the open field and elevated zero maze and shock-startle response of 12-month-old wild-type mice injected with MA once (1mg/kg) 30 min prior to behavioral testing. MA treatment resulted in behavioral sensitization in the open field, consistent with studies in younger mice. There was an increased activity in the elevated zero maze and an increased shock-startle response 30 and 60 min post-injection. Since histamine mediates some effects of MA in the brain, we assessed whether 12-month-old mice lacking histidine decarboxylase (*Hdc*^{-/-}), the enzyme required to synthesize histamine, respond differently to MA than wild-type (*Hdc*^{+/+}) mice. Compared to saline treatment, acute and repeated MA administration increased activity in the open field and measures of anxiety, though more so in *Hdc*^{-/-} than *Hdc*^{+/+} mice. In the elevated zero maze, opposite effects of MA on activity and measures of anxiety were seen in *Hdc*^{+/+} mice. In contrast, MA similarly increased the shock-startle response in *Hdc*^{-/-} and *Hdc*^{+/+} mice, compared to saline-treated genotype-matched mice. These results are similar to those in younger mice suggesting that the effects are not age-dependent. Overall, single or repeated MA treatment causes histamine-dependent changes in 12-month-old mice in the open field and elevated zero-maze, but not in the shock-startle response.

Keywords

HDC; mouse; open field; elevated zero-maze; shock startle

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1. Introduction

According to the National Institute on Drug Abuse (NIDA), the prevalence of methamphetamine (MA) abuse is increasing across the United States (Maxwell, 2005). MA is a schedule II drug; it is a white, odorless and bitter-tasting crystalline powder most commonly smoked or taken orally. This addictive stimulant leads to several side effects including insomnia, irritability, and increased anxiety (Anglin et al., 2000; Brecht et al., 2004; Ernst et al., 2000; Sulzer et al., 2005). Certain individuals appear to be more susceptible to the side effects associated with first-time and repeated MA use (Cruickshank and Dyer, 2009). Due to high rates of polydrug use and environmental exposures associated with MA production, these effects are hard to study in controlled experiments with humans. Therefore, rodent models are used to examine potential physiological or genetic modulators that may explain different responses to MA use.

Animal studies have established that there are dose-dependent responses to acute and repeated MA administration at 1mg/kg, resulting in increased locomotion and stereotypic behavior (Brien et al., 1978; Itzhak, 1997; Milesi-Halle et al., 2005). Most commonly, 3- to 6-month-old mice have been used in animal studies of MA-induced behavioral changes (Fukushima et al., 2007; Watanabe and Yanai, 2001). Age-dependent analyses indicate that 6-month-old mice display the highest sensitivity to MA at first administration and the lowest sensitivity after repeated administration compared to younger mice (Kuribara et al., 1996). Little is known about the potential effects of MA in 12-month-old mice. As age also appears to modulate MA-related neuronal effects (Sabol et al., 2000), more studies are needed in older mice in order to further understand the mechanisms of response.

Histamine (HA) is produced in the posterior hypothalamus (Miklos and Kovacs, 2003; Panula et al., 1984; Panula et al., 1989), where histidine decarboxylase (HDC) converts L-histidine to HA (Ohtsu et al., 2001). HA is distributed through an extensive network of fibers projecting to various regions of the central nervous system, including the cerebral cortex, amygdala, and hippocampus (Brown et al., 2001; Haas and Panula, 2003; Nakamura et al., 2004). Neuronal HA functions as a neurotransmitter through three postsynaptic (H_1 , H_2 , and H_4) receptors and one pre-synaptic (H_3) receptor (Hill et al., 1997). The H_3 receptor (H_3R) functions as a negative feedback; i.e. stimulation of H_3R inhibits HA release. HA has been shown to regulate the effects of MA in the rat brain (Ito et al., 1996; Ito et al., 1997a; Ito et al., 1997b). In addition, repeated administration of MA increases HDC activity in the striatum and cortex in rats and HA levels peak at 60 min post-injection (Ito et al., 1996). In mice, MA leads to the release of HA in various brain regions, including the cortex and striatum, with peak HA levels at 60 min post-injection (Dai et al., 2004). In male mice younger than 5 months of age, HA and its precursor, L-histidine, inhibit MA-induced stereotyped behavior and behavioral sensitization to MA. These effects are blocked in the presence of H_1 or H_2 receptor antagonists (Kitanaka et al., 2007; Kitanaka et al., 2010; Onodera et al., 1998). Antagonism of the H_3R enhances MA-induced stereotypic hyperactivity in young male mice (Munzar et al., 1998; Okuda et al., 2009; Toyota et al., 2002). To study effects of long-term HA deficiency, HDC targeted ES cell-mediated gene knockouts ($Hdc^{-/-}$) mice were produced that have only minimal levels of HA remaining in their organs due to diet and/or HA-producing bacteria in the gut (Ohtsu et al., 2001). Young (less than 3 months old) male $Hdc^{-/-}$ mice, which have little or no neuronal HA (Ohtsu et al., 2001) show enhanced MA-induced locomotor activity and behavioral sensitization at 60 min post-injection (Kubota et al., 2002). These data support a strong association between MA and HA in young mice, but it is unclear whether such an association also exists in older mice.

Both young and old male $Hdc^{-/-}$ mice are more anxious than wild-type ($Hdc^{+/+}$) with heightened sensitivity in younger mice (Acevedo et al., 2006; Dere et al., 2003; Dere et al., 2004). In addition, when comparing $Hdc^{-/-}$ mice to their wild-type counterparts, the former display age-dependent impairments in object recognition, spatial memory retention in water-maze probe trials, and memory retention in the passive avoidance test (Acevedo et al., 2006). Therefore, age should be considered as a factor when examining the response to drugs such as MA that may impair cognitive ability. Currently, there are no studies on the effects of MA in $Hdc^{-/-}$ mice older than 6 months.

The aim of this study was to determine the effects of acute and repeated MA administration on behavioral performance in the open field and elevated zero-maze and the shock-startle response in 12-month-old $Hdc^{+/+}$ and $Hdc^{-/-}$ mice.

2. Results

2.1. Body weight

At 12 months of age, mice were injected daily with MA (1mg/kg) or saline (SA). During the injection period, there were no effects of MA on body weights of the mice (Table 1).

2.2. MA-related open-field behavior of 12-month-old $Hdc^{+/+}$ mice

The effect of daily MA or SA administration on open-field behavior in $Hdc^{+/+}$ mice was assessed 30 min and 60 min post-injection. A Repeated Measures (REM) Analysis of Variance (ANOVA) for time-by-treatment effects across days was conducted for all open field measures. There was an overall effect of treatment for active time ($F_{(11,102)} = 5.00, p < 0.01$, Fig. 1A–B), distance moved ($F_{(11,102)} = 41.40, p < 0.0001$, Fig. 1D–E) and time in the center ($F_{(11,102)} = 9.90, p < 0.003$, Fig. 1G–H). There was no overall effect of time on any open field performance measure between 30 min and 60 min groups. For distance moved there was an effect of day ($F_{(11,102)} = 10.71, p < 0.0001$, Fig. 1D–E) with all groups moving around less by the third day. There was a time-by-day interaction for active time ($F_{(11,102)} = 6.80, p < 0.002$) and distanced moved ($F_{(11,102)} = 5.41, p < 0.007$). Post-hoc tests indicated that the 12-month-old mice were more active and moved more when tested 30 min post MA injection on day 3 but less active and moved less 60 min post MA injection on day 1 (Fig. 1A–B). These data indicate that the start of behavioral sensitization is evident at 30 min post MA injection. There were no effects on time spent in the center of the open field, based on when they were tested or injection type, suggesting that in 12-month-old wild type, MA does not induce measures of anxiety in the open field test 30 min or 60 min post injection.

2.3. Effects of histamine on MA-related open-field behavior

The effects of daily MA or SA administration on open-field behavior in $Hdc^{-/-}$ and $Hdc^{+/+}$ mice was assessed at 60 min post-injection as conducted previously in younger mice (Kubota et al., 2002). REM ANOVA for genotype-by-treatment across days was conducted for all open field measures. Genotype affected all measures, including activity, distance moved and time spent in the center of the open field ($p < 0.0001$, Fig. 1). For the amount of activity, there was an effect of treatment ($F_{(11,96)} = 5.14, p < 0.03$) and a genotype-by-treatment interaction ($F_{(11,96)} = 57.32, p < 0.0001$, Fig. 1B–C) with the MA-treated $Hdc^{-/-}$ mice being hyperactive. Analysis of distance moved indicated an effect of treatment ($F_{(11,96)} = 26.97, p < 0.0001$) and a genotype-by-treatment interaction ($F_{(11,96)} = 38.23, p < 0.0001$, Fig. 1E–F). On each day, MA-injected mice moved more than SA-treated mice ($F_{(11,96)} = 4.24, p < 0.02$). MA-treated $Hdc^{-/-}$, but not $Hdc^{+/+}$, mice showed higher active times and distance moved on day 2 and day 3 than genotype-matched SA-treated mice (Figs. E–F). There was no evidence of behavioral sensitization to repeated MA exposure in the $Hdc^{+/+}$ mice. There was an effect of genotype ($F_{(11,96)} = 13.48, p < 0.0001$) on the percent time

spent in the center, regardless of treatment group (Fig. 1H–I). Although the *Hdc*^{-/-} MA-injected mice were hyperactive, they spent less time in the open areas of the open field. Therefore, HA may modulate the effects of MA depending on where the mice prefer to spend their time.

2.4. Effects of time and number of MA injections on performance of *Hdc*^{+/-} mice in the elevated zero maze

We next determined whether a single and four daily MA injections have differential effects on elevated zero maze performance. Mice were initially tested on day 1 at 60 min or on day 4 at 30 or 60 min post-injection. There were no associations or interactions when conducting day-by-treatment ANOVAs (Fig. 2). When comparing MA-related behavior in the elevated zero maze on day 4, between 30 and 60 min post-injection and using ANOVA for time-by-treatment, there was an effect of treatment on distance moved ($F_{(3,24)} = 19.40$, $p < 0.0001$, Fig. 2A), velocity ($F_{(3,24)} = 13.94$, $p < 0.0001$, Fig. 2B) and percent time spent in the open areas ($F_{(3,24)} = 5.78$, $p < 0.03$, Fig. 2C). The discrepancy between lower distance moved and increased velocity may be explained by increased rest periods in the SA-treated mice, and slower but continuously moving MA-treated mice. Overall, a single MA injection and four MA injections on day 4 had similar effects on elevated zero maze performance 30 and 60 min post injection.

2.5. Effects of MA on the elevated zero-maze performance of *Hdc*^{-/-} and *Hdc*^{+/-} mice

On the day following the last day of open-field testing (day 4), the effects of MA and SA on performance in the elevated zero maze were assessed. There was a genotype-by-treatment interaction for both distance moved ($F_{(3,45)} = 5.516$, $p < 0.03$, Fig. 2A) and velocity ($F_{(3,45)} = 11.22$, $p < 0.003$, Fig. 2B). In contrast to *Hdc*^{+/-} mice, *Hdc*^{-/-} mice treated with MA moved farther and faster than those injected with SA. For the percent time spent in the open areas of the maze, there was an effect of genotype ($F_{(3,45)} = 17.39$, $p < 0.0001$) and a genotype-by-treatment interaction ($F_{(3,45)} = 8.907$, $p < 0.006$, Fig. 2C). Compared to mice treated with SA, MA-injected *Hdc*^{+/-} mice spent more time in the open areas of the elevated zero maze than did their *Hdc*^{-/-} counterparts. There was a dramatic genotype-dependent effect of MA on the percent of time spent in the open areas of the elevated zero maze.

2.6. Effects of time and number of MA injections on the shock startle response of *Hdc*^{+/-} mice

To determine whether a single or five once daily injections have differential effects on the shock-startle response, *Hdc*^{+/-} mice were administered MA or SA and tested 60 min post-injection. REM ANOVA for day-by-treatment across trials indicated an effect of treatment ($F_{(63,504)} = 15.04$, $p < 0.001$), day ($F_{(63,504)} = 33.87$, $p < 0.001$) and trial ($F_{(63,504)} = 23.53$, $p < 0.001$) (Fig. 3A–B). In addition, there was an interaction between day and treatment ($F_{(63,492)} = 2.26$, $p < 0.002$) with the SA group showing more sensitivity to shock on day 5. Thus on days 1 and 5, MA-treated mice displayed similar effects of an enhanced shock-startle response. REM ANOVA for time-by-treatment across trials indicated a treatment ($F_{(63,492)} = 64.32$, $p < 0.001$) and trial ($F_{(63,492)} = 26.74$, $p < 0.001$) (Fig. 3B–C) with no indication that the time the mice were tested post-injection was different.

2.7. Effects of MA on the shock-startle response of *Hdc*^{-/-} and *Hdc*^{+/-} mice

On the day following elevated zero-maze testing (day 5), the effects of MA on the shock-startle response were assessed at 60 min post-injection. Once again, there was an effect of treatment ($F_{(63,608)} = 57.37$, $p < 0.0001$) and trial ($F_{(63,608)} = 47.01$, $p < 0.0001$, Fig. 3B,D). Overall, independent of treatment, *Hdc*^{-/-} mice were less sensitive to the shock-induced startle response than were *Hdc*^{+/-} mice, as indicated by an effect of genotype ($F_{(63,608)} =$

11.31, $p < 0.001$, Fig. 3B,D). This indicates that HA might be involved in the shock startle response, independent of MA treatment.

3. Discussion

As MA use is of growing concern, understanding the initial response to the drug may help in understanding why only some individuals become addicted to it. There are many factors to consider including age and genetic predisposition. This study examined older mice (12-month-old) to compare to previous studies in < 6 month-old mice (Brien et al., 1978; Fukushima et al., 2007; Itzhak, 1997; Kuribara et al., 1996; Milesi-Halle et al., 2005; Watanabe and Yanai, 2001). Not every individual develops the same side effects related to their MA exposure, even those who report anxiety effects vary in the type and degree of symptoms (Anglin et al., 2000). Commonly, rodent research has focused on behavioral sensitization effects in open field paradigm to use as a model for human sensitization; however, there are several other behavioral paradigms that may help to understand MA-related responses. Therefore, we also assessed measures anxiety and activity in the elevated zero maze and the shock-startle response.

During the first part of the 5-day paradigm, we examined 10 min of open field behavior after daily MA injections over 3 consecutive days. We injected MA (1mg/kg) expecting only a slight increase in activity and distance moved, as previously reported in younger mice (Mori et al., 2004). Our data indicated differences in active time and distance moved in the open field when mice were tested at 30 or 60 min post-injection. At 30 min post-injection, active time and distanced moved increased by day 3 indicating the start of behavioral sensitization. Unexpectedly, at 60 min post-injection on day 1, the mice were less active and slower in MA-related responses. Activity and distance moved increased over the days as expected in this behavioral sensitization paradigm. The lack of MA-related differences 60 min post-injection response on day 3 appears to be caused by variability or agitation in the SA-injected group movement and activity after the injection itself, as all other SA groups steadily declined over the days. Overall, these data suggests that 12-month-old $Hdc^{+/+}$ wild type mice are hyposensitive to MA compared to younger mice.

Compared to 12-month-old $Hdc^{+/+}$ mice, 12-month-old $Hdc^{-/-}$ mice were more sensitive to the effects of MA in terms of open-field behavior at 60 min similar to previous studies in younger mice (Kubota et al., 2002). Compared to the center of the open field, MA had dramatic genotype-dependent effects on the amount of time spent in the open areas of the elevated zero maze. Compared to genotype-matched mice treated with SA, MA-treated $Hdc^{+/+}$ mice spent more time in the open areas of the elevated zero-maze than did $Hdc^{-/-}$ mice. $Hdc^{-/-}$ mice showed a lower shock-startle response than $Hdc^{+/+}$ mice, but both genotypes showed an enhanced shock-startle response following MA treatment. Although MA increased both active times and distance moved in the open field in both genotypes, our results show that the responses of 12 month-old male mice are similar to those of younger mice, suggesting that MA-induced hyperactivity is not age-dependent (Iwabuchi et al., 2004; Kubota et al., 2002; Watanabe and Yanai, 2001).

In the elevated zero maze, MA treatment affected both velocity and where the mice spent their time in a genotype-dependent fashion. While MA reduced the velocity of the $Hdc^{+/+}$ mice, it increased the velocity of $Hdc^{-/-}$ mice. In contrast to velocity, MA increased the time spent in the open areas in $Hdc^{+/+}$ mice, while it decreased this measure in $Hdc^{-/-}$ mice. As MA-injected $Hdc^{+/+}$ mice spent almost 50% of their time in the open areas of the elevated zero-maze, it is possible that they do not find these open areas to be anxiety-provoking. Results showing that the opposite effects of MA on time spent in the open areas are seen in the 12 month-old $Hdc^{-/-}$ mice, indicate that histamine is required for the effects

of MA to reduce velocity and increase time spent in the open areas of the elevated zero maze. Follow-up studies aimed to identify whether this effect is similar in younger *Hdc*^{-/-} mice may help to determine whether this effect is age-dependent.

To determine if a particular histamine receptor is responsible for MA-related behavioral changes or whether it is simply due to the levels of histamine in the brain in older mice, further studies will be needed. Studies indicate that young *H₁R* knockouts (*H₁R*^{-/-}) display decreased locomotion in the open field (Inoue et al., 1996) and young *H₃R*^{-/-} are more active and less anxious in both the open field and the elevated zero maze (Rizk et al., 2004). With respect to MA effects, young *H₁R*^{-/-} exposed to MA show increased locomotor activity, young *H₂R* knockouts (*H₂R*^{-/-}) are not affected, but that young *H₁R*^{-/-}/*H₂R*^{-/-} double knockouts show hyperactivity similar to that of *Hdc*^{-/-} mice (Iwabuchi et al., 2004). These data support the idea that the level of histamine in the brain alters the MA response and not necessarily a particular histamine receptor.

In contrast to what has been found in the open field and elevated zero maze, our data indicate that MA increases the shock-startle response in both *Hdc*^{+/+} and *Hdc*^{-/-} mice similarly. This suggests that the effects seen after MA injections are not related to histamine neurotransmission. The overall lower shock-startle response of the 12 month-old *Hdc*^{-/-} mice compared to that of the *Hdc*^{+/+} mice suggests that histamine modulates the shock startle response. Our data is consistent with evidence that *H₃R*^{-/-} mice display hypersensitivity to shock startle (Rizk et al., 2004). The number of injections (not the time at which they were tested post-injection) was a factor in our paradigm with the SA groups being more sensitive to shock on day 5, which is likely due to repeated injections or handling. Overall, shock startle response may not be a sensitive measure for MA-related behavioral responses.

We recognize that low levels of HA might still be present in the brains of the animals due to HA-containing fish extracts in the diet and HA-producing bacteria in the gut. However, this study does offer a contribution to the field, as it is the first to show that at 12 months of age behavioral responses to MA in male mice are HA-dependent. In addition, this study is the first to examine the effect of MA treatment on zero maze performance. Additional MA doses females mice need to be examined in the future. Sex differences have been indicated in other MA behavioral sensitization paradigms (Milesi-Halle et al., 2005). The short 5 to 7 day paradigm offers the ability to study acute response to MA with additional open field behavior without excessive handling and fatigue issues. However, more tests need to be included for the development of an appropriate paradigm. Injections at additional time intervals would also be beneficial in the future to examine the MA response before and during peak levels of histamine occurrence.

In summary, MA affects performance in the open field and elevated zero maze in a HA-dependent fashion but MA affects the shock-startle response in a HA-independent fashion.

4. Methods

4.1. Animals

Homozygous mice lacking exon 6–8 and part of exon 9 of the HDC gene (*Hdc*^{-/-}) male mice, generated as described (Ohtsu et al., 2001) using homozygous mating, were backcrossed onto the C57Bl6/J (*Hdc*^{+/+}) background for 6 generations. The mice were 12-month-old at the time of testing. The mice were kept on a 12/12 hr light/dark schedule (lights on at 6 AM) with chow (PicoLab Rodent Diet 20, #5053; PMI Nutrition International, St. Louis, MO) and water given *ad libitum*. To maintain stable weights, all mice were provided with soft food during the injection period.

4.2. Injections

The (+)-methamphetamine hydrochloride (1mg/kg) was obtained from the Research Triangle Institute (Research Triangle Park, NC) through the National Institute of Drug Abuse drug supply program. The methamphetamine was diluted with 0.9% of sodium chloride (saline) to the appropriate concentrations and a volume between 0.05 and 0.10 ml was injected intraperitoneally. Injections were administered once daily, between 8 AM and 11 AM (time adjusted to run animals in pairs), for five days, unless indicated otherwise. To adjust for weight loss or gain, each mouse was weighed daily. MA had no effect on the body weights of the mice (Table 1).

4.3. Behavioral testing

Animals were housed individually beginning 48 hours prior to the first behavioral test. All tests were performed 3 or 60 min post MA injection. Injection types were set up in random order with tester unaware of injection type. The sequence of the behavioral tests was: open field (day 1–3), elevated zero-maze (day 4) and shock-startle (day 5), unless specified otherwise. All procedures were according 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.

4.4. Open field

Mice were placed in a 40.64cm × 40.64cm, brightly lit, open arena (luminescence 200 lx) that was equipped with infrared photocells interfaced with a computer (Kinder Scientific, Poway, CA). Active time and distance moved (reflecting all new beam breaks) and fine movements (reflecting single new beam breaks) were recorded for ten min. Anxiety was operationally defined by decreases in time spent in the center (Paulus et al., 1999; (Choleris et al., 2001). To assess measures of anxiety in the open field, time spent in the center zone (20.32cm × 20.34cm) and the peripheral zone were analyzed separately.

4.5. Elevated Zero-maze

Mice were placed in a custom-built elevated zero maze consisting of two enclosed areas and two open areas (6 cm wide) (Kinder Scientific, Poway, CA). Mice were placed in the closed part of the maze and allowed free access for 10 min. A video tracking system (Noldus Information Technology, Sterling, VA, set at six samples per second) was used to calculate the distance moved, velocity, and time spent in the open and closed areas. Mice that are anxious in the elevated zero maze spend less time in the open areas (Shepherd et al., 1994).

4.6. Shock-startle

Mice were tested in a single approximately 12-min session for shock-startle response using startle chambers (Kinder Scientific, Poway, CA). After 5 min acclimation, the baseline response was measured (three measures of no stimulation (ns)). Subsequently, a slight foot shock was given, ascending from 0.02–0.30 milliamps (mA) using increments of 0.02 mA with random inter-trial intervals ranging from 10 to 150 milli-seconds (msec) within a 500 msec recording window. The startle response was measured as the maximum force on the sensing platform (in Newton (N)).

4.7. Statistical analyses

Data were analyzed with SPSS software (SAS Institute Inc., Cary, NC). Following initial repeated-measures 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 assessing the effects of treatment and genotype, interactions between these factors were assessed. A probability value (*p*) of less than 0.05 was considered significant.

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Fig. 1.

Effects MA on open field behavior of $HDC^{+/+}$ and $HDC^{-/-}$ mice. At 30 min post injection on day 3, $HDC^{+/+}$ mice MA were more active (A) and had increased distances moved (D), compared to 60 min post-injected group showing decreased active time (B) and distance moved (E) on day 1. Over the three days, there was no difference in % time spent in the center of the open field (G–H). $HDC^{-/-}$ mice were hyperactive (C) and had increased distance moved (F) over all three days at 60 min post-injection compared to $HDC^{+/+}$ mice. (I) There was no difference in treatment effects, but there was a difference in genotypes in the % time spent in the center of the open field with $HDC^{-/-}$ mice spending less time in the center of the open field over the three days. * $p < 0.05$, ** $p < 0.01$ genotype/time/day versus genotype-matched SA-injected mice. $n = 7$ –13 mice per treatment.

Fig. 2. Effects MA on elevated zero maze performance of *HDC*^{+/+} and *HDC*^{-/-} mice. Only *HDC*^{-/-} MA-treated mice moved more (A) and were faster (velocity) (B) compared genotype-matched SA-injected mice. (C) *HDC*^{+/+} mice injected with MA spent more time in the open areas of the maze, but MA-injected *HDC*^{-/-} mice spent less time in the open areas of the maze. **p* < 0.05 *HDC*^{+/+} versus *HDC*^{-/-} mice within treatment, #*p* < 0.05 versus genotype-matched SA-injected mice. *n* = 7–13 mice per treatment and genotype.

Fig. 3.

Effects MA on the shock-startle response of $HDC^{+/+}$ and $HDC^{-/-}$ mice. $HDC^{+/+}$ MA-injected mice were hypersensitivity to shock on day 1 (A), on day 5 at 60 min post-injection (B), and on day 5 at 30 min post-injection. While overall less sensitive to shock, $Hdc^{-/-}$ mice injected with MA did display an increased shock startle response. $*p < 0.05$ versus genotype/day/time-matched SA-injected mice. $n = 7-13$ mice per treatment and genotype.

Table 1Body Weights of SA- and MA-treated $Hdc^{-/-}$ and $Hdc^{+/+}$ mice

Genotype	Treatment	Day 1 Weight (g)	Day 3 Weight (g)	Day 5 Weight (g)
$Hdc^{+/+}$	saline	31.9 ± 1.5	31.9 ± 1.5	29.2 ± 1.7
$Hdc^{+/+}$	MA	30.3 ± 0.4	30.3 ± 0.4	30.1 ± 0.5
$Hdc^{-/-}$	saline	37.0 ± 1.9	37.5 ± 1.5	37.2 ± 1.5
$Hdc^{-/-}$	MA	35.8 ± 1.6	34.2 ± 1.6	32.9 ± 1.4

All measures shown are averages ± standard error of the mean (± SEM).
 $n = 8-10$ mice per treatment and genotype