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Prepulse inhibition in HIV-1 gp120 transgenic mice after withdrawal from chronic methamphetamine

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Abstract

HIV infection is frequently comorbid with methamphetamine (METH) dependence. Both factors are associated with impairment in inhibitory function that continues even after abstinence from the drug. Deficits in prepulse inhibition (PPI), a measure of sensorimotor gating, are induced by acute stimulant administration, but the combined effect of HIV and chronic METH exposure on PPI is not well characterized. We quantified baseline acoustic startle and PPI in mice expressing the HIV-1 gp120 envelope protein (gp120tg) and in wild-type (WT) littermates; thereafter, we administered a chronic regimen of METH or vehicle and tested startle and PPI after 7 days of drug withdrawal. We hypothesized that METH-treated gp120tg mice would exhibit PPI deficits compared with vehicle-treated WT or gp120tg animals. Before METH administration, drug-naive female gp120tg mice exhibited decreased PPI compared with female WT mice, whereas male gp120tg mice exhibited increased startle compared with other groups. After drug withdrawal, no consistent genotype effect was observed, but METH-treated mice exhibited increased PPI compared with vehicle, in contrast to previous reports of acute METH-induced PPI deficits. In summary, PPI impairment in HIV could depend on factors such as sex, whereas changes in PPI following METH withdrawal may depend on the quantity and duration of drug exposure.

Keywords

gp120; HIV; methamphetamine; mouse; prepulse inhibition; sensorimotor gating

Introduction

HIV-1 virus infection is frequently characterized by impairment in executive function, memory and inhibition linked to abnormalities in the basal ganglia and frontal cortex, collectively described as HIV-associated neurocognitive disorders (HAND; Antinori *et al.*, 2007). Inhibitory deficits, defined as the inability to attenuate an action or thought (Goodwin and Jamison, 1990), remain common in the era of combined antiretroviral therapy and are

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Conflicts of interest

M.A. Geyer holds an equity interest in San Diego Instruments. For the remaining authors, there are no conflicts of interest.

associated with poor everyday functioning and high-risk behaviors, including the use of drugs such as methamphetamine (METH; Semple *et al.*, 2006). Similar to HIV-infected individuals, METH-dependent individuals exhibit impaired inhibition, as demonstrated by poor performance on neurocognitive tests such as the Stroop and Wisconsin Card Sorting Task, elevated rates of self-reported disinhibition on the Frontal Systems Behavioral Scale, and the propensity to engage in risky sexual activities (Salo *et al.*, 2002; Monterosso *et al.*, 2005; Woods *et al.*, 2005; Cattie *et al.*, 2012; Meade *et al.*, 2012). Comorbid METH dependence also increases neurocognitive deficits observed in HIV infection and augments HIV-associated neuropathology linked to poor inhibitory function, including neuronal loss and glial activation in the frontal cortex (Chang *et al.*, 2002, 2005; Rippeth *et al.*, 2004; Carey *et al.*, 2006; Chana *et al.*, 2006). Given the failure of combined antiretroviral therapy to effectively address inhibitory deficits associated with HIV and concurrent drug use, more investigation is required to elucidate the biological mechanisms and factors that underlie this phenomenon.

Although the manifestation of neurocognitive impairment in HIV-infected individuals is typically assessed by traditional neuropsychological assessment and/or self-report, some of the earliest neurological abnormalities in this disorder may be distinguished by more subtle disruption of inhibition related to sensorimotor gating (Polich *et al.*, 2000). Gating represents a process by which excess or trivial sensory information is filtered out of awareness, enabling an individual to focus attention on the most salient or relevant stimuli (Braff and Geyer, 1990). One of the most common measures of sensorimotor gating is prepulse inhibition (PPI), in which the magnitude of a startle response to tactile or acoustic stimuli is reduced by the prior presentation of a nonstartling prepulse (Geyer and Swerdlow, 2001). PPI is regulated by a network of neural structures, including a cortico-striato-pallido-thalamic loop that involves regions implicated in inhibitory function in both HIV and METH (Chang *et al.*, 2002; Chung *et al.*, 2007). PPI deficits are observed across a wide variety of neuro-psychiatric populations (Braff *et al.*, 2001; Perry *et al.* 2001) and have been induced by cross-species pharmacological manipulations in rodents, primates, and humans (Geyer *et al.*, 2001). Acute administration of both direct and indirect dopamine (DA) agonists, including amphetamine and METH, disrupts PPI and has been used to model dopaminergic abnormalities and preattentive deficits associated with disorders such as schizophrenia. Although HIV infection is characterized by DA abnormalities and pathology in the neurocircuitry that regulates PPI, effects that may be exacerbated by comorbid METH use (Cadet and Krasnova, 2007), few studies have examined sensorimotor gating in this disorder (Minassian *et al.*, 2013). In contrast to self-report and neuropsychological tasks that are impacted by factors such as motivation and fatigue, PPI quantifies an involuntary response that may also serve as a more specific indicator of altered inhibitory function (Feifel *et al.*, 2009). In addition, PPI can be tested in both rodents and humans, enabling cross-species comparisons that explicate HIV-related neuropathology (Fitting *et al.*, 2006c, 2007). Sensorimotor gating has not been assessed extensively in models of HIV, but one recent study observed that acute METH administration induced greater PPI deficits in HIV-1 transgenic (tg) rats compared with wild-type (WT) animals (Moran *et al.*, 2012). This experimental design, however, is incongruent with the typical course of METH use in humans, in which the negative effects of the drug are associated with chronic exposure. In summary, the consequence of extended METH administration on PPI in an animal model of HIV has not been previously examined.

The objective of this study was to examine the effect of a chronic METH regimen on inhibitory deficits quantified by PPI in transgenic mice that constitutively express the gp120 protein (Toggas *et al.*, 1994). Prior studies indicate that the combination of HIV infection and METH dependence is associated with impairment in inhibitory performance even after several months of abstinence from the drug (Rippeth *et al.*, 2004). To parallel the human

data, we chose to assess sensorimotor gating in mice after 1 week of METH withdrawal, similar to previous work (Henry *et al.*, 2013). We initially hypothesized that drug-naive gp120 transgenic mice (gp120tg) would exhibit impaired PPI relative to WT animals during baseline testing before METH administration. Second, we proposed that METH-treated gp120tg mice would exhibit lower PPI after METH withdrawal compared with vehicle-treated gp120tg mice and WT animals given either METH or vehicle treatment.

Methods

Subjects

This study was part of a larger examination of the individual and combined effects of HIV and METH conducted by the Translational Methamphetamine AIDS Research Center (TMARC). Male and female transgenic mice expressing the HIV-1 envelope glycoprotein gp120 were obtained from the lab of Dr Eliezer Masliah at the University of California, San Diego. Gp120 is expressed in astrocytes under the control of a modified murine glial fibrillary acidic protein (GFAP) in animals generated from a mixed C57BL/6 × Sv129 (SJL/BL6/129) background (Toggas *et al.*, 1994) and previously crossed with WT BDF1 mice from Charles River. Mice from the F6 BL6/129 × BDF1 generation (8–9 months old, n = 12–13/group) were tested in the current study and their nontransgenic littermates were used as controls. The genotype was confirmed by PCR analysis of tail DNA.

Mice were separated by sex and group and were housed in a climate-controlled environment with a reversed day/night cycle (lights on at 20:00 h, off at 08:00 h). Behavioral testing was conducted between 09:00 and 18:00 h. The animals were given free access to food (Haran Teklad, Madison, Wisconsin, USA) and water for the duration of the testing. All procedures were approved by the UCSD Institutional Animal Care and Use Committee and conformed to NIH guidelines.

Drug regimen

METH (Sigma, St. Louis, Missouri, USA) was dissolved in saline and administered subcutaneously at a 5 ml/kg injection volume (freebase weight). Stock solutions of the drug were prepared every 3–4 days and diluted as needed during the drug regimen. We administered an escalating dose-multiple binge METH regimen that was first tested in rats (Kuczenski *et al.*, 2007) and was subsequently demonstrated to increase exploratory behavior in mice (Henry *et al.*, 2013). This treatment schedule was originally developed to mimic the gradual dose progression in human METH addicts (Segal and Kuczenski, 1997). Most previous studies used subchronic regimens (5–10 drug injections) and/or relatively short periods of exposure (1 week) to examine the effect of repeated METH or amphetamine on PPI (Druhan *et al.*, 1998; Russig *et al.*, 2003; Arai *et al.*, 2008; Nakato *et al.*, 2010). In the present study, we utilized this drug schedule to represent the escalation/binge behaviors that typically characterize METH dependence and produce neurodegenerative effects associated with METH use (Kuczenski *et al.*, 2007).

In this study, gp120tg and WT mice were treated three times per day (10:00; 13:15; 17:30 h) for 14 days with vehicle (saline) or escalating doses of METH, starting with 0.1 mg/kg and increasing to 4.0 mg/kg, with a stepwise increase of 0.1 mg/kg per injection. After this 14-day period, animals received four daily injections of 6.0 mg/kg METH or vehicle at 2-h intervals (10:00, 12:00, 14:00, and 16:00 h) during an 11-day ‘binge’ period (Fig. 1).

Fresh syringes were used for every injection given to each mouse.

Apparatus

Behavioral testing was performed as described previously (Geyer and Dulawa, 2003; Powell *et al.*, 2008). The startle response was assessed in eight startle chambers (SR-LAB; San Diego Instruments, San Diego, California, USA). Each chamber contained a clear nonrestrictive Plexiglas cylinder resting on a platform below high-frequency speakers that produced a constant background noise of 65 dB(A) and emitted the acoustic stimuli during the test. Mouse startle responses produce cylinder vibrations, which were converted to analog signals by an attached piezoelectric unit and stored as digitized data on a computer. At each stimulus onset, 65 consecutive 1 ms readings were obtained to determine the average amplitude of the acoustic startle response. SR-LAB equipment was calibrated regularly to ensure consistently accurate measurement.

Prepulse inhibition session

The test session was designed to assess variations in both the prepulse intensity and the interstimulus interval (ISI) on the basis of previously published protocols (Varty *et al.*, 2006; Young *et al.*, 2010b, 2011). Each session was initiated with a 5-min acclimation period during which the animals were habituated to the 65 dB(A) background noise. Startle pulses were presented for 40 ms, prepulse stimuli were presented for 20 ms, and the average intertrial interval between stimulus presentations was 15 s (range 7–23 s). Every other trial was a no stimulus (NOSTIM) trial, in which no acoustic stimulus was presented. The startle session was divided into five blocks. Blocks 1 and 5 each included five pulse-only trials, in which a 120 dB(A) pulse was presented alone. Block 2 assessed PPI and included four trial types (10 of each), including 120 dB(A) startle pulse intensities presented alone or preceded by 69, 73, or 81 dB(A) prepulse stimuli. Prepulses were administered 100 ms before the pulse stimulus. Block 3 assessed the startle response to different pulse intensities [80, 90, 100, 110, 120 dB(A)], but did not include any prepulse trials. In block 4, the ISI between prepulse and pulse was varied; mice were presented with 120 dB(A) pulses alone or preceded by a 73 dB(A) prepulse separated by a 25, 50, 100, 200, or 500-ms interval (four trials for each interval).

Experimental design

Baseline startle response and PPI were assessed in drug-naive 8–9-month-old male and female gp120tg and WT mice (n = 25–26/group). This age group was initially selected on the basis of prior work indicating the presence of behavioral deficits in 9–12-month-old gp120tg mice (D'Hooge *et al.*, 1999; Maung *et al.*, 2012). After the first test, animals were baseline-matched to receive either the chronic METH regimen or saline treatment, on the basis of PPI response during the 81 dB(A) trials. Five days after baseline testing, METH or vehicle administration was initiated in the four groups (male WT, male gp120tg, female WT, female gp120tg) with 12–13 mice under each treatment condition. Mice were weighed every 3–4 days during METH treatment to assess the effect of the chronic drug exposure on body weight. After 7 days of withdrawal from the chronic METH schedule, acoustic startle and PPI were quantified. This 7-day withdrawal period was selected on the basis of evidence of impaired cognitive performance in the Morris water maze at this time point in METH-treated gp120tg mice (Dr Eliezer Masliah, personal communication).

Dependent measures and statistical analyses

The amplitude of the startle response was quantified as the average startle magnitude during the 65-ms recording window. Habituation to the startle response was assessed as the percentage decrease in startle amplitude in pulse-alone 120-dB(A) trials from block 1 to blocks 2, 3, 4, and 5. The percentage of PPI for each type of prepulse intensity was calculated as [100 − (prepulse amplitude/pulse amplitude) × 100].

Statistical analyses were carried out using SPSS. Startle responding and PPI were assessed separately for blocks 2, 3, and 4 using mixed analysis of variance (ANOVA; drug × genotype × sex) with prepulse intensity (block 2), pulse intensity (block 3), and ISI (block 4) as within-subjects factors. Further assessments used analysis of covariance (ANCOVA) with startle reactivity as a covariate to determine whether group differences in PPI may have been impacted by alterations in startle responding. Post-hoc differences were assessed using Tukey's honestly significant difference with an α-level of 0.05.

Results

Baseline session

We observed a significant interaction between pulse intensity, sex, and genotype for acoustic startle responding [$F(4,96) = 2.6$, $P < 0.05$; Fig. 2a]. Male gp120tg mice tended to show increased startle relative to the other groups across all pulse intensities, with a significant sex by genotype interaction for the 100-dB pulse [$F(1,99) = 6.6$, $P < 0.05$]. Post-hoc tests indicated that male gp120tg animals exhibited increased startle relative to the other three conditions ($P < 0.05$) for the 100-dB stimulus. Male mice demonstrated a slight but significant increase in movement compared with female mice during the NOSTIM trials [$F(1,99) = 6.7$, $P < 0.05$], but there was no effect of genotype.

In block 2, PPI was significantly increased at higher prepulse intensities [$F(1,99) = 89.6$, $P < 0.001$] and there was a significant interaction between genotype and sex [$F(1,99) = 6.4$, $P < 0.05$]; however, there was no main effect of either factor or interaction with PPI intensity. Subsequent analyses carried out separately for each sex revealed that female gp120tg mice exhibited significantly reduced PPI compared with female WT mice [$F(1,50) = 5.4$, $P < 0.05$], but genotype differences in male mice did not reach significance [$F(1,49) = 2.1$, NS; Fig. 2b]. To determine whether PPI differences were affected by changes in startle reactivity, these ANOVAs were repeated with block 2 pulse-alone startle responding included as a covariate. PPI in female gp120tg mice remained significantly lower than that in female WT mice [$F(1,49) = 4.6$, $P < 0.05$], whereas genotype differences in male mice were not observed [$F(1,48) = 0.6$, NS].

In block 4, when PPI was assessed across varying ISIs, we also observed a significant sex by genotype interaction [$F(1,99) = 5.4$, $P < 0.05$], as well as an interaction between genotype and ISI level [$F(4,396) = 2.6$, $P < 0.05$; Fig. 2c]. In female mice, there was a trend toward reduced PPI in gp120tg mice relative to WT mice across all ISI levels [$F(1,50) = 3.0$, $P = 0.09$], in addition to a significant interaction between ISI and genotype [$F(1,47) = 3.0$, $P < 0.05$]; no significant differences were observed in male mice. When startle reactivity was included as a covariate, female gp120tg mice again exhibited a trend toward reduced PPI compared with female WT mice [$F(1,49) = 3.5$, $P = 0.07$], but the male groups still did not differ [$F(1,49) = 1.2$, NS]. Post-hoc tests indicated that female gp120tg mice exhibited lower PPI relative to female WT mice with an ISI of 500 ms ($P < 0.05$) and 25 ms ($P < 0.05$; Fig. 2c). We did observe a trend toward increased PPI in gp120tg mice compared with WT mice at the 50-ms ISI ($P = 0.08$), a result driven primarily by higher PPI in the male gp120tg animals; however, this was attenuated when startle reactivity was included as a covariate ($P = 0.15$).

We detected either a trend or a significant interaction between genotype and sex for the percent habituation to startle between the first block and blocks 3 [$F(3,99) = 3.9$, $P = 0.05$], 4 [$F(3,99) = 5.0$, $P < 0.05$], and 5 [$F(3,99) = 3.3$, $P = 0.07$]. This pattern was characterized by a reduction in habituation in female gp120tg mice compared with female WT mice (Fig. 4a), although group differences did not reach significance with the Tukey post-hoc test.

Seven-day methamphetamine withdrawal

The METH regimen was tolerated well by the animals, and all mice completed the drug treatment. We did not observe any significant main effect of drug or drug by genotype interaction on mouse body weight during METH treatment; however, gp120tg mice did exhibit lower weight overall compared with WT mice [$F(1,47) = 4.4$, $P < 0.05$].

No significant group or interaction effects were observed for the startle response after drug withdrawal (Fig. 3a). In the NOSTIM trials, there were trends toward decreased movement in METH-treated mice compared with vehicle-treated animals [$F(1,88) = 3.9$, $P = 0.052$], as well as greater movement in male mice relative to female mice [$F(1,88) = 3.9$, $P = 0.052$].

We observed no significant effect or interaction for sex or genotype with a repeated-measures ANOVA for PPI in block 2, but METH-treated mice exhibited significantly higher PPI relative to vehicle-treated mice [$F(1,88) = 6.2$, $P < 0.05$; Fig. 3b]. This effect remained significant even when block 2 responding to pulse-alone trials was included as a covariate [$F(1,88) = 6.5$, $P < 0.05$]. To further examine these findings, we assessed PPI separately for male and female mice at each prepulse intensity level. There were no significant main effects of genotype or genotype-drug interactions for either sex. METH treatment significantly increased PPI relative to vehicle treatment in male mice at the 69 dB [$F(1,43) = 5.6$, $P < 0.05$] and 81 dB [$F(1,43) = 4.2$, $P < 0.05$] prepulse levels, with a trend toward higher PPI at the 73 dB prepulse [$F(1,43) = 4.0$, $P = 0.05$]. METH-treated female mice also exhibited a trend toward higher PPI compared with vehicle-treated female mice, but drug treatment effects did not reach significance [69 dB: $F(1,43) = 2.7$, $P = 0.11$; 73 dB: $F(1,43) = 0.78$, NS; 81 dB: $F(1,43) = 1.25$, NS].

When the ISI was varied for PPI trials in block 4, we observed significant interactions between genotype and ISI level [$F(4,85) = 6.2$, $P < 0.001$] and between sex and ISI level [$F(4,85) = 3.4$, $P < 0.05$; Fig. 3c]. Similar to the findings in block 2, METH-treated mice exhibited a trend toward higher PPI compared with vehicle-treated mice with a 100-ms ISI [$F(1,88) = 3.1$, $P = 0.08$]; this effect reached significance when startle reactivity was included as a covariate [$F(1,87) = 6.1$, $P < 0.05$]. When the data were analyzed separately by sex, we observed that female METH-treated mice exhibited significantly higher PPI compared with female vehicle-treated mice with a 100-ms ISI [$F(1,44) = 4.5$, $P < 0.05$]. We also observed trends toward a genotype by drug interaction for male mice in the 50-ms ISI [$F(1,44) = 4.5$, $P < 0.05$] and 100-ms ISI [$F(1,44) = 4.5$, $P < 0.05$] trials, with a significant interaction for the 200-ms ISI [$F(1,44) = 4.5$, $P < 0.05$]. However, the genotype by drug trends and interaction in male mice were not maintained when startle reactivity was included as a covariate. Male mice tended to show higher PPI compared with female mice with a 500-ms ISI [$F(1,88) = 3.9$, $P = 0.05$], whereas male gp120tg mice showed greater PPI relative to male WT mice with a 50-ms ISI [$F(1,44) = 8.0$, $P < 0.01$], a result driven by higher PPI in the METH-treated animals.

Female mice showed reduced percent habituation to startle between block 1 and block 2 compared with male mice [$F(1,88) = 4.7$, $P = 0.05$] (Fig. 4b); no other effects or interactions as regards genotype, drug treatment, or sex were observed for habituation across the session.

Discussion

Neuropsychiatric disorders are frequently characterized by deficits in PPI, but relatively little is known about gating impairment in neuroviral disease, especially in the context of concurrent substance use. Our results indicated that female but not male gp120tg mice exhibited PPI deficits compared with WT mice before drug administration. This effect was not augmented in METH-treated mice after withdrawal, contrary to our hypothesis; in

contrast, after 7 days of drug withdrawal, PPI was higher in male and female METH-treated animals relative to vehicle-treated animals. When startle reactivity was included as a covariate, the effect of genotype on baseline PPI was maintained in female mice and the effect of METH treatment remained significant after withdrawal; however, there were no significant genotype by drug interactions for either sex. Interestingly, recent work shows that administration of this METH regimen induced greater exploratory behavior (hole investigations) in female mice after 1 week of withdrawal compared with vehicle-treated female mice, but no differences were observed in male animals (Henry *et al.*, 2013). In that study, METH-treated female gp120tg mice also showed the highest level of exploration relative to the other female groups, indicating a combined effect of drug treatment and HIV protein expression (Henry *et al.*, 2013). It is not clear why METH withdrawal appears to increase exploration but reverse PPI deficits in female gp120tg mice, but these phenomena may be mediated by altered dopaminergic and noradrenergic function (Yamashita *et al.*, 2006; Young *et al.*, 2010a). Although PPI has not been examined extensively in individuals with HIV, one recent study has reported that HIV+ participants as a group did not demonstrate PPI deficits compared with healthy individuals; however, HIV+ individuals with HAND exhibited impaired PPI relative to cognitively intact HIV+ individuals (Minassian *et al.*, 2013). This report, along with our current data, suggests that abnormalities in inhibitory function assessed by sensorimotor gating do not occur as a global phenomenon in HIV, but may emerge in association with higher-order cognitive deficits or biological variations affected by sex. It is worth noting that the human study included primarily male HIV+ participants (86%); hence, it is not yet clear whether the sex differences observed in gp120tg mice will translate to the human population. Greater PPI deficits in HIV+ individuals were also associated with worse performance in working memory, but were unrelated to other cognitive domains (Minassian *et al.*, 2013). Whereas the relationship between PPI and cognitive function is inconsistent (Young *et al.*, 2009), PPI is reported to be correlated with working memory in C57BL/6 mice (Singer *et al.*, 2013). Future studies could examine the relationship between PPI and other cognitive domains in gp120tg animals to determine whether there is an association similar to the link between PPI impairment and HAND in HIV+ individuals (Minassian *et al.*, 2013).

Our findings contribute to the limited literature describing PPI and acoustic startle in rodent models of HIV. Previous reports show that hippocampal injection of gp120 reduced PPI and increased startle responding in adult but not neonatal Sprague–Dawley rats (Fitting *et al.*, 2007); in addition, hippocampal injection of the HIV transactivator of transcription protein decreased percent PPI in 1–3-month-old male but not female Sprague–Dawley rats (Fitting *et al.*, 2006a, 2006b). Moran *et al.* (2012, 2013) reported sensorimotor gating alterations in HIV-1 transgenic female rats (maximal PPI at a shorter ISI interval) and HIV-1 transgenic male rats (lower PPI with acute METH exposure) compared with WTrats, but neither study tested both male and female rats; hence, potential sex differences in this model are not clear. Female subjects across several species (human, rat, and mouse) tend to exhibit lower PPI, especially during a certain period of the estrus cycle (Koch, 1998; Ison and Allen, 2007), although some reports indicate that sex differences in mice are rare (Willott *et al.*, 2003). Elevated levels of estrogen may impact mesoaccumbal DA, consequently affecting sensorimotor gating. METH treatment may also differentially affect rodents on the basis of sex, as female rodents are reported to show greater DA transporter density and metabolize the drug more slowly than male rodents (Bhatt and Dluzen, 2005; Milesi-Halle *et al.*, 2005). The mechanisms that account for the sex differences in our data are unclear, but might be elucidated by determining whether male and female gp120tg mice show marked differences in DA function.

The present study, to our knowledge, is the first report indicating that withdrawal from chronic METH treatment leads to an improvement in PPI. This finding differs from those of

numerous papers indicating that both acute and chronic amphetamine and METH treatment impair sensorimotor gating during and after drug exposure (Ralph *et al.*, 1999; Peleg-Raibstein *et al.*, 2006; Chao *et al.*, 2012). One key feature of the current method is the amount and intensity of METH administration. Previous papers reporting stimulant-induced impairment in PPI during drug withdrawal typically use subchronic protocols that involve 5–10 drug injections and/or drug exposure for 1 week (Murphy *et al.*, 2001; Tenn *et al.*, 2003; Arai *et al.*, 2008; Nakato *et al.*, 2010). In the current report, we utilized a procedure explicitly designed to mimic escalation/binge behaviors associated with METH dependence, administering a total of 86 injections of drug or vehicle over a 25-day regimen before assessing sensorimotor gating (Kuczenski *et al.*, 2007). Although this protocol differs from prior work, several reasons justify its use, including: (i) an improved representation of human METH exposure; (ii) inducing tolerance to the drug that reportedly minimizes the hyperthermic effect of higher METH doses and; (iii) evidence of neuropathology in the neocortex and limbic system, regions that modulate PPI (Segal and Kuczenski, 1997; Segal *et al.*, 2003; Kuczenski *et al.*, 2007). Preliminary replication studies with our current regimen indicate that METH exposure decreases PPI near the end of the chronic treatment (unpublished observations); pretreatment versus post-treatment alterations in PPI will be described in a subsequent report. A systematic comparison of effects of chronic METH administration on sensorimotor gating over various doses and time points will help elucidate the extent to which drug exposure could have differential effects on PPI function. The neurobiological mechanisms underlying the current findings with METH remain highly speculative, but could potentially involve alterations in neurotransmitter systems that modulate PPI, including DA, norepinephrine, and γ-aminobutyric acid (Segal *et al.*, 2005; Groman *et al.*, 2012).

There are several limitations to consider in this study. Expression of the gp120 protein, although inducing neurotoxic effects to the rodent brain that closely mirror the neuropathology of HIV, is not a perfect representation of the disease. One difference is that the animals express the HIV-1 envelope protein in astrocytes, which are not a site of productive viral infection in the human brain. These transgenic mice also express the protein constitutively since birth, which may induce neurotransmitter alterations that do not accurately reflect biological processes that occur with adult HIV infection. The chronic METH regimen was selected to mimic a gradual dose of METH progression and is reported to minimize hyperthermic responses to the higher METH doses (Segal *et al.*, 2003; Kuczenski *et al.*, 2007); however, we did not quantify temperature changes in this mouse cohort and cannot exclude hyperthermia as a contributing factor. We assessed PPI after a week of withdrawal on the basis of earlier reports of METH effects on inhibitory functioning (Dalley *et al.*, 2007) and pilot data indicating gp120tg cognitive impairment at this interval (Dr Eliezer Masliah, personal communication). However, the behavioral effects of the drug may vary over different time points, as suggested by both rodent and human studies on chronic METH use (Cattie *et al.*, 2012). Subsequent studies will quantify PPI both during and after this METH regimen and assess sensorimotor gating in other HIV models, such as expression of the transactivator of transcription protein.

Conclusion

Sensorimotor gating was impaired in female mice expressing the HIV gp120 protein, whereas acoustic startle was increased in male gp120tg mice. Contrary to expectations, chronic METH administration did not reduce PPI after a week of drug withdrawal, but instead increased gating. These findings highlight clinical work indicating that the cognitive effects of METH in HIV+ individuals may largely depend upon variable factors such as the length of abstinence, total quantity of use, age, and sex (Iudicello *et al.*, 2010). Future cross-species assessment of sensorimotor gating in HIV+ patients and preclinical disease models

will clarify relevant HIV-related neuropathology and interactions with comorbid substance use.

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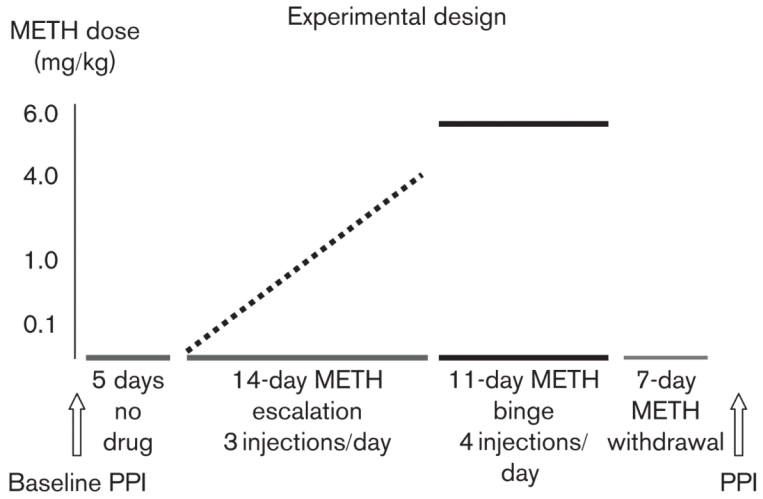

Fig. 1.

Schematic representation of the experimental timeline. Mice were tested for baseline prepulse inhibition (PPI) before the commencement of a chronic 25-day methamphetamine (METH) regimen, including an escalation period of 14 days, during which the dose was increased from 0.1 to 4.0 mg/kg (freebase), and an 11-day 'binge' interval of 6 mg/kg injections. PPI was measured again after 7 days of withdrawal from METH.

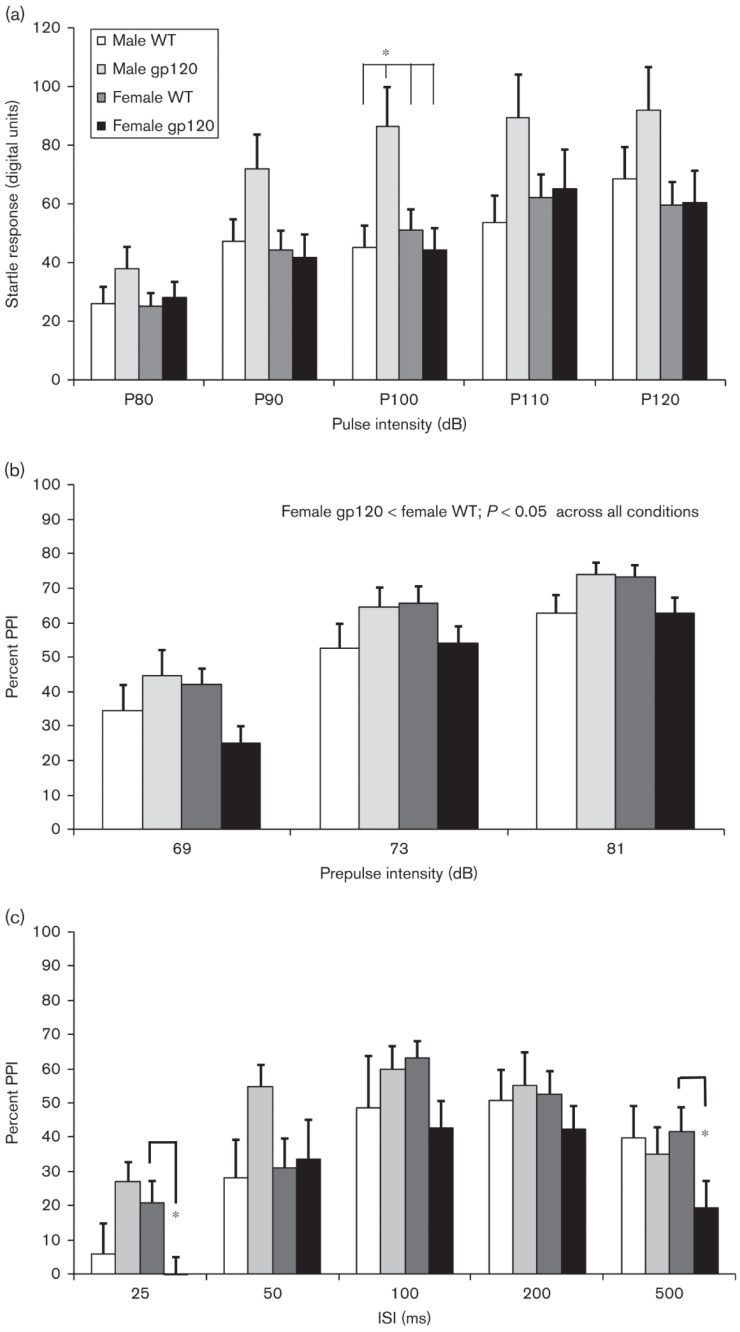

Fig. 2.

Baseline acoustic startle and prepulse inhibition (PPI) were assessed in 9-month-old wild-type (WT) and gp120 transgenic mice (gp120) before administration of the drug regimen (*n* = 25–26 per group). (a) Male gp120 transgenic mice exhibited increased startle response relative to other groups during P100 dB pulse-only trials. Genotype did not significantly affect PPI in male mice, but female gp120 transgenic mice showed a significant main effect of reduced sensorimotor gating compared with WT mice across (b) prepulse intensities in block 2 and (c) interstimulus intervals (ISI) in block 4, including 25 and 500 ms. Data are shown as means ± SEM. **P* < 0.05.

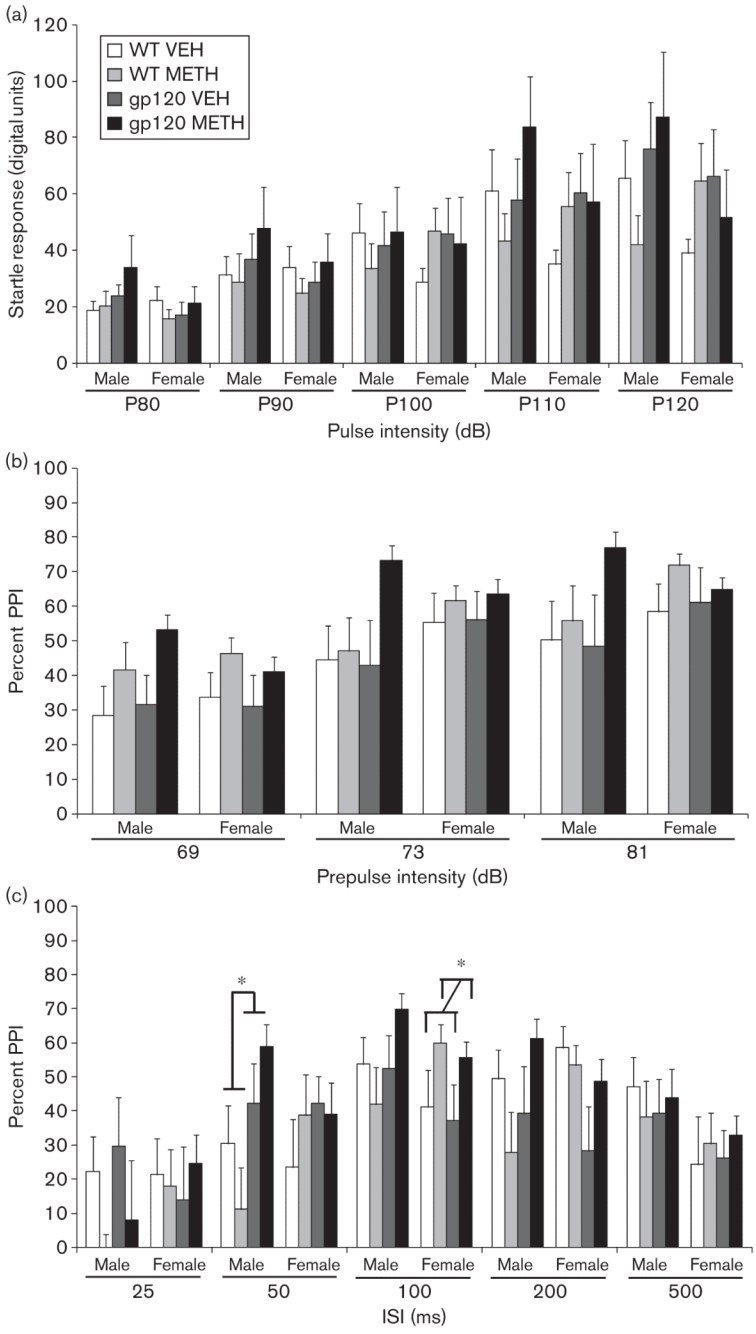

Fig. 3.

Acoustic startle and prepulse inhibition (PPI) in the eight treatment groups after 7 days of methamphetamine (METH) withdrawal (n = 10–13/group). There were no significant group effects on (a) startle response or any effect of genotype on PPI in block 2; however, METH treatment increased overall PPI relative to vehicle (VEH). (b) Male gp120 transgenic mice exhibited greater PPI compared with male wild-type (WT) mice only under the 50-ms interstimulus interval (ISI) condition in block 4, whereas female METH-treated mice exhibited higher PPI relative to vehicle-treated female mice at (c) 100-ms ISI; no genotype differences were observed in female mice. Overall, METH-treated mice exhibited greater

PPI compared with vehicle-treated mice in (b) block 2 and under the (c) 100-ms ISI condition in block 4. *$P < 0.05$.

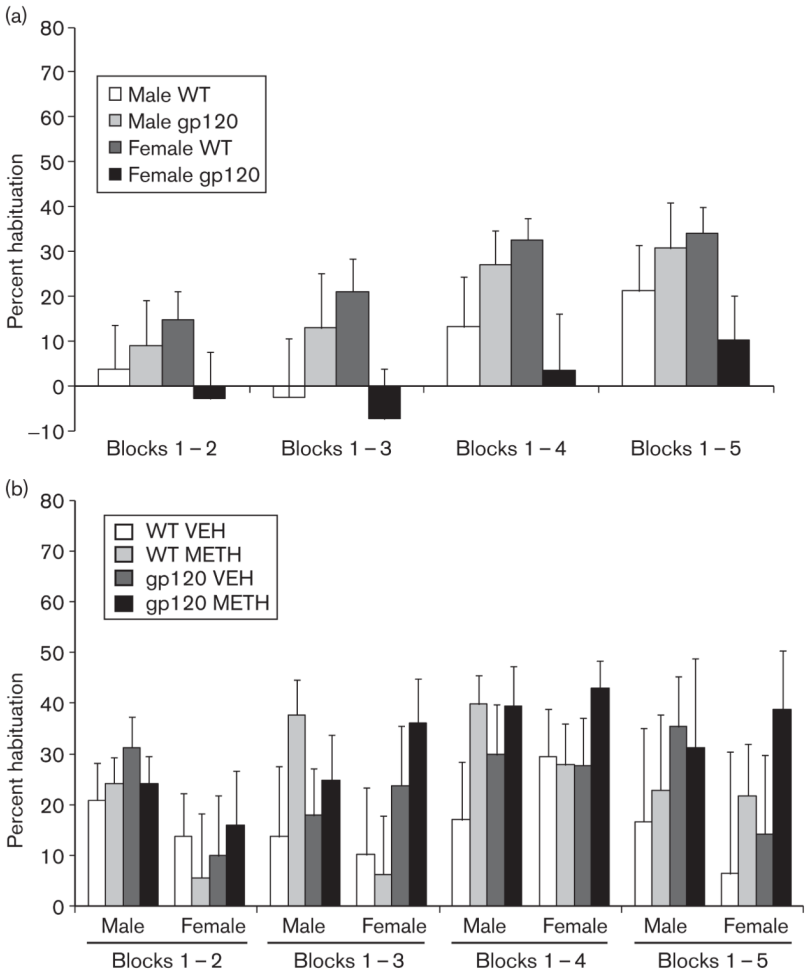

Fig. 4.

Percent habituation to the pulse-only startle response, from block 1 to blocks 2 through 5, (a) during baseline testing (n = 25–26/group) and (b) after 7 days of METH withdrawal (n = 10–13 per group). A significant genotype by sex interaction was noted for block 1–4 habituation at (a) baseline ($P < 0.05$), although individual group differences did not reach significance with the Tukey post-hoc test. gp120, gp120 transgenic mice; METH, methamphetamine; VEH, vehicle; WT, wild type.