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ORIGINAL ARTICLE

Methamphetamine-Induced Behavioral and Physiological Effects in Adolescent and Adult HIV-1 Transgenic Rats

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Abstract We recently reported that six consecutive days of treatment with a moderate dose of methamphetamine (METH) induced greater behavioral sensitization in adult HIV-1 transgenic (HIV-1 Tg) rats than in adult Fischer 344/NHsd (F344) non-transgenic, wild-type control animals. In the present study, we evaluated the effects of a moderate dose of METH on the brains of adolescent versus adult HIV-1 Tg male rats using both behavioral (METH-induced, stereotypic head movement) and physiological (rectal body temperature) parameters. We found that both the acute and behavior-sensitizing effects of METH were greater in HIV-1 Tg rats compared with controls and also in adolescent rats compared with adult animals, regardless of HIV-1 status. We determined that acute hyperthermic effects of METH as well as tolerance to METH-induced hyperthermia were greater in HIV-1 Tg rats than in controls. Taken together, these results suggest that both the neuroadaptations seen in HIV infection and the immaturity of the adolescent brain are associated with increased sensitivity to the psychoactive and behavior-sensitizing properties of METH. Thus, HIV-infected individuals and adolescents may be more vulnerable to the development of METH abuse and dependence than non-infected individuals and adults.

Keywords methamphetamine · HIV-1 · adolescent brain · hyperthermia

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Introduction

Methamphetamine (METH) is a potent sympathomimetic amine with a high potential for long-term abuse. Repeated use of METH can result in a variety of neurocognitive deficits that are attributed, in part, to neurotoxicity in the dopaminergic neurotransmitter system (Kalechstein et al. 2008), metabolite changes in the basal ganglia (Sekine et al. 2002), and neuroadaptations in cortico-striatal-limbic circuitry (Li and Sinha 2008). Current models of repetitive drug use and subsequent drug dependence implicate the incentive-sensitization of the limbic system and the inefficient inhibitory regulation of drug use by the prefrontal cortex (Feil et al. 2010). The adolescent substance user may be especially vulnerable to developing substance abuse because of an immature prefrontal cortex. According to a recent survey reported by the Substance Abuse and Mental Health Services Administration (2009), approximately 850,000 Americans 12 years of age or older used METH at least once in 2008, and, of this population, roughly 95,000 were first-time users. Conse-

quently, substance abuse appears to be a major risk factor for an acquired "developmental disorder" (Anderson and Teicher 2009).

Another vulnerable population with increased risk to the effects of METH is the HIV-infected population. Substance abuse is a common co-morbidity in those infected with HIV-1 (Chang et al. 2005; Kopinsky et al. 2007). Changes in brain structures and behavior that are associated with either METH abuse or HIV infection may be potentiated or show interactive effects when both conditions are present (Chang et al. 2005; Jernigan et al. 2005). Neuropathological changes associated with HIV infection are exacerbated by drug use, can stimulate immune activation in HIV-infected individuals (Carrico et al. 2008), and produce sensitization in the immune system (Assis et al. 2009). Pre-clinical and clinical observations have shown that HIV-associated brain alterations may occur in the dopaminergic neurotransmitter system, such as a decrease in dopamine transporter (DAT) activity (Wang et al. 2004; Ferris et al. 2008). The interactive effects of HIV-associated neuroalterations and METH-induced hyperthermia may cause an even greater reduction in DATs. It is possible that decreased presynaptic DATs in HIV patients may, in turn, lead to up-regulation of post-synaptic dopaminergic receptors and increased sensitivity to the stimulating and reinforcing properties of METH. Neuropsychological deficits involving dopamine-mediated frontal lobe function, such as impaired executive and psychomotor function, have also been identified in HIV-infected individuals (Chang et al. 2005; Ferris et al. 2008). Therefore, like the adolescent, the prevalence of METH use in the HIV population may be partially mediated by impaired inhibitory control (Li and Sinha 2008).

Our laboratory has investigated the non-infectious HIV-1 transgenic (HIV-1 Tg) rat, (Reid et al. 2001) as an animal model of HIV-1 infected individuals on stable highly active anti-retroviral therapy [HAART] (Peng et al. 2010). The HIV-1 Tg rat exhibits cognitive impairments which parallel those seen in HIV patients with HIV-associated neurocognitive disorders (Antinori et al. 2007; Vigorito et al. 2007; LaShomb et al. 2009). Recently, we also demonstrated that behavioral sensitization (BS) of METH-induced, stereotypic head movement is enhanced in the HIV-1 Tg rat (Liu et al. 2009). The augmented psychomotor responses that emerge with repeated, intermittent drug administration are enduring, and thus, BS has become a frequently used animal model of drug addiction (Robinson and Berridge 2001). METH-induced increases in brain metabolism, as indicated by hyperthermia, are correlated with its behavior-activating properties (Brown et al. 2007). Thus, METH-induced hyperthermia is altered by previous exposure to METH as well as maladaptive immune responses (Sanchez-Alavez et al. 2004). This relationship may be more complex in the HIV-1 Tg rat because of metabolic changes that are associated with the persistent presence of the viral proteins (Pruznak et al. 2008; Peng et al. 2010). Because temperature dysregulation may be caused by the presence of the viral proteins, the effects of METH-induced hyperthermia could be exacerbated in the HIV-1 Tg rat.

In the present study, we investigated the effects of repeated METH exposure in adolescent and adult male HIV-1 Tg rats and male F344 wild-type (WT) controls. Male rats were used to avoid the possible confounding sex-related effects on our outcome measures. Specifically, we evaluated BS and METH-induced hyperthermia to test the hypothesis that incentive-sensitization, as measured by METH-induced, stereotypic head movement, is potentiated in the HIV-1 Tg rat and at a younger age, and that it can be dissociated from METH-induced hyperthermia.

Materials and methods

Animals

Sixteen male F344 WT rats and 16 male HIV-1 Tg rats were obtained from Harlan (Indianapolis, IN, USA). The animals came from two litters: one litter was 4 weeks of age at the onset of the study (adolescent groups; F344, n=8; HIV-1 Tg, n=8), and the other was 12 weeks of age at the onset of the study (adult groups; F344, n=8; HIV-1 Tg, n=8). Prior to the onset of any experimental procedure, the rats were allowed to acclimate to the vivarium for 1 week. The animals were housed in a temperature-controlled environment (22±5°C) that was maintained on a 12:12-h light–dark cycle (7:00 AM–7:00 PM), and food (Harlan Teklad™ Mouse/Rat Laboratory Diet 7102) and water were provided ad libitum. All experimental procedures were conducted during the light cycle and in accordance with the Seton Hall University Institutional Animal Care and Use Committee.

Home cages were removed from the vivarium and brought into the experimentation room for all procedures. Thus, injection administration was paired with the home cage, and all post-injection observations and temperature measurements were recorded while the animals were in their home cages. The home cages were returned to the colony room after completion of all daily procedures, and the animals were left undisturbed until the next day of experimentation.

Saline pretreatment

Environmental novelty or stressors can elicit altered behavior or physiology in rodents. Handling and habituation

procedures can reduce or eliminate environmental modulation of behavior and, importantly, without affecting the development of stimulant-induced BS (Crombag et al. 2001). For instance, the rectal probe thermometry-induced hyperthermia can be eliminated with only 60-min of habituation (Dallmann et al. 2006). Our preliminary studies also demonstrated that a 2-day adaptation period was sufficient in reducing stress-induced hyperthermia. Subsequent pilot studies further demonstrated that subjects habituated to an i.p. injection procedure and an experimental context after just 1 day of saline pretreatment, as indicated by a significant reduction in rearing and head movements within a 60-min post-injection time period. Therefore, the animals used in the present study were given a 2-day adaptation period to eliminate the effects of these procedures on head movement behavior and core body temperature. Prior to the METH treatment, all animals were administered saline (2 mL/kg, i.p.) once per day on two consecutive days. Subsequently, rectal body temperatures were measured using a flexible probe with a sensor tip attached to a traceable digital thermometer (Fisher Scientific, Morris Plains, NJ, USA).

Methamphetamine treatment, behavioral observations, and rectal probe thermometry

Rats were assigned to one of two treatment groups—METH group or saline group. METH ([+]methamphetamine hydrochloride, Catalog no. M-8750, Sigma-Aldrich Co., St. Louis, MO, USA) was dissolved in sterile 0.9% saline (1.25 mg/mL) and prepared fresh for daily use. Once daily on six consecutive days, i.p. injections of either METH (1.25 mg/mL) or saline were administered at a volume of 2 mL/kg. This dose was selected based on our preliminary dose–response studies that demonstrated optimal elicitation of stereotypic head movement behavior.

A post-injection time sampling procedure was utilized to quantify rodent head movements via live observations and to measure core body temperature via rectal probe thermometry. Head movements were scored as previously described (Liu et al. 2009) during three 2-min observation intervals that took place at 45, 90, and 135 min post-injection on all six treatment days. In short, one trained experimenter counted the frequency of all head movements that were characterized as complete or partial up–down movement, circular movement (clockwise or counterclockwise), diagonal movement, or any combination of the three during each 2-min post-injection interval. The total number of head movements that were observed from each rat during the 45, 90, and 135 min post-injection intervals were summed together to generate a daily score for head movement activity. Although it would be of interest to separate the sub-types of repetitive activities and evaluate the qualitative characteristics of METH-induced stereotypies in HIV-1 Tg adolescent and adult rats, only a quantitative analysis of METH-induced, stereotypic head movement was incorporated into this particular observation procedure. As such, the experimenter did not differentiate between the repetitive activities, and head movement scores represented the combined number of all head movement sub-types noted above. Rectal body temperature was measured at 60 min post-injection on all six treatment days.

Statistical analysis

All data are represented as the mean±SEM. SPSS 16 (SPSS 11.1.0, Inc., Chicago, IL, USA) was used for data management and analysis. P values ≤ 0.05 were considered statistically significant.

Several data points from the behavioral measure were missing completely at random (MCAR). Listwise deletion was used to treat the missing data because it is a conservative technique that leads to unbiased parameter estimates when data are MCAR. Specifically, four cases were omitted from all statistical analyses that were conducted on rodent head movement. After performing a complete case analysis, the behavioral data were analyzed with a four-factor, mixed ANOVA with strain (F344; HIV-1 Tg), age (adolescent; adult), and drug (saline; METH) as between-subjects factors and day (days 1, 2, 3, 4, 5, and 6) as a within-subjects factor. Additional ANOVAs were used post hoc to evaluate predicted interactions and any other observed interactions of interest.

HIV-1 Tg rats had significantly ($p<0.05$) lower baseline body temperatures than F344 WT controls, regardless of age (data not reported here). It was, therefore expected that HIV-1 Tg rats would have lower core body temperatures than F344 WT controls during six treatment days, regardless of treatment (i.e., saline or METH) by age (i.e., adolescent or adult) groups. Thus, an analysis with standardized scores was conducted to evaluate change in temperature (compared with baseline) across 6 days of treatment. Baseline temperature measurements from all eight groups on day 1 of saline pretreatment were considered as the groups of reference for temperature measurements taken at 60 min post-injection on six consecutive treatment days. Standardized scores ($z$scores) were calculated by subtracting the mean of the baseline control group from the individual score of each rat and dividing by the standard deviation (of the corresponding baseline control group). Standardized scores provide a distribution identical to the distribution of raw scores and allow for comparisons between groups from different strains. Negative and positive $z$scores indicate a decrease and increase, respectively, in body temperature between treatment days and baseline. These $z$scores were analyzed by means of a four-

factor, mixed ANOVA with strain, age, and drug as between-subjects factors and day as a within-subjects factor. The overall four-way, mixed ANOVA was followed with post hoc tests to assess predicted interactions.

Results

Behavioral data

Figure 1 illustrates the behavioral data (i.e., number of head movements) for all eight groups on six consecutive days of treatment. The overall four-way ANOVA (see Fig. 1) yielded several significant main effects and interactions. A robust psychomotor response was elicited in all METH-treated rats, as indicated by a significantly greater number of head movements than that observed in saline-treated rats [$F_{(1,\ 20)}$=1886.290, p<0.001, η_p^2=0.990]. Post hoc analyses were conducted on a significant day × drug interaction [$F_{(5,\ 100)}$=59.548, p<0.001, η_p^2=0.749] and demonstrated that BS of METH-induced, stereotypic head movement developed over six treatment days, whereas the number of head movements observed in saline-treated rats remained relatively constant.

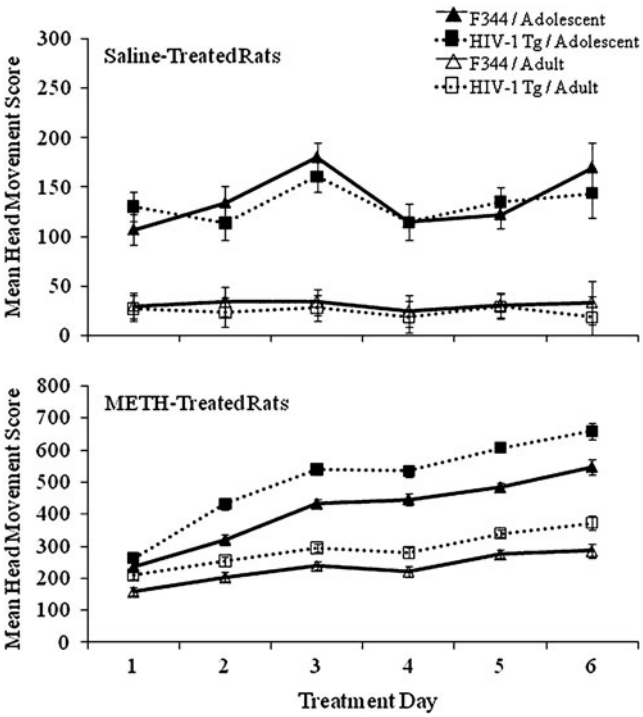

Fig. 1 Mean (±SEM) daily head movement score for drug (saline or METH) by strain (F344 or HIV-1 Tg) by age (adolescent or adult) groups on six consecutive treatment days. (*Top*) Daily head movement activity for all saline-treated rats. (*Bottom*) Daily head movement activity for all METH-treated rats. *Closed markers* denote head movement scores for adolescent rats, and *open markers* denote means for adult rats. *Solid lines with triangular-shaped markers* illustrate means for F344 WT controls, and *dashed lines with square-shaped markers* indicate means for HIV-1 Tg rats

Strain comparisons: effects of the HIV-1 transgene on head movement

There was a significant strain × drug interaction [$F_{(1,\ 20)}$= 42.898, p<0.001, η_p^2=0.682] (Fig. 2). On average, all HIV-1 Tg rats exhibited a significantly enhanced acute response to METH administration compared with all F344 rats, whereas the behavioral response observed after saline administration did not differ between HIV-1 Tg rats and F344 WT controls.

Age comparisons

A significant age × drug × day interaction [$F_{(5,\ 100)}$=9.633, p<0.001, η_p^2=0.325] was identified (Fig. 3). Overall, the adolescent rats displayed more head movement behavior (p<0.001) than the adult rats regardless of strain or drug treatment. Moreover, this age difference increased over days under METH treatment, but not under saline treatment.

Temperature data

Figure 4 depicts the mean $z$score temperature values for all saline- and METH-treated rats as a function of strain, age, and treatment day. The average $z$score for all METH-treated rats was significantly higher than for all saline-treated rats [$F_{(1,\ 24)}$ 120.730, p<0.001, η_p^2=0.834], demonstrating that METH treatment caused hyperthermia.

A significant strain × age × drug interaction was found in the analysis conducted with the standardized temperature scores [F(1, 24)=10.925, p<0.01, η_p^2=0.313] (Fig. 5). Saline-treated HIV-1 Tg adolescent rats exhibited a decrease in body temperature compared with baseline, and the standardized temperature scores for this group were significantly lower than all other saline-treated groups. No differences in standardized temperature scores were observed between any other saline-treated groups. METH-induced hyperthermia was observed in all of the METH-treated rats, as indicated by positive standardized temperature scores, i.e., an increase in temperature compared with baseline. Post hoc comparisons showed that (1) in comparison with all other METH treatment groups, METH-induced hyperthermia was significantly enhanced in adolescent HIV-1 Tg rats; (2) compared with adult F344 rats, METH-induced hyperthermia was augmented in adult HIV-1 Tg rats; and (3) METH-induced hyperthermia in adolescent F344 rats did not differ from that of adult rats regardless of strain. The significant four-

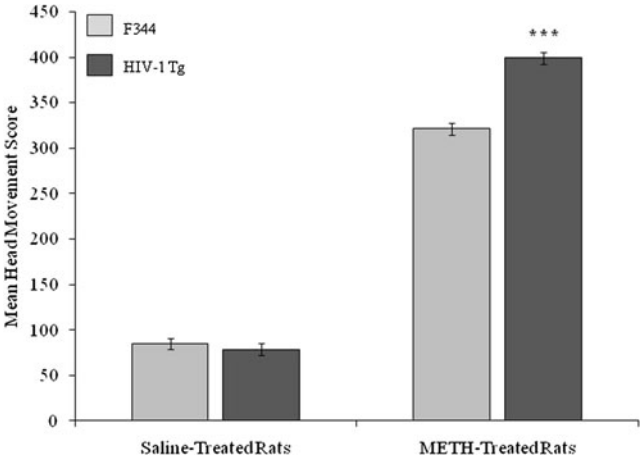

Fig. 2 Overall head movement behavior for drug (saline or METH) by strain (F344 or HIV-1 Tg) groups. ***$p<0.001$ compared with METH-treated F344 WT controls

way interaction [$F(5, 120)=3.119$, $p<0.05$, $\eta_p^2=0.115$; see Fig. 4] demonstrated that METH-induced hyperthermia decreased from day 1 to 2 in all METH-treated rats. The attenuation of METH-induced hyperthermia continued between days 2 through 5 in adolescent HIV-1 Tg rats, whereas no additional decrement in METH-induced hyperthermia was observed in any other group. Standardized temperature scores for all saline-treated F344 rats (i.e., adolescent and adult) remained relatively constant across six treatment days, whereas the standardized temperature scores for saline-treated HIV-1 Tg adolescents and adults, respectively, gradually decreased between days 1 through 6 and dropped between days 3 and 6.

Discussion

Consistent with our hypotheses, we demonstrated that METH-induced, stereotypic head movement is enhanced in HIV-1 Tg rats and in adolescent rats compared with controls. A clear dissociation between METH-induced BS and tolerance to METH-induced hyperthermia was also identified. Furthermore, both acute METH-induced hyperthermia and the attenuation of METH-induced hyperthermia were augmented in HIV-1 Tg rats

Animal models of addiction can be evaluated within an incentive-sensitization framework whereby neural systems that regulate incentive salience (wanting) become sensitized with repeated drug exposure, and the sensitized drug wanting is misattributed to the associated environmental stimuli (Robinson and Berridge 1993, 2004, 2008). Notably, wanting and liking are mediated by separate neural pathways (Berridge and Kringelbach 2008), and sensitization of drug wanting can occur while tolerance develops to the hedonic drug properties. Dissociation between BS of METH-induced stereotypies (a behavioral manifestation of incentive-sensitization) and desensitization to METH-induced hyperthermia were identified in the present study and may reflect distinct processes related to drug wanting and liking.

In a previous study (Liu et al. 2009), we demonstrated that six consecutive days of treatment with a moderate dose of METH elicited greater BS of METH-induced, stereotypic head movement in adult HIV-1 Tg rats than in F344 rats. In the present study, we extended those findings and demonstrated that, in comparison with F344 control rats, HIV-1 Tg rats also have a more robust acute response to a moderate dose of METH. This study further demonstrated that, compared with adult rats, the acute and behavioral-sensitizing effects of a moderate dose of METH are enhanced in adolescent rats. These findings were evident by the age × drug × day interaction which indicated that the effects of METH and age are not addictive. The HIV-1 Tg adolescent rats exhibited the largest number of head movements out of all four METH groups, followed, in order, by F344 adolescent rats, HIV-1 Tg adult rats, and F344 adult rats. Although there was no strain × age × drug interaction, the difference in head movements between strains (with HIV-1 Tg rats exhibiting a significantly greater number of METH-induced head movements than F344 rats) was enhanced in the adolescent rats. It is possible that the interactive effects of METH, HIV-1, and adolescence observed in the present study would reach statistical significance with larger sample sizes.

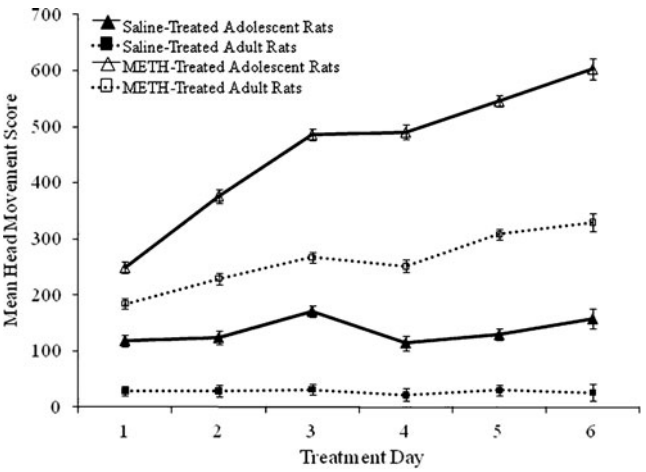

Fig. 3 Group means (±SEM) for daily head movement activity for drug (saline or METH) by age (adolescent or adult) groups on six consecutive days of treatment. *Closed markers* denote daily head movement scores for saline-treated rats and *open markers* denote means for METH-treated rats. *Solid lines with triangular-shaped markers* illustrate means for adolescent rats, and *dashed lines with square-shaped markers* indicate means for adult rats

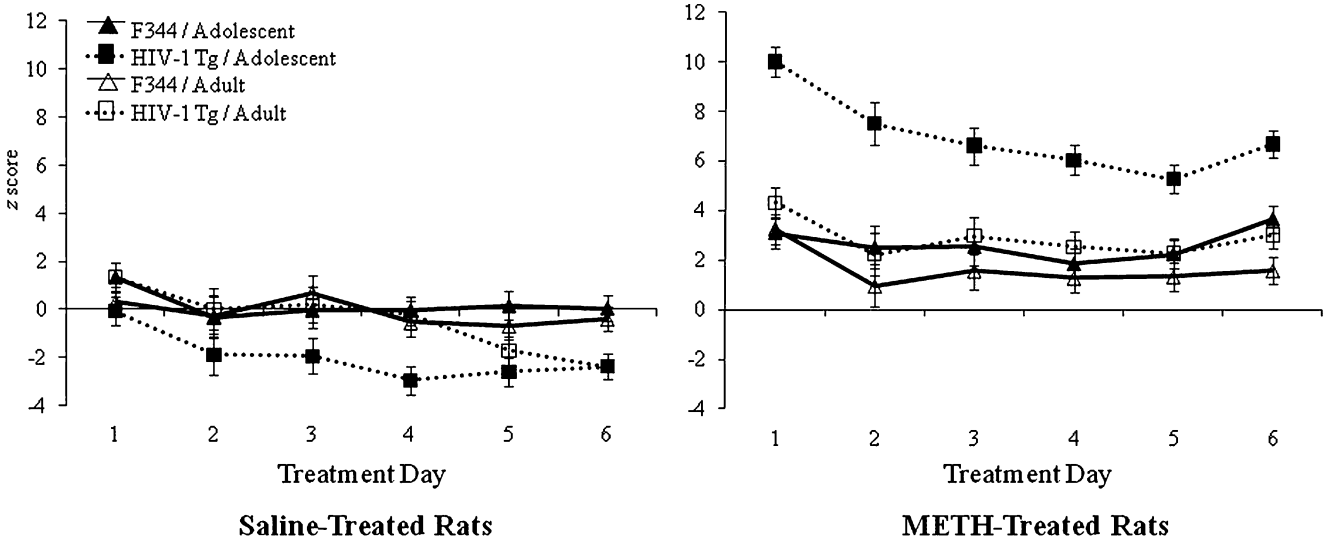

Fig. 4 The *z*score values corresponding to rectal temperature as a function of strain (F344 or HIV-1 Tg), age (adolescent or adult), and treatment day (day 1, 2, 3, 4, 5, or 6) for saline-treated rats (*left panel*) and METH-treated rats (*right panel*). *Negative z scores* indicate rectal temperatures below baseline (0); *positive z scores* indicate rectal temperatures above baseline (0). *Closed markers* denote standardized temperature scores for adolescent rats, and *open markers* denote standardized temperature scores for adult rats. *Solid lines with triangular-shaped markers* illustrate standardized temperature data for F344 WT controls, and *dashed lines with square-shaped markers* indicate mean standardized scores for HIV-1 Tg rats

The METH-induced stereotypies that were observed and were enhanced in both HIV-1 Tg and adolescent rats parallel the purposeless, stereotypic behaviors that "punders" may exhibit. Punding, a "stereotyped behavior characterized by an intense fascination with a complex, excessive, non-goal-oriented, repetitive activity" (Fasano et al. 2008), is observed in psychostimulant addicts and may be mediated by frontal–striatal circuits (Huevel et al. 2009), the same pathways that have been implicated in incentive-sensitization. Thus, these findings suggest that incentive-sensitization, indicated by BS of METH-induced, stereotypic head movement, is enhanced by both brain injury associated with exposure to neurotoxic viral proteins (in the HIV-1 Tg rats) and the immaturity of the adolescent brain. These findings also imply that drug wanting can increase at a faster rate in HIV-infected individuals and adolescents than in non-infected individuals and adults, respectively. Drug wanting leads to pathological drug-seeking and drug-taking behaviors, and both HIV-infected individuals and adolescents may be more susceptible to this impulsive–compulsive pathology.

Rectal body temperatures were measured in the present experiment, and METH-induced hyperthermia was evident. While METH-induced hyperthermia can lead to neurotox-

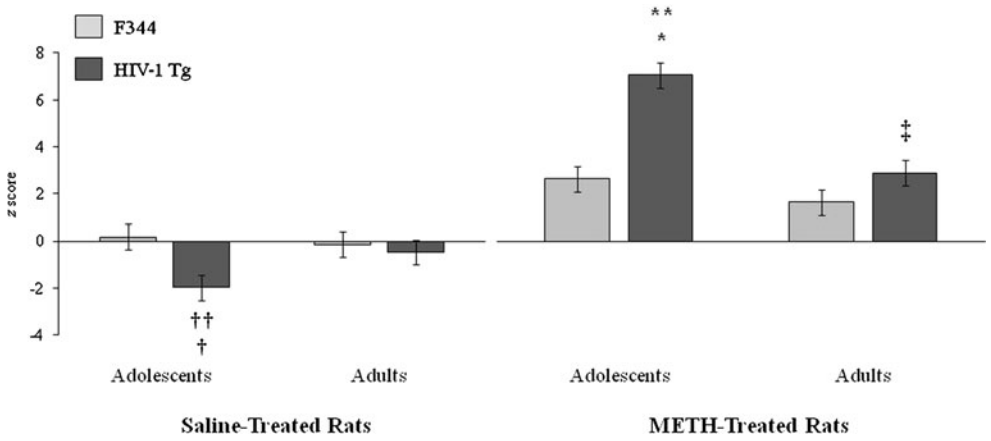

Fig. 5 The *z*score values corresponding to rectal temperature as a function of age (adolescent or adult) and strain (F344 or HIV-1 Tg) for saline-treated rats (*left panel*) and METH-treated rats (*right panel*). Baseline (0); †$p<0.05$ compared with adult F344 rats; ††$p<0.01$ compared with both F344 adolescent and HIV-1 Tg adult rats; *$p<0.05$ compared with both F344 adolescent and HIV-1 Tg adult rats; **$p<0.01$compared with adult F344 rats; ‡$p<0.05$ compared with adult F344 rats

icity and sometimes fatality (Callaway and Clark 1994), the hyperthermic effects of METH can be dissociated from the behavior-sensitizing effects (Itzhak et al. 1998). Furthermore, METH-induced BS can occur without concurrent neurotoxicity (Belcher et al. 2006). Additionally, tolerance can develop to the neurotoxic effects of METH in rats that are sensitized (Abekawa et al. 1997), and tolerance to METH-induced neurotoxicity may be partially mediated by attenuation of METH-induced hyperthermia (Baucum et al. 2004; Riddle et al. 2002). In our study, HIV-1 Tg and F344 rats developed tolerance to the hyperthermic effects of METH simultaneous with the development of METH-induced BS. Furthermore, tolerance to the hyperthermic effects of METH was enhanced in the adolescent HIV-1 Tg rats. This was evident by the four-way interaction which demonstrated that METH-induced hyperthermia decreases over days but at an extended rate in adolescent HIV-1 Tg rats. When differences in baseline temperature between strains were taken into account and standardized temperature scores were calculated, it was also determined that acute METH-induced hyperthermia was enhanced in the HIV-1 Tg rat. In summary, these findings indicate that, in comparison with F344 controls, HIV-1 Tg rats exhibited a more robust acute response to the hyperthermic effects of METH, enhanced desensitization to the hyperthermic effects of a moderate dose of METH over six consecutive days of treatment, and that the effect of strain on METH-induced physiological responses was potentiated in the adolescents.

It is possible that the hyperthermic effects that were observed in the present study are mediated by neural systems that support the hedonic value of METH. METH-induced BS can emerge simultaneously with desensitization to the rewarding properties of the drug (Itzhak et al. 2002), and, in fact, this is a major tenet of the incentive-sensitization approach. Taken together, it appears that the HIV-1 Tg rat is more sensitive to two long-lasting outcomes that are associated with METH use: (1) the stimulating and behavioral-sensitizing effects of a moderate dose of METH and (2) the acute hyperthermic and hyperthermic-desensitizing effects of a moderate dose of METH. These findings suggest that neural alterations associated with the virus mediate both enhanced incentive-salience and hedonic desensitization. These alterations would be consistent with the psychopathology of METH abuse, i.e., increased drug-wanting in the presence of decreased drug-liking, and imply the propensity for an accelerated transition between METH use to abuse and dependence in HIV-infected individuals and adolescents. Zakharova et al. (2009) demonstrated that a METH-induced conditioned place preference (CPP) developed earlier in adolescent rats than in adult rats, and, therefore, adolescents may be more sensitive to the rewarding effects of psychostimulants early on. It is possible that HIV-associated brain alterations also increase sensitivity to psychostimulant reward during initial use. Future studies that evaluate the hedonic properties of METH, e.g., a CPP or self-administration paradigm, need to be utilized to confirm these hypotheses.

Taken together, the results from the present study suggest that HIV-infected individuals and adolescents, and possibly even more so, HIV-infected adolescents, have a predisposition towards addiction-related psychopathology. Given that recent neuro-developmental studies show continued structural and functional brain development in young adults through the third decade (Paus et al. 2008), many younger HIV-infected individuals may be more vulnerable to becoming drug dependent when they experiment with illicit drugs such as METH. Implementing HIV awareness and prevention programs, as well as METH prevention and intervention programs during adolescence, a time period associated with increased sensitivity to drugs with abuse potential, may effectively reduce the incidence of HIV infection and METH addiction.

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