



CROSS SENSITIZATION BETWEEN THE BEHAVIOR SENSITIZING AND ANXIETY-LIKE EFFECTS OF METHAMPHETAMINE IS ENHANCED IN THE HIV-1 TRANSGENIC RAT

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INTRODUCTION

Methamphetamine (METH) abuse and the Human Immunodeficiency Virus (HIV) are highly comorbid illnesses, and over the past decade this comorbidity has come to be known as a double epidemic (Chang, et al., 2005). METH can aggravate and promote the neuropathological deformations caused by HIV, resulting in severe cognitive and motor deficits and affective disturbances. Among the HIV population, those who use METH have poorer prognosis and develop HIV-related pathology sooner than non-users (Cloak, et al., 2004). The study of METH use and HIV in an animal model may advance the development of adequate treatments for the HIV-infected, METH-using population.

The recently created noninfectious HIV type 1 (HIV-1) transgenic (Tg) rat (Reid, et al., 2001) displays many of the immune irregularities and clinical abnormalities seen in HIV patients. Further, it has been demonstrated that the HIV-1 Tg rat exhibits cognitive deficits similar to those seen in HIV patients (LaShomb, et al., 2008; Vigorito, et al., 2007), and has a greater sensitivity to the analgesic effects of morphine (Chang & Vigorito, 2006). Thus, the HIV-1 Tg rat may be a useful animal model for evaluating the effects of METH in the presence of continuous HIV infection on brain function and behavior. To elucidate the interactions between METH and HIV-1 on behavioral sensitization (BS), drug context effects, and stressful events, the present study implemented the HIV-1 Tg rat in BS and contextual fear conditioning paradigms.

METHOD

Animals

Twenty-three experimentally naïve, male Fischer 344 (F344) rats and 23 experimentally naïve, male HIV-1 Tg rats were used as subjects. Animals ranged between eight and twelve weeks of age throughout testing.

Drugs and Solutions

METH [(+)-methamphetamine hydrochloride, Sigma Aldrich Co., St. Louis, MO] was dissolved in sterile 0.9% saline immediately prior to injections, and administered via 27-gauge/1cc/syringes. Throughout the drug treatment phase METH was administered at dose of 0.0 mg/kg (saline) or 2.5 mg/kg, i.p. Respectively, during the BS challenge test and test for conditioned responding to the drug-paired context animals received 0.5 mg/kg METH and saline.

Procedures

Two procedures were executed simultaneously to evaluate 1) sensitization and drug context effects associated with METH treatment and 2) the effects of METH on the context pre-exposure facilitation effect (CPFE). The time course for all experimental procedures and testing phases took place over a 12-day time period.

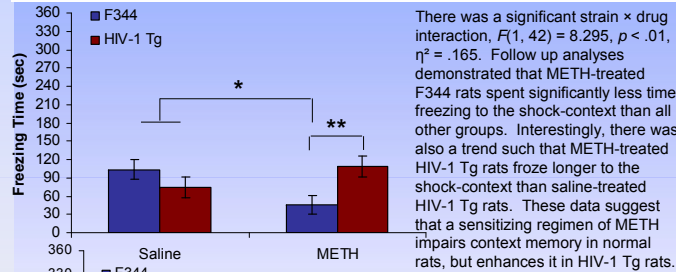
	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5	Phase 6	Phase 7	Phase 8
	Context pre-exposure	Habituation	Drug treatment	Immediate shock exposure	Test for freezing	BS challenge test	Test for conditioned responding	Tissue Collection
Day	1	2	3-7	8	9	10-11	10-11	12

Note. Twelve day procedure was replicated six times. Phases 6 and 7 were systematically varied both between and within replications to ensure that all rats had the same amount of METH exposure prior to the BS challenge test and the test for conditioned responding to the drug-paired context.

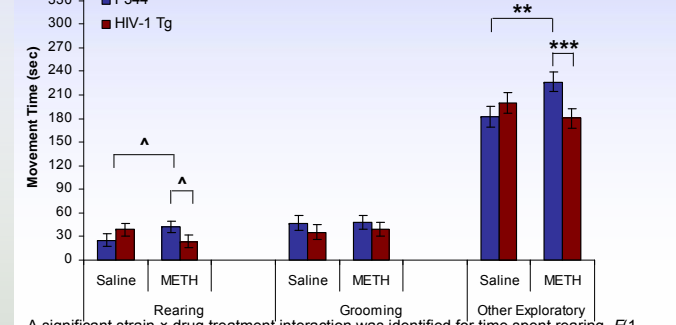
CPFE PROCEDURE SUMMARY

DAY	1	3	4	5	6	7	8	9
	CONTEXT PRE-EXPOSURE	DAILY METH OR SALINE TREATMENT			IMMEDIATE SHOCK EXPOSURE		TEST FOR FREEZING TO THE SHOCK-CONTEXT	

RESULTS: CPFE

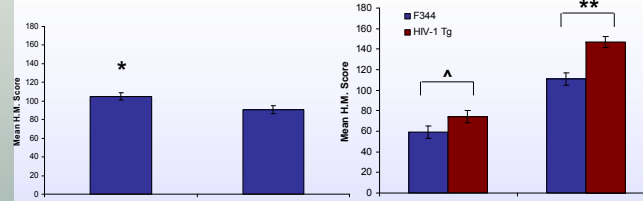


There was a significant strain × drug interaction, $F(1, 42) = 8.295, p < .01, \eta^2 = .165$. Follow up analyses demonstrated that METH-treated F344 rats spent significantly less time freezing to the shock-context than all other groups. Interestingly, there was also a trend such that METH-treated HIV-1 Tg rats froze longer to the shock-context than saline-treated HIV-1 Tg rats. These data suggest that a sensitizing regimen of METH impairs context memory in normal rats, but enhances it in HIV-1 Tg rats.



A significant strain × drug treatment interaction was identified for time spent rearing, $F(1, 42) = 4.174, p < .05, \eta^2 = .09$, and engaging in other exploratory movement, $F(1, 42) = 6.26, p < .05, \eta^2 = .13$, while in the shock-context.

RESULTS: BS CHALLENGE TEST



There was a significant effect of context, $F(1, 37) = 6.088, p < .05, \eta^2 = 1.41$, such that rats that received a low challenge dose in Context B exhibited, on average, significantly greater METH-induced head movement than that of rats that received a low challenge dose in Context D.

Follow up analyses on a strain × drug pretreatment interaction revealed that saline-pretreated HIV-1 Tg rats had a more robust acute response to a low challenge dose than saline-pretreated F344 rats. Additionally, METH-treated HIV-1 Tg rats exhibited augmented BS.

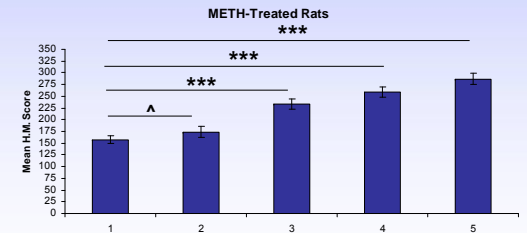
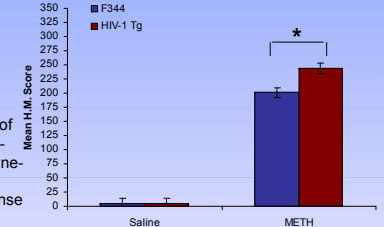
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RESULTS: DRUG TREATMENT (5 DAYS)

The main effect of drug, $F(1, 38) = 556.932, p < .001, \eta^2 = .936$, demonstrated the psychoactivating effects of METH.

A significant strain × drug interaction was assessed further, and an effect of strain was found between the METH-treated rats ($p < .05$), but not the saline-treated rats, such that HIV-1 Tg rats exhibited a more robust acute response to METH.



There was a significant main effect of day, $F(4, 160) = 61.395, p < .001, \eta^2 = .754$, such that the number of METH-induced stereotypic head movements significantly increased each day. These data demonstrate that BS developed across five days of treatment with a moderate dose of METH. No strain × day interaction was identified for METH-treated rats.

Note. ^ indicates $p < .06$; * indicates $p < .05$; ** indicates $p < .01$; *** indicates $p < .001$

DISCUSSION

The HIV-1 Tg rat appears to have a greater sensitivity to the stimulating and behavior sensitizing effects of METH than normal F344 controls. This is evident in that HIV-1 Tg rats exhibited a more robust acute response to moderate (2.5 mg/kg) and low (0.5 mg/kg) doses of METH. BS developed in HIV-1 Tg and F344 rats over five days, and was later confirmed with a low challenge dose. Although both METH-pretreated groups displayed BS, HIV-1 Tg rats exhibited augmented BS of METH-induced head movements compared to F344 controls. Additionally, during the BS challenge test, all rats that were given a low dose of METH in Context B exhibited more stereotypic head movement than rats given the low dose in Context D. This demonstrates environmental modulation of METH-induced responding, and the lack of a context × strain interaction indicates that the differences observed in the HIV-1 Tg rat can be attributed to neuroalterations associated with the virus, and not interactions between environmental modulation of METH-induced responses and the virus. A sensitizing regimen of METH impaired the CPFE in F344 rats. However, a sensitizing regimen of METH enhanced the CPFE in HIV-1 Tg rats.

Taken together, these data indicate that cross sensitization between METH-induced BS and METH-induced emotional sensitivity to stress may be augmented in the HIV-1 Tg rat. Hypersensitivity to the stimulating, behavior sensitizing, and anxiety-like effects of METH in the HIV-1 Tg rat may be mediated by neuroalterations associated with the presence of viral proteins. The findings of this study suggest that the prevalence of METH use and addiction in the HIV population may be mediated by greater sensitivity to the stimulating and anxiety-like effects of the drug. Specifically, HIV-1 may potentiate incentive-sensitization, increasing drug wanting at a faster rate in HIV-infected METH users than in non-infected users. Moreover, HIV-1 may enhance vulnerability to stress-induced relapse. Further studies implementing the HIV-1 Tg rat will be necessary to elucidate the complex drug-environment interactions that were identified in the present study.

Acknowledgments

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