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 neurodegenerative and functional impairments caused by HIV, resulting in severe cognitive and motor deficits and effective disturbances. Among the HIV population, those who use METH have poorer prognosis and develop HIV-related pathology sooner than non-users (Ciofalo, 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 rats exhibit cognitive deficits similar to those seen in HIV patients (LaShomb, et al., 2008; Vigorito, et al., 2007), and has a greater sensitivity to the anesthetic effects of morphine (Chang & Vigorito, 2006). Thus, the HIV-1 Tg rats 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 naive, male Fischer 344 (F344) rats and 23 experimentally naive, male HIV-1 Tg rats were used as subjects. Animals ranged between eight and twelve weeks of age throughout testing.

Drugs and Solutions

METH ([i]-methamphetamine hydrochloride, Sigma Aldrich Co., St. Louis, MO) was dissolved in sterile 0.9% saline immediately prior to injection, and administered via 27gauge/1cc/syringe. 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 Morris contextual 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 pretreatment 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.

RESULTS: CPFE

There was a significant strain x drug interaction, F(1, 42) = 8.295, p < .01, n² = .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 in HIV-1 Tg rats.

RESULTS: DRUG TREATMENT (5 DAYS)

The main effect of drug, F(1, 38) = 556.932, p < .001, n² = .936, demonstrated psychoactivating effects of METH. A significant strain x 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.

REFERENCES

•Reitz, M., & Bryant, J.  An HIV-1 transgenic rat that develops HIV-related pathology and immunologic dysfunction.

DISTRIBUTION

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 stereotype 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 x 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.

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