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Intrahippocampal injections of Tat: Effects on prepulse inhibition of the auditory startle response in adult male rats

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Abstract

The presence of human immunodeficiency virus (HIV-1) in the brain mediates the pathogenesis of HIV-associated dementia complex (HAD), partially through the viral toxins gp120 and Tat. This study characterized potential deficits in sensorimotor gating, as measured by prepulse inhibition (PPI), following hippocampal administration of Tat. Adult, male Sprague–Dawley rats were bilaterally injected with 50 μg Tat or saline (1 μl volume), into the hippocampus. Following 7 weeks of recovery, all animals were tested using the auditory startle response (ASR) with habituation, control, and PPI trials. Assessment of ASR habituation [100dB(A) white noise stimulus, 70dB(A) background, 5-min acclimation period, 36 habituation trials with fixed interstimulus interval (ISI) of 10 s] demonstrated a significant ~50% reduction in the overall peak ASR amplitude, but no change in peak ASR latency, nor an effect on the rate of habituation. PPI measures demonstrated robust alterations in sensorimotor gating. The PPI test (ISI of 0, 8, 40, 80, 120, or 4000 ms, 6-trial blocks, Latin-square) showed an attenuated response on peak ASR amplitude during the control trials (0 and 4000 ms ISI), but not on the PPI trials (8–120 ms ISI). Most striking was the rightward shift in ISI for maximal inhibition of the response ($\chi^2(1)=4.7$, $p \leq 0.03$). There was no significant peak ASR latency effect during the control trials (<1 ms) of the PPI test, although there was the suggestion of a slowing of the response (4 ms, ~15%) across PPI trials. Collectively, the present data suggest that intrahippocampal injections of Tat have adverse effects on cognitive processing, as indexed by sensorimotor gating.

Keywords: HIV-1 associated dementia complex; Tat; Intrahippocampal; Prepulse inhibition

1. Introduction

The total number of people living with the human immunodeficiency virus (HIV) in 2005 is estimated to be ~40.3 million, with ~4.9 million new HIV-infections (UNAIDS, 2005). Data suggest that up to two-thirds of HIV/AIDS patients eventually develop significant symptomatology related to the HIV-associated dementia complex (HAD) before the terminal phase of their disease (Price and Brew, 1988). HAD is referred to as a subcortial dementia and is characterized by cognitive, motor and behavioral dysfunction (Brew et al., 1988; Kelly et al., 1996; Price et al., 1988). The development of HAD is believed to be caused by exposure of the central nervous system (CNS) to the HIV-1 retrovirus at an early phase in systemic infection (Annunziata, 2003; Belman et al., 1988; Belman, 1997; Brew et al., 1988). Neuropathology findings in animal and human research give evidence for a primary and persistent HIV-1 associated infection of the brain (Belman et al., 1988; Brew et al., 1988; Fauci, 1988; Price et al., 1988). Release of viral products into the brain by infected microglial and monocyte/macrophage cells, is considered to be one of the crucial factors in the pathogenesis of HIV-1 associated neurological manifestations (Annunziata, 2003; Bansal et al., 2000; Behnisch et al., 2004; Brew et al., 1988; Bruce-Keller et al., 2003; Catani et al., 2003; Fauci, 1988; Nath et al., 2000a; Price et al., 1988).

Among the viral products that are released by HIV-1 infected cells are the envelope glycoprotein gp120 and the nonstructural protein Tat (Bansal et al., 2000; Behnisch et al., 2004; Brenneman et al., 1988; Catani et al., 2003; Cheng et al., 1998; Fauci, 1988; Nath et al., 2000a,b). Neurotoxicity induced by gp120 has been reported to be mediated primarily by *N*-methyl-D-aspartate (NMDA) receptor mechanisms (Holden et

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al., 1999). In contrast, Tat appears to promote HIV-1 neurotoxicity by interacting directly with neurons and causing oxidative stress (Aksenov et al., 2003, 2006; Aksenova et al., 2006, 2005). The hippocampus is believed to be particularly susceptible to neuronal injury. Several neuropathological studies have demonstrated loss of a subset of neurons in hippocampal tissue from HIV-infected individuals (Masliah et al., 1992) and in monkeys infected with simian immunodeficiency virus (Luthert et al., 1995). Findings further suggest that Tat causes neuronal damage, synaptic alterations, and glial activations in the hippocampal region, including the CA1, CA3/4, and dentate gyrus (Behnisch et al., 2004; Bruce-Keller et al., 2003; Cheng et al., 1998; Maragos et al., 2003; Nath et al., 2000b).

Cognitive impairments that are linked with HAD include poor attentional abilities, deficits in memory, and reduced alertness (Brew et al., 1988; McArthur and Grant, 1996; Nath et al., 2000a; Price et al., 1988). Primarily, reduced attention and slowness of information processing are reported to be most prevalent in patients with HAD (Kelly et al., 1996; McArthur and Grant, 1996). Sensory processing, an early component in the attention process, is often measured through use of the auditory startle response (ASR) (Hoffman and Ison, 1980). The ASR is a constellation of reflexes elicited by a sudden, relatively intense stimulus. It offers many advantages as a behavioral measure of CNS activity and can be assessed in numerous species, including humans, rats, mice, rabbits, and pigeons (Hoffman and Ison, 1980; Swerdlow et al., 2000a). The ASR is mediated by a neural circuit consisting of 3–4 synapses that demonstrate several forms of plasticity, such as sensitization, habituation, and prepulse inhibition (PPI) (Hoffman and Ison, 1980; Price et al., 1988). PPI is induced by presenting a prepulse that is a relatively weak sensory stimulus, prior to the startle stimulus. The mechanism underlying this inhibited response is the process of sensorimotor gating, i.e., filtering incoming sensory stimuli and protecting the mechanism from extraneous stimuli (Hoffman and Ison, 1980; Swerdlow et al., 2001a). It is suggested that PPI reflects the operation of a preattentive mechanism that serves to reduce disruptive effects of an intense stimulus on the processing of a prior weak stimulus (Graham, 1979). According to previous research, PPI is modulated by a complex neuronal circuit including the limbic system and frontal cortex, basal ganglia, and pons (Fendt et al., 2001; Swerdlow et al., 2000a). In preclinical research it is well established that the hippocampus is involved in the neural control of central inhibitory mechanisms (Caine et al., 1991, 1992, 2001; Swerdlow et al., 2001b). The similarity of PPI functions obtained from a variety of species (i.e. humans, rats, mice, rabbits, and pigeons) makes animal models in studying deficits in sensorimotor gating very compelling and an important measure in the investigation of the neural basis of different clinical conditions (Hoffman and Ison, 1980; Swerdlow et al., 2000a).

An alteration of PPI reflects a disturbance of the ability to gate subsequent sensory information (Swerdlow et al., 2001b). Research demonstrates that PPI is reduced in specific neuropsychiatric disorders and experimental manipulations of the hippocampus in animals characterizing deficient inhibition in sensory and cognitive domains (Swerdlow et al., 2000b). The purpose of this study was to examine Tat effects in adult male rats on attentional processes, as indexed by sensorimotor gating, following intracerebral hippocampal Tat injections.

In the present study PPI was assessed by peak ASR amplitude and peak ASR latency across a range of ISIs (8–120 ms). Further, the determination of ISI functions rather than percent PPI was employed as a theoretically more sensitive method to study Tat-induced alterations in PPI (Hoffman and Ison, 1980; Parisi and Ison, 1979) and may further elucidate the mechanisms underlying pre-attentional processes, as indexed by sensorimotor gating.

2. Methods

2.1. Animals

Sixteen male Sprague–Dawley rats (~120 days of age) obtained from Harlan Sprague Dawley, Inc. (Indianapolis, IN), were pair housed throughout the experiment. Rodent food (Pro-Lab Rat, Mouse Hamster Chow #3000, NIH diet #31) and water were available *ad libitum*. The animals were maintained according to the National Institute of Health (NIH) guidelines in AAALAC-accredited facilities. The animal facility was maintained at 21°±2 °C, 50%±10% relative humidity and had a 12-h light: 12-h dark cycle with lights on at 0700 h (EST). Rats were handled prior to any procedures to minimize stress during behavioral testing. The Institutional Animal Care and Use Committee (IACUC) of the University of South Carolina approved the animal protocol for this research.

2.2. Experimental design

Rats were randomly assigned to one of two treatment groups that received bilateral hippocampal injections of 1 μl volume saline ($n=8$) or 50 μg Tat ($n=8$). Dosage parameters were based upon previous reports (Aksenov et al., 2003; Bansal et al., 2000). One animal died during surgery. Following 3 weeks recovery from surgery animals were tested in an ASR test for habituation, and a PPI test that included control and PPI trials. Since no Tat effects were found in the initial PPI test, animals were tested one month later. Habituation data were collected at 140 days of age and the PPI test was administered at 170 days of age.

2.3. Surgery

Animals were anesthetized with a mixture of ketamine (100 mg/kg/ml) and xylazine (3.3 mg/kg/ml) and placed in the KOPF stereotaxic instrument. Injections were placed into the dentate hilus region of the hippocampus. A midline sagittal incision was made in the scalp. Three holes at each side of the hippocampus were drilled on the skull to inject into dorsal, mid and ventral hippocampus using the following set of coordinates: −3.5 mm AP, 1.4 mm ML, −3.8 mm DV; −5.9 mm AP, 3.3 mm ML, −3.8 mm DV; and −6.2 mm AP, 4.6 mm ML, −7.7 mm DV. The neuroanatomy of the rat hippocampus requires three separate injection sites to completely affect the entire structure. Each injection was 50 μg Tat in 1 μl saline. The 1 μl injection volume was released over 1 min after a 1-min resting period that

allowed the tissue to return to its original conformation. The needle was withdrawn over 2 min to prevent reflux. Tat had no significant effect on body weight or growth.

2.4. Histology

Following completion of behavioral testing, animals were sacrificed (pentobarbital overdose) and brain tissue collected. Cryostat-cut sections (20 μm) through the hippocampal injection sites were collected and Nissl-stained to confirm injections and assess pathology.

2.5. Apparatus

The startle platform (SR-Lab Startle Reflex System, San Diego Instruments, Inc.) was enclosed in a 10 cm thick double-walled, 81×81×116-cm isolation cabinet (external dimensions) (Industrial Acoustic Company, INC., Bronx, NY). Each animal was tested individually in the dark with a high-frequency loudspeaker, that produced a background white noise (70dB(A)) and was mounted inside the chamber 31 cm above the Plexiglas cylinder. The startle chamber consisted of a Plexiglas cylinder 8.75 cm in internal diameter resting on a 12.5×20-cm Plexiglas stand. The animal's response to the stimulus produced deflection of the Plexiglas cylinder, which was converted into analog signals by a piezoelectric accelerometer. Response sensitivities were calibrated using a SR-LAB Startle Calibration System. Sound levels were measured and calibrated with a sound level meter (Extech Instruments: Waltham, MA) with the microphone placed inside the Plexiglas cylinder. The signals were then digitized (12 bit A to D) and saved to a hard disk. Use of the A-weighting scale followed the recommendation of Current Protocols in Neuroscience (Geyer and Swerdlow, 2004).

2.6. Testing procedures

2.6.1. ASR habituation test

In order to obtain an adequate level of habituation adult rats were exposed to a 36-trial session. Rats were placed in the startle chamber and exposed to 5 min of 70dB(A) background noise followed by 36 pulse trials of a 100dB(A) white noise stimulus with a 20 ms duration, according to a fixed 10 s ISI. The primary measure of the reflex response is the 'peak'. The peak is reported in terms of its maximum amplitude and its latency to the maximum response (peak). Thus, the dependent measures included peak ASR amplitude, and peak ASR latency.

2.6.2. PPI test

One month following ASR habituation assessment all adult rats were tested for approximately 20 min. Animals were first exposed to a 5-min acclimation period of 70dB(A) background of white noise, followed by 36 trials with 0, 8, 40, 80, 120, and 4000 ms ISI, assigned by Latin-square design. The 0 and 4000 ms ISI trials were control trials in order to provide baseline ASR within the PPI test. The stimulus intensity was 100dB(A) with a pulse duration of 20 ms and the prepulse stimulus intensity was 85dB(A) with a pulse duration of 20 ms duration. The ISI interval that we report represents the time from the offset of the prepulse stimulus to the onset of the startle stimulus. For PPI the dependent measures analyzed were peak ASR amplitude, peak ASR latency, and percent PPI. Percent PPI is typically expressed as percent of inhibition in startle amplitude (Geyer and Swerdlow, 2004), most commonly used in applied settings at a prepulse of 100 ms ISI, relative to pulse only trials (0 ms ISI) (Caine et al., 2001; Davis et al., 1990; Martinez et al., 2000; Swerdlow et al., 2000b, 2001b).

An estimate of PPI for ISI 100 ms was calculated using the average response at the ISIs of 80 and 120 ms. Percent PPI was computed according to the following formula: % PPI=[(0 ms ISI trials−100 ms ISI trials)/0 ms ISI trials]*100.

2.7. Statistical analysis

All data were analyzed using analysis of variance (ANOVA) techniques (SPSS, 2005; SYSTAT, 2004; Winer, 1971). A one-way ANOVA, with treatment as a between-subjects factor was conducted for the ASR control trials, and percent PPI (at 100 ms ISI). A two-way mixed ANOVA, with treatment as a between-subjects factor, and trial as a repeated measure, was conducted on ASR habituation trials and all PPI trials across ISIs (8–120 ms). Violations of sphericity in repeated measures factor of the mixed-model ANOVA were precluded with orthogonal decomposition of the overall term or addressed with the Greenhouse–Geisser df

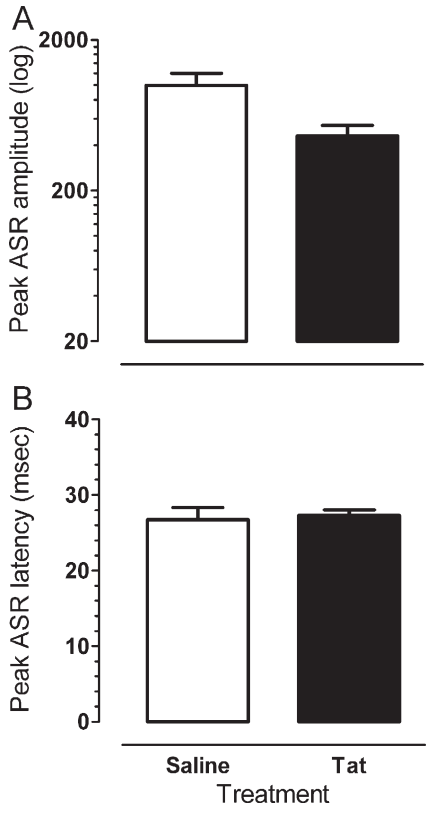

Fig. 1. (A) Mean (±SEM) peak ASR habituation amplitude was significantly reduced in Tat-treated males relative to saline rats. (B) Mean (±SEM) peak ASR latencies on ASR habituation trials in saline and Tat-treated rats. Data are collapsed across all 36 ASR habituation trials. There was no trial by treatment interaction, suggesting similar rates of habituation.

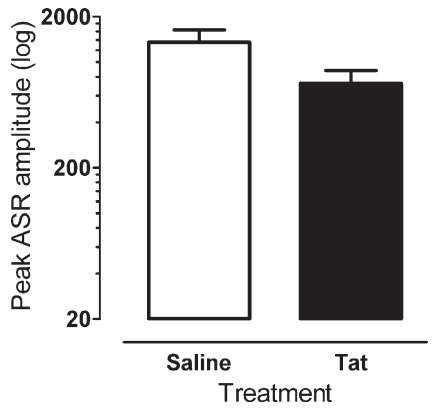

Fig. 2. Mean (±SEM) peak ASR amplitude on control trials (0 and 4000 ms ISI combined) revealed a significant treatment effect.

correction factor (Winer, 1971). In the present study, sphericity was violated in the mixed-model ANOVA for peak ASR amplitude. Separate orthogonal trend analyses of PPI trials were employed for each treatment to determine the shape of the ISI function (e.g., linear, quadratic trends). In addition, for peak response the ISI in which the peak occurred was recorded across all PPI trials (8–120 ms ISIs) and placed into two categories. Category one included ISIs 08 and 40 ms and category two included ISIs 80 and 120 ms. Because the ISI data is categorical in nature, the Pearson Chi-square, uncorrected for continuity was applied. An alpha level of $p \leq 0.05$ was considered significant for all statistical tests.

3. Results

3.1. ASR habituation test

One Tat-injected animal was excluded from the habituation assessment; due to procedural errors it did not show any sensitivity to the 36 habituation trials. A mixed-model ANOVA on peak ASR amplitude revealed a significant trial effect, $F(35, 385) = 5.1$, $p_{GG} < 0.001$ [$F(1, 11) = 22.0$, $p \leq 0.001$, linear; $F(1, 11) = 16.4$, $p \leq 0.01$, quadratic], and a significant treatment effect, $F(1, 11) = 5.5$, $p \leq 0.04$, but no trial × treatment interaction [$F(35, 385) < 1.0$]. Thus, Tat produced a significant ~50% attenuation of the overall peak ASR amplitude, but did not affect the rate of habituation. A mixed-model ANOVA on peak ASR latency revealed a significant trial effect, $F(35, 385) = 2.1$, $p \leq 0.001$ [$F(1, 11) = 5.4$, $p \leq 0.04$, cubic], no treatment effect [$F(1, 11) < 1.0$], and no trial × treatment interaction [$F(35, 385) < 1.0$], suggesting similar latencies across habituation trials for saline and Tat-treated rats. Fig. 1A illustrates the treatment effect with a significant ~50% reduction of the peak ASR amplitude. Fig. 1B illustrates the similar habituation ASR latencies for saline and Tat-treated animals collapsed across all 36 trials.

3.2. PPI test

Control trials (0, 4000 ms ISI combined). A one-way ANOVA on peak ASR amplitude revealed a significant treatment effect [$F(1, 12) = 9.6$, $p \leq 0.01$, confirming the findings in the

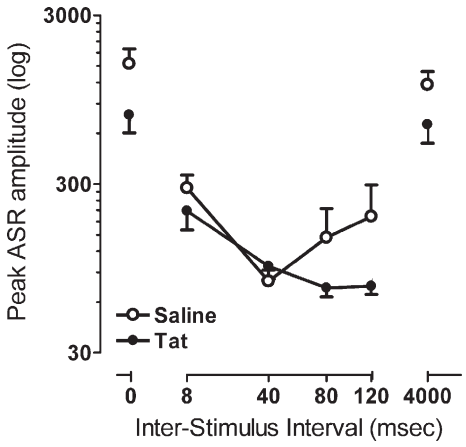

Fig. 3. Mean (±SEM) peak ASR amplitude across ISIs (0–4000 ms). Although an ANOVA on PPI trials across ISIs revealed no overall significant treatment effect, a significant ISI × treatment interaction was observed. Most notable is the significant rightward shift in ISI for maximal inhibition of the response for Tat-treated animals.

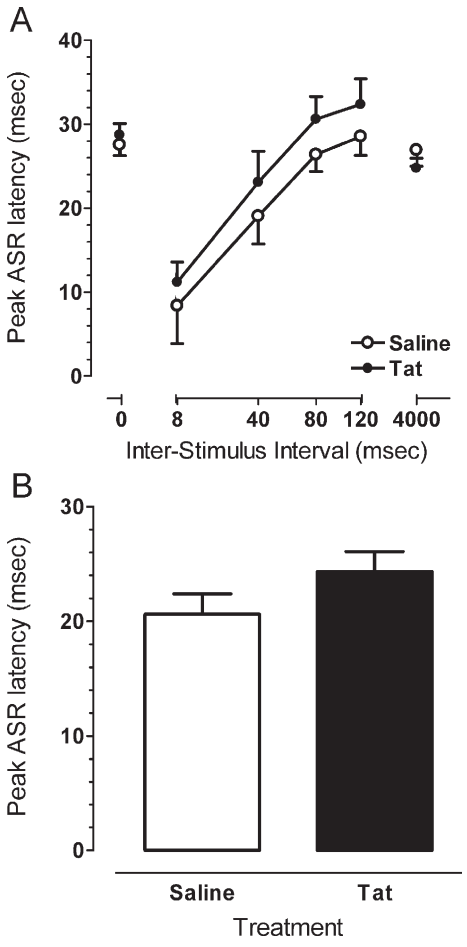

Fig. 4. (A) Mean (±SEM) peak ASR latency across ISIs (0–4000 ms). An ANOVA on PPI trials across ISIs revealed no significant effects. (B) Mean (±SEM) peak ASR latency for saline-and Tat-treated rats on PPI trials collapsed across ISIs (08–120 ms), suggested a slowing in response (4 ms, ~15%) by Tat, although not statistically significant.

habituation trials with a reduction of the baseline ASR by Tat. Specifically, peak ASR amplitude revealed an ~45% reduction of amplitude response in Tat-treated animals compared to saline-treated rats, as illustrated in Fig. 2. For peak ASR latency no significant treatment effect was noted [$F(1, 12) < 1.0$].

Percent PPI. A one-way ANOVA conducted on percent PPI of startle amplitude for ISI 100 ms revealed no treatment effect [$F(1, 12) < 1.0$].

PPI trials (8–120 ms ISI). A mixed-model ANOVA conducted on peak ASR amplitude revealed a significant ISI effect with a prominent quadratic trend [$F(1, 12) = 18.9$, $p \leq 0.001$], but no effect for treatment [$F(1, 12) < 1.0$]. However, most importantly the treatment × ISI interaction was significant [$F(1, 12) = 7.8$, $p \leq 0.02$, quadratic], indicating that Tat altered the amplitude of the inhibition response as a function of ISI. Separate trend analyses for both treatment groups revealed a significant quadratic trend for saline-treated rats [$F(1, 6) = 16.1$, $p \leq 0.01$] in contrast to a linear trend for Tat-treated animals [$F(1, 6) = 13.7$, $p \leq 0.01$]. The significant alteration of peak ASR function by Tat suggests Tat-induced effects on the process of sensorimotor gating, indexed by PPI. This finding is supported by a rightward peak shift by Tat across ISIs (8–120 ms) [$\chi^2(1) = 4.7$, $p \leq 0.03$]. Both the significant alteration of peak ASR function and the rightward peak shift indicate a Tat-induced effect on PPI. Fig. 3 illustrates the peak ASR amplitude across ISIs (0–4000 ms).

A mixed-model ANOVA conducted on peak ASR latency revealed a significant effect for PPI trials (8–120 ms ISI) with a prominent linear trend, [$F(1, 12) = 43.3$, $p \leq 0.001$], but no effect for treatment [$F(1, 12) = 2.2$, $p \leq 0.16$) or treatment × ISI interaction [$F(3, 36) < 1.0$]. Fig. 4A illustrates the peak ASR latency across ISI (0–4000 ms). A slowing in response latency (4 ms, ~15%) collapsed across ISIs (08–120 ms) was suggested, although no significant treatment effect was noted (Fig. 4B).

3.3. Histology

Analysis of Nissl-stained sections through the hippocampus confirmed placement of injection sites into the dentate hilus region of the hippocampal formation. Saline-injected animals displayed little pathology, whereas Tat-injected animals displayed damage to the dentate region with the truncation of the terminal end of the pyramidal cell fields and the granule cells in the inferior blade of the dentate gyrus (Fig. 5). Massive cellular necrosis was not observed in either the hippocampal subfields or the dentate gyrus following intrahippocampal Tat injection.

4. Discussion

The present experiment investigated potential alterations in adult male rats in sensorimotor gating, as measured by PPI, following bilateral intrahippocampal administration of 50 μg Tat. Behavioral testing examined ASR on habituation, control and PPI trials using the dependent measures of peak ASR amplitude and peak ASR latency. Intrahippocampal Tat injections produced robust alterations in the baseline ASR and the temporal relation between the prepulse and the ASR, as indexed by the ISI function across PPI trials (8–120 ms ISI). Intrahippocampal Tat injections in adult male rats produced significant differences between saline- and Tat-treated animals, specifically in peak ASR amplitude measures.

The baseline peak ASR amplitude on the 36 ASR habituation trials and the control trials was significantly attenuated by Tat, relative to saline-injected rats. The startle reflex protects animals from blows, loud sounds or predatory attacks before any directed evasive or defensive actions can be performed (Yeomans and Frankland, 1996). An attenuation of this startle reflex by Tat suggests an alteration in responsivity to stimulus input and how the organism processes stimulus events.

Alterations produced by Tat across PPI trials were most evident in peak ASR amplitude, as Tat-induced a rightward peak-shift relative to the saline-treated rats. No significant alterations were observed on the ISI function of peak ASR latency; however, an attenuating effect of Tat was demonstrated with the suggestion of a slowing of the response (4 ms, ~15%) collapsed across PPI trials (8–120 ms ISI). The present results are in agreement with the findings of a recent Tat study that demonstrated alteration in the ISI function across PPI trials throughout development (Fitting et al., 2006). Thus, in addition to an attenuation of the startle reflex, indexed by the baseline ASR, a disruption of pre-attentive

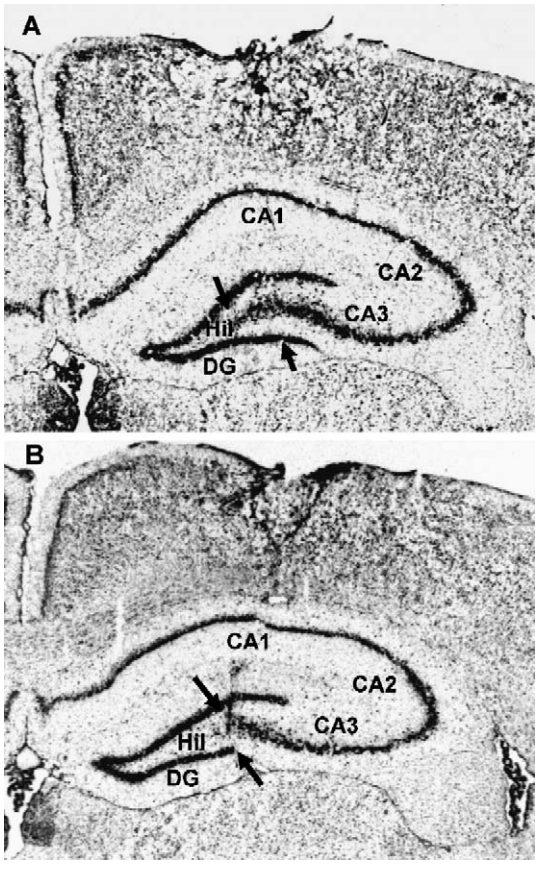

Fig. 5. Nissl-stained hippocampal tissue sections of saline (A) and Tat-injected animals (B). Arrows indicate the truncation of the pyramidal cell fields and the granule cells in the inferior blade of the dentate gyrus. *Note: CA1-3 fields of hippocampus, DG: dentate gyrus, Hil: hilus dentate gyrus.

processes was noted and suggests adverse effects on cognitive processing, as indexed by sensorimotor gating.

It is important to note that percent PPI (at 100 ms) did not exhibit any significant Tat-induced effects, indicating that the amplitude of the inhibition response was not attenuated by Tat. The determination of ISI functions appeared more sensitive to Tat-induced alterations in PPI and ought to be considered for future research assessing Tat-induced neurotoxicity. It is important to note that these functional alterations by Tat were only evident on the peak ASR amplitude measure within PPI trials (8–120 ms ISI), and not on the measure of ASR latency across all ISI. The dependence of detecting significant alterations on the characteristic of peak ASR amplitude and not peak ASR latency might reflect some basic properties of the way the nervous system is organized to deal with sensory input (Hoffman and Ison, 1980) and needs further investigation.

Resembling the findings of the present study, clinical reports of HIV-1 infected patients diagnosed with HAD demonstrated robust alterations in event-related brain potentials (ERPs) (Castello et al., 1998; Fein et al., 1995; Goodwin et al., 1996). ERP recordings are an important method to test neuropsychological function and are among the earliest readily quantifiable alterations observed in HAD (Fein et al., 1995; Goodwin et al., 1996; Schroeder et al., 1996; Castello et al., 1998). The P3 component has been shown to be particularly sensitive to the cognitive decline associated with HIV-1 dementia (Fein et al., 1995; Goodwin et al., 1996). There is also compelling evidence of alteration in the ERP N2 latency component, with the amplitude of the delay increasing as a function of severity of HAD (Schroeder et al., 1996). Interesting parallels between the rodent PPI and human ERP component studies are reported by relating both paradigms at a physiological and/or functional level (Swerdlow et al., 2000a). PPI is thought to reflect the functioning of a pre-attentive filtering system whereby the prepulse exerts an inhibitory influence until the processing of the prepulse is complete (Hoffman and Ison, 1980; Swerdlow et al., 2000a). Limbic circuitry, primarily the hippocampus, regulates PPI and is also thought to be a primary substrate for suppression of the ERP (Swerdlow et al., 2000a). Specifically, the dentate gyrus of the hippocampal formation appears to disrupt PPI in the rat by a mechanism distinct from that of dopamine agonists (Caine et al., 1991, 1992). The dentate gyrus of the hippocampus also appears to be implicated in sensorimotor gating deficits as seen in schizophrenic patients (Braff et al., 1978; Cadenhead et al., 2000; Davatzikos et al., 2005; Nowakowski et al., 2002). Thus, an alteration in PPI by Tat was noted and suggests a disruption of pre-attentive processes (Swerdlow et al., 2001b), and may serve as an experimental model for the ERP deficits seen in HAD patients.

In this study intrahippocampal Tat injections produced a lesion of the dentate gyrus with the truncation of the terminal end of the pyramidal cell fields. These findings generally support previous studies suggesting that Tat causes neuronal damage, synaptic alterations and glial activation in the hippocampal regions, including CA1, CA3/4 and the dentate gyrus (Behnisch et al., 2004; Bruce-Keller et al., 2003; Cheng et al., 1998; Maragos et al., 2003; Nath et al., 2000b); however, the Tat-induced pathology was limited relative to some prior reports (Maragos et al., 2003). Several neuropathological studies have demonstrated loss of a subset of neurons in hippocampal tissue from HIV-infected individuals (Masliah et al., 1992) and in monkeys infected with simian immunodeficiency virus (Luthert et al., 1995). Further, selective populations of neurons seem to be vulnerable to viral protein-induced neurotoxicity, with dopaminergic neurons being particular susceptible (Aksenov et al., 2006; Nath et al., 2000a; Wallace et al., 2006).

The present experiment demonstrates that intrahippocampal injection of Tat in adult male rats had adverse effects on sensorimotor gating, as indexed by PPI. The assessment of ISI function with PPI by measuring peak amplitude and peak latency across a range of ISIs (i.e., 8, 40, 80, 120) is critically important for the detection of Tat alterations in sensorimotor gating and/or attentional processes. In contrast, the commonly employed metric of percent PPI demonstrated no differential treatment effect. Although Tat was found to attenuate the baseline ASR, on habituation and control trials, these alterations do not cloud the interpretation of the shift in peak inhibition across the ISI function. Our laboratory recently found that intrahippocampal Tat injections in neonatal rats may cause similar effects in sensorimotor gating, as indexed by PPI (Fitting et al., 2006). Tat injections in neonatal rats produced sex-dependent alterations in the pre-attentive processes of sensorimotor gating at 30 and 60 days of age. Data collected from a second group, that were tested only once at 90 days of age, suggested that the observed adverse Tat effects for males and females early in development were maintained with age. Tat did not alter the integrity of the hippocampal infra hilar area of the dentate gyrus itself but altered the width of the pyramidal cell fields in the CA areas and the granule cell fields of the superior blade of the dentate gyrus. It is suggested that the increased field width is most likely a consequence of disaggregation of the pyramidal cells induced by early cell loss following the neonatal Tat exposure. It will be important for future research to further explore the neural circuitry of the Tat-induced alterations in PPI, which likely include the hippocampus.

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