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HIV, Tat and Dopaminergic Transmission

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Abstract

Human Immunodeficiency Virus (HIV) is a progressive infection that targets the immune system, affecting more than 37 million people around the world. While combinatorial antiretroviral therapy (cART) has lowered mortality rates and improved quality of life in infected individuals, the prevalence of HIV associated neurocognitive disorders is increasing and HIV associated cognitive decline remains prevalent. Recent research has suggested that HIV accessory proteins may be involved in this decline, and several studies have indicated that the HIV protein transactivator of transcription (Tat) can disrupt normal neuronal and glial function. Specifically, data indicate that Tat may directly impact dopaminergic neurotransmission, by modulating the function of the dopamine transporter and specifically damaging dopamine-rich regions of the CNS. HIV infection of the CNS has long been associated with dopaminergic dysfunction, but the mechanisms remain undefined. The specific effect(s) of Tat on dopaminergic neurotransmission may be, at least partially, a mechanism by which HIV infection directly or indirectly induces dopaminergic dysfunction. Therefore, precisely defining the specific effects of Tat on the dopaminergic system will help to elucidate the mechanisms by which HIV infection of the CNS induces neuropsychiatric, neurocognitive and neurological disorders that involve dopaminergic neurotransmission. Further, this will provide a discussion of the experiments needed to further these investigations, and may help to identify or develop new therapeutic approaches for the prevention or treatment of these disorders in HIV-infected individuals.

Introduction

There have been a number of excellent reviews detailing the effects of HIV-1 Tat on the CNS, and a growing body of research suggests that HIV infection specifically damages and/or dysregulates the dopaminergic system in the CNS (Cass et al., 2003; Czub et al.,

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2004; Ferris et al., 2008; Fitting et al., 2015; Gaskill et al., 2013; Gaskill et al., 2014; Koutsilieri et al., 2004; Purohit et al., 2011). A number of recent studies suggest that these changes to the dopaminergic system specifically involve Tat; therefore, this review will focus specifically on the Tat protein and its effect on dopaminergic neurotransmission. This review will briefly discuss both the pathogenesis of HIV in the CNS and dopamine neurotransmission in the brain, and then review what is known about the Tat protein itself. This will be followed by discussion of the model systems used to explore the effects of Tat on the dopaminergic system, the direct effects of Tat on neuropathogenesis and the brain regions implicated in Tat modulation of cognitive function. The review will then explore the direct impact of Tat on the dopamine transporter and on the dopamine receptors. Finally, the discussion will briefly discuss the specific impact of Tat on the dopaminergic effects of psychostimulants, as well as other drugs of abuse. Although the impact of Tat on neuropathogenesis has been covered at length recently (Dahal et al., 2015; Hauser and Knapp, 2014; Maubert et al., 2015; Mediouni et al., 2015a), these sections will provide a distinct viewpoint on the subject, focusing specifically on the potential synergistic effects of Tat and drug abuse on dopaminergic neurotransmission.

I. HIV Neuropathogenesis

Globally, approximately 37 million people are infected with the human immunodeficiency virus. In 2014, more than 1.2 million people died as a result of this infection (UNAIDS 2015). HIV is a lentivirus which principally targets the immune system, primarily infecting CD4+ T-cells, macrophages and monocytes. Untreated, HIV infection progressively destroys the immune system, leading to the development of acquired immunodeficiency syndrome (AIDS) (Derdeyn and Silvestri, 2005; Moir et al., 2011; Stevenson, 2003). The development of combinatorial antiretroviral therapy (cART) has successfully reduced rates of death and improved length and quality of life (UNAIDS, 2015; Weber et al., 2013), transitioning HIV infection from a terminal to a chronic diagnosis (Deeks et al., 2013). This success has increased the prevalence of HIV, particularly among vulnerable populations, such as drug abusers (El-Bassel et al., 2014). Currently, the prevalence of HIV is 22 times higher among injection drug users than among the general population (Beyrer et al., 2010; Crime, 2014; Mathers et al., 2008) and even the use of non-injection drugs greatly increases the risk of acquiring HIV (Kipp et al., 2011). The mechanism(s) by which different types of drugs of abuse increase the risk of acquiring or exacerbating HIV is not clear, and understanding these processes is critical, as drug abuse exacerbates the development of AIDS in both the periphery and in the central nervous system (CNS) (Baum et al., 2009; Lucas et al., 2006). The direct effects of HIV infection on the reward pathway and drug-seeking behavior are not fully understood, but numerous studies have suggested HIV affects the dopaminergic system (Aylward et al., 1993; Berger et al., 1994; Chang et al., 2008; Itoh et al., 2000; Jenuwein et al., 2004; Kieburtz et al., 1991; Nath et al., 2000; Obermann et al., 2009a; Sardar et al., 1996; Scheller et al., 2010; Wang et al., 2004).

While a majority of studies on HIV focus on the effects on the peripheral immune system, infection of the CNS is a growing health concern. HIV enters the CNS rapidly following initial infection (Davis et al., 1992; Valcour et al., 2012). Infection of the CNS leads to a constellation of neurocognitive impairments, including cognitive dysfunction, behavioral

changes, motor deficits, and dementia, that are currently known as HIV-associated neurocognitive disorders (HAND) (Antinori et al., 2007; Navia et al., 1986; Price et al., 1988; Sacktor et al., 2002; Simioni et al., 2010). Prior to the implementation of cART (combinatorial antiretroviral therapy, then called HAART) in 1996, around 16% of HIV-infected individuals manifested HIV encephalitis (Davies et al., 1998), and between 5 and 20% were diagnosed with HIV-associated dementia (HAD) (Janssen et al., 1989; Maschke et al., 2000; McArthur et al., 1994; Sacktor, 2002). With cART, the more severe neurological manifestations have become rare (Ellis et al., 2007; Heaton et al., 2010a; Joska et al., 2010; Sacktor, 2002), but 40 – 70% of infected individuals still suffer from HAND (Cysique et al., 2004; Heaton et al., 2010a; Heaton et al., 2011a; Simioni et al., 2010; Tozzi et al., 2005). Further, the prevalence of HAND is increasing as these individuals have longer life expectancy (Brew and Chan, 2014; Heaton et al., 2010b; Simioni et al., 2010). HAND is still found among individuals with viral suppression (Heaton et al., 2011b; Robertson et al., 2007), which suggests that factors other than viral replication are involved. A number of studies indicate that drug abuse may exacerbate both the neuropathogenesis of HIV and the neurocognitive impact of infection in both cART-naïve and cART-treated individuals (Chana et al., 2006; Langford et al., 2003b; Meade et al., 2011a; Meyer et al., 2014; Nath, 2010; Starace et al., 1998). However, other studies show that drug-abuse does not increase the neurological deficits induced by HIV+ infection (Basso and Bornstein, 2003; Byrd et al., 2011b; Grassi et al., 1995); hence, the precise impact of drug abuse on HIV neuropathogenesis remains unclear.

HIV is thought to enter the brain primarily by using infected monocytes as “Trojan Horses” to move across the blood-brain barrier (Izquierdo-Useros et al., 2010; Kim et al., 2003; Peluso et al., 1985). Within the brain, the monocytes mature into macrophages and produce new HIV virions, spreading the infection throughout the brain. In the CNS, HIV primarily infects perivascular macrophages and microglia (Gonzalez-Scarano and Martin-Garcia, 2005; Joseph et al., 2015; Kure et al., 1990). The presence of HIV has also been shown in astrocytes both *in vitro* (Eugenin and Berman, 2007) and *in vivo* (Churchill et al., 2009; Tornatore et al., 1994), but the mechanism of entry into these cells, and the overall role of astrocytes in HIV neuropathogenesis remains unclear (Gray et al., 2014; Joseph et al., 2014; Luo and He, 2015). Infected cells, primarily macrophages, monocytes and microglia produce and secrete a variety of inflammatory host and viral factors, including cytokines, chemokines and viral proteins. These factors result in chronic neuroinflammation and neurotoxicity, which are thought to be central to the development and persistence of HAND (Gannon et al., 2011; Gill et al., 2012; Hong and Banks, 2015; Kraft-Terry et al., 2009; Zayyad and Spudich, 2015).

II. The Transactivator of Transcription (Tat)

Among the neurotoxic viral proteins released by infected cells is the viral protein Tat (Chang et al., 1997; Ensoli et al., 1993; King et al., 2006; Rayne et al., 2010a). Tat is short for trans-activator of transcription, and is required for the successful transcription of full-length HIV mRNA. This protein is one of the first genes expressed in the HIV replication cycle. The viral mRNA of Tat consists of two exons. The first exon is comprised of amino acids 1 – 72, and contains the transcriptional functions of the protein. The second exon, comprised of

amino acids 73 – 101 or amino acids 73 – 86, houses the integrin binding domains. The longer form of Tat (~101 aa) is far more common and is found in the majority of HIV clinical isolates, while the shorter form of Tat (~86 aa) is mostly found in laboratory adapted strains and is the result of a single nucleotide polymorphism in the second exon which creates a stop codon (Campbell et al., 2005; Jeang, 1996; Jeang et al., 1999). Perhaps due to the prevalence of this premature stop codon in the laboratory-adapted, clade B strains of HIV that are common in North America and Western Europe, the shorter form of Tat is much more commonly used in research. Some studies examining multiple forms of Tat have shown functional differences between the shorter and wild type forms of Tat (Bertrand et al., 2013; Campbell et al., 2005), while others do not find such differences (Ma and Nath, 1997). Thus, the effects of wild-type Tat on many of the biological functions studied using the shorter forms of Tat are unclear.

The first exon of Tat can be divided into a number of distinct regions generally defined as the N-Terminal (residues 1–21), cysteine-rich (residues 22–37), core (residues 38–48), basic, protein transduction or arginine-rich (residues 49 – 60) and glutamine-rich or C-Terminal (residues 60 – 72) domains (Campbell and Loret, 2009; Derse et al., 1991; Jeang et al., 1999; Kuppuswamy et al., 1989), as depicted in Figure 1. Each of these regions has been found to have numerous distinct functions, although many functions also span more than one region. For example, the placement of tRNA onto the viral RNA genome involves the cysteine-rich, the core, and the basic and glutamine-rich domains (Kameoka et al., 2002). While the minimal functional domain of Tat encompasses the first 48 amino acids, the role of specific residues in the N-terminal domain, a proline rich region, is undefined (Derse et al., 1991; Jeang et al., 1999). Mutation studies have shown that the cysteine-rich domain is necessary for the transactivation function of Tat (Green and Loewenstein, 1988; Jeang et al., 1999; Kuppuswamy et al., 1989; Rice and Carlotti, 1990), and coordinates Zn^{2+} binding, which induces folding of the protein and stabilizes the interaction of Tat with microtubules (Egele et al., 2008; Tahirov et al., 2010). This region has also been shown to induce synaptodendritic injury in hippocampal cell culture (Bertrand et al., 2013). The core domain is also necessary for Tat to mediate transactivation, and the residues in this region increase the specificity of binding to the TAR RNA complex and are necessary for Tat function (Jeang et al., 1999; Rana and Jeang, 1999). The arginine-rich or basic domain contains the well-conserved sequence RKKRRQRRRAP. This sequence is critical to the nuclear localization function of the protein, and to the interaction of Tat with the TAR RNA complex, which is a short stem-loop structure in HIV RNA (TAR RNA) bound to a number of cellular factors (Dingwall, 1991; Jeang et al., 1999; Rana and Jeang, 1999; Vives et al., 1997). This region also enables Tat to translocate across the plasma membrane into the cytosol (Futaki et al., 2001), and is responsible for interactions with phosphatidylinositol-4,5-bisphosphate ($PI(4,5)P_2$) that lead to the accumulation of Tat on the cytosolic side of the plasma membrane (Rayne et al., 2010b). The glutamine-rich region is also important for binding the TAR complex (Bayer et al., 1995; Churcher et al., 1993), which greatly enhances transactivation (Green et al., 1989). One study found that mutations in this region alter the ability of Tat to induce T-cell apoptosis (Campbell et al., 2004). The second exon of Tat houses the integrin binding modality. Some studies also indicate that it is necessary for the transactivation function *in vitro* (Campbell and Loret, 2009).

Several forms of Tat, including full length Tat-101, a shorter form comprised of only the first exon, Tat 1-72, and another form made up of the first exon and small portion of the second exon, Tat 1-86, are commonly used to study the effects of Tat on the CNS (Aksenova et al., 2009; Eugenin et al., 2007; King et al., 2010; Mishra et al., 2008; Moran et al., 2014) (Figure 1). Although there are numerous studies using these different forms of Tat, the existing literature lacks a comprehensive comparison of different Tat forms on cellular functions in the CNS and specifically dopamine neurotransmission. This review will touch on some of the differences below, but future studies are needed to address this critical knowledge gap.

Tat acts as a transcriptional regulator of HIV gene expression by binding to the TAR element, as well as a complex of cellular transcription factors, such as P-TEFb. These interactions upregulate transcription from the HIV long terminal repeat (LTR) at least 1000-fold and promote the elongation phase of HIV transcription (Feinberg et al., 1991; Jeang et al., 1999; Karn and Stoltzfus, 2012). Tat has also been shown to interact with a number of different host proteins and affect a variety of cellular functions, interacting with different cellular structures and signaling pathways, as well as triggering angiogenesis and cell growth (Bagashev and Sawaya, 2013; Emerman and Malim, 1998; Ptak et al., 2008; Romani et al., 2010). Additionally, numerous studies indicate that Tat can be neurotoxic, acting through diverse pathways (Aksenov et al., 2003; Fields et al., 2015; King et al., 2006; Nath, 2002; Silvers et al., 2007).

To initiate the HIV transcription process, Tat is produced during the first round of abortive transcription, before transcription of the full length viral DNA or most other viral proteins. Once translated, Tat returns to the nucleus to enable transcription of full length HIV (Jones and Peterlin, 1994; Kao et al., 1987). In addition to these intracellular functions, Tat is also secreted from infected cells in a temperature dependent manner without lysis of the infected cell (Chang et al., 1997; Ensoli et al., 1990; Ensoli et al., 1993; Rayne et al., 2010a) and *in vitro* studies demonstrate that Tat can be taken up rapidly by H9, HeLa and U937 cells through lipid-raft dependent micropinocytosis (Frankel and Pabo, 1988; Mann and Frankel, 1991; Wadia et al., 2004). These findings are supported by our own data in Figures 2 – 4, which show uptake of Tat from conditioned media by HEK 293 cells, midbrain mouse microglia and midbrain mouse neurons after 48 hours. *In vivo*, immunohistochemical staining was used to identify Tat protein in monocytes, astrocytes and oligodendrocytes in the frontal cortex and white matter of 3 HIV-infected patients (Del Valle et al., 2000), and in the cytoplasm of astrocytes and microglia in gray and white matter from 10 HIV-infected brains (Bonwetsch et al., 1999). A third study also used immunohistochemistry to identify Tat positive cells in the subcortical frontal white matter of 3 out of 4 HIV-infected brain specimens (Hofman et al., 1994). Although the movement and localization of Tat *in vivo* are not fully resolved, these data suggest that Tat could be taken up by CNS-specific cells in infected areas of the brain. A number of studies have found that low-level HIV replication persists in the CNS of HIV-infected individuals on cART (Chun et al., 2005; Dahl et al., 2014; Eden et al., 2010; Ferretti et al., 2015; Hatano et al., 2010; Palmer et al., 2008). Thus, even in cART-treated patients, Tat could be locally released into the central nervous system by HIV-infected macrophages, microglia or monocytes and influence the surrounding cells.

In both cART-naïve and cART treated patients, HIV infection of the CNS produces substantial neuropathology in dopaminergic regions. This includes high levels of HIV infection (Brew et al., 1995; Glass et al., 1995), basal ganglial atrophy (Aylward et al., 1995; Aylward et al., 1993; Becker et al., 2011; Hestad et al., 1993), nigral degeneration (Itoh et al., 2000; Reyes et al., 1991), impaired striatal activity (Ortega et al., 2015; Plessis et al., 2015), altered metabolism and metabolite ratios (Gongvatana et al., 2013; Rottenberg et al., 1987; Yiannoutsos et al., 2004) and increased neuroinflammation (Vera et al., 2016). Decreased expression of both D2 receptors and tyrosine hydroxylase (TH), the rate-limiting enzyme for the dopamine synthesis, as well as changes in the dopamine concentrations, abnormal dopamine metabolism and altered dopamine transporter (DAT) expression and function in the basal ganglia, as measured by fMRI, have been shown to correlate with the cognitive deficits in HIV patients (Chang et al., 2008; di Rocco et al., 2000; Kumar et al., 2011; Obermann et al., 2009b; Zauli et al., 2000). Overall, these data suggest that the infection of CNS macrophages and microglia, and the subsequent release of Tat in dopaminergic regions of the CNS may be one mechanism by which HIV negatively impacts the dopaminergic system. As HIV infection has become a chronic disease, this interaction could persist for the life of the infected individual, causing progressively greater dopaminergic dysfunction. Thus, it is critical to improve our understanding of these effects and to better develop therapeutic strategies that maintain normal dopaminergic function in long-term HIV-infected individuals.

III. Caveats Regarding the Use of Tat in Model Systems

Most studies examining the impact of Tat on dopaminergic neurotransmission are performed *in vitro* or in rodent models, although some studies have also been performed in primate models. Table 1 describes the model system, type and amount of Tat used in the studies referenced in this review. Both *in vitro* systems and animal models provide an important modality for evaluating the effects of HIV on the dopaminergic system *in vivo*, and have provided invaluable contributions to our understanding of the mechanisms of HIV- and Tat-mediated neuropathology. Although the data from some of the studies in these systems are now being reexamined, it is important to note that these early studies identified important concepts and knowledge gaps in the field. Recent technical and methodological advances have enabled us to build upon these data, leading to new advances in the field while clarifying both the benefits and limitations of each model system. Thus, careful evaluation of data from these systems requires the consideration of a few caveats. First, it is not clear how accurately the amount of Tat used in these studies mimics that found in the CNS of HIV-infected individuals. This is because the precise concentration of Tat and other HIV proteins in the CNS of HIV-infected individuals, and how those concentrations vary across different regions of the CNS, is not known. This is an area that requires further study, and without it the physiological relevance of these systems will remain unclear.

What is known is that Tat is secreted from infected cells (Ensoli et. al., 1990, 1993, Chang et. al., 1997, Rayne et. al., 2010) and taken up rapidly by endocytosis (Frankel and Pabo et. al., 1988, Mann et. al., 1991). This is also shown in Figures 2, 3 and 4, as well as in supplemental Figure 1. These figures demonstrate that HEK 293 cells (Fig. 2, Suppl. Fig. 1), midbrain mouse microglia (Fig. 3) and midbrain mouse neurons (Fig. 4) can both release

and take up Tat_{101} from the surrounding milieu. While the data presented here, as well as other studies have shown uptake of Tat produced by infected cells, the extent to which this occurs in human CNS cells such as neurons, astrocytes and microglia is not well-defined. In HIV-infected primary CD4+ T-cells, while 2/3 of the Tat produced was released, the concentration resulting from that release was only 0.25 nM Tat[1] (Rayne et al., 2010b). The concentration of Tat in the serum of HIV+ individuals is around 0.1 nM, and from 0.1 and 0.4 nM in the media of cultures of HIV_{IIIB} infected human H9 T-cells or cultures of transfected mouse T53 cells (Albini et al., 1998; Westendorp et al., 1995). It is still not clear how much Tat is present in specific regions of the human CNS, although 1 – 3 nM Tat can potentiate or inhibit neurotransmitter release in rodent or human synaptosomes (Feligioni et al., 2003; Musante et al., 2010; Zucchini et al., 2013). Further, the neurotoxic concentration of Tat *in vivo* is unknown, although the amount of Tat needed to generate neurotoxicity *in vitro* has been studied extensively and found to be as low as 1 nM (Agrawal et al., 2012; Bansal et al., 2000; Eugenin et al., 2003). Again, this suggests that very low amounts of Tat could potentially impact neurological function. Like many small molecules, local concentrations of Tat may be greater in different compartments, especially in highly infected regions, such as the lymph nodes, lungs or specific regions of the CNS. However, because the concentration and distribution of Tat in the human brain are not known, the extent to which Tat mediates these effects in humans remains unclear.

These concerns are particularly acute regarding the analysis of data from animal models with constitutive protein expression, because these models do not produce viral proteins by means of the same regulatory process(es) as HIV infection. In these systems Tat is not produced from the same type(s) or quantities of cells, nor from the same brain regions, as it is in natural infection. Additionally, the Tat protein aggregates regularly, so it is possible that constitutive production of Tat may produce larger and/or less active Tat multimers (Hategan et al., 2016). Thus, degree to which the concentration, distribution and multimerization of Tat in the CNS of these animal models approximates HIV-infected human CNS is not clear, and therefore careful consideration must be given to the data derived from these systems.

The final caveat, which applies more specifically to animal models examining the effects of Tat on the dopaminergic system, is the dissimilar size of the human brain relative to the brains of primates and rodents (Barton and Harvey, 2000; MacLeod et al., 2003). These increases in size not only lead to changes in the number of specialized sub-regions of the CNS, they also create significant changes in the microstructure of the CNS (Passingham, 2009). Furthermore, while mammalian dopaminergic systems overall are fairly similar, (Joel and Weiner, 2000; Johnston et al., 1990; Murphy et al., 1996) there are substantial anatomical differences between rodents and primates, as well as some between humans and lower primates. For example, in primates there is a distinct separation between the caudate and the putamen that does not exist in rodents. There are species specific differences in the proximity and orientation of globus pallidus and subthalamic nucleus, and the dopaminergic

[1]To better compare all experiments, the molar concentration of HIV-Tat in each experiment was calculated from the reported amounts of Tat used in these studies. The molecular weight of HIV-1 Tat is 9860 Daltons (Da), or 9860 grams per mole. This means that 9860 g of Tat (approximately 1 mole) in 1000 mL is approximately 1 M, and that 9860 ng in 1 mL is approximately 1μM. Using this calculation, 1 ng/mL is equivalent to 0.1 nM, and 4 ng/mL is equivalent to 0.4 nM.

terminals in those regions, relative to other dopamine-rich brain regions, and changes in the amount and destination of striatal projections (Joel and Weiner, 2000; Zeiss, 2005). Primates and rodents also show distinct ratios of different types of neurons in the substantia nigra (Poirier et al., 1983). Primates have greater levels of dopaminergic innervation in the thalamus than do rodents (Garcia-Cabezas et al., 2009), while humans have significantly greater levels of dopaminergic innervation in the frontal cortex than do macaques (Raghanti et al., 2009). Additionally, there are differences in the metabolism of dopamine and other biogenic amines in rodents, primates and humans (Meiser et al., 2013). This could lead to changes in the concentration and/or distribution of dopamine in the CNS, as well as the response to different dopaminergic drugs. For example, the ratios of monoamine oxidases (MAO) A and B are different in rodent versus primate brains, resulting in most dopamine oxidation being carried out by MAO-A in rodent brains but MAO-B in primate brains (Garrick and Murphy, 1980; Napolitano et al., 1995). These comments are not to say that data from in vitro studies and animal models should be ignored, as they are extremely valuable sources of information regarding the direct and indirect impact of HIV proteins on dopaminergic neurotransmission. However, the important caveats associated with these systems must be carefully considered when interpreting the data.

IV. Dopaminergic Neurotransmission, HIV infection and Tat

Dopamine (DA) plays a critical role in a number of CNS functions, including motor control, reward, cognition, motivation, executive function, and maternal behavior (Beaulieu and Gainetdinov, 2011; Klanker et al., 2013; Nieoullon, 2002; Nutt et al., 2015). Although clusters of dopaminergic neurons can be found in several different regions of the CNS, the majority of dopamine neurotransmission occurs within four known pathways, which are shown in Figure 5. These pathways are the nigrostriatal pathway (pink), the tuberoinfundibular pathway (orange), and the mesolimbic (red) and mesocortical pathways (yellow). In the brain, dopamine is synthesized in dopaminergic and adrenergic neurons, where the rate-limiting enzyme tyrosine hydroxylase (TH) converts L-tyrosine to L-DOPA, the precursor of dopamine (Flatmark, 2000; Hornykiewicz, 2002). Dopamine can be released via two distinct mechanisms. The first mechanism is through classical vesicular release, while the second mechanism is through DAT-mediated dopamine efflux (Gainetdinov et al., 1997; Goodwin et al., 2009; Jones et al., 1999b; Khoshbouei et al., 2003; Wall et al., 1995). The second mechanism, DAT-mediated dopamine efflux, has been predominantly studied in the context amphetamine and methamphetamine regulation of dopamine release. Like other neurotransmitters, dopamine is released from synaptic vesicles fused with the plasma membrane following an action potential (Sulzer and Galli, 2003; Sulzer et al., 2005), shown in Figure 6. However, dopamine-transporter mediated dopamine efflux transports dopamine from inside the neuron to outside via an action potential-independent mechanism (Sulzer and Galli, 2003; Sulzer et al., 2005), albeit under certain conditions, such as exposure to amphetamines, as detailed in Figure 7. Therefore, changes in the firing rate of dopamine neurons and DAT-mediated dopamine efflux directly affect dopamine concentration in the synapse and extracellular space (Butler et al., 2015).

Early in the HIV epidemic, it was shown that HIV infection impacts the dopaminergic system and dopamine metabolism in the CNS (Berger et al., 1994; di Rocco et al., 2000;

Kieburtz et al., 1991; Koutsilieri et al., 1997; Koutsilieri et al., 2002a; Koutsilieri et al., 2002b; Larsson et al., 1991; Nath et al., 2000; Sardar et al., 1996; Silvers et al., 2006). Even in the era of cART, several studies have shown HIV infection alters dopamine concentrations and metabolism in the brain (Horn et al., 2013; Kumar et al., 2009; Kumar et al., 2011; Meulendyke et al., 2014; Scheller et al., 2010). Elevated dopamine has been shown to increase HIV infection of macrophages, the primary target for and source of HIV in the CNS (Gaskill et. al., 2009, 2014), potentially creating a vicious cycle by which dopaminergic dysfunction spurs greater infection, which then exacerbates dopaminergic dysfunction. While previous studies have examined the effects of HIV infection and viral protein expression on dopamine neurotransmission indirectly by evaluating changes in dopaminergic proteins, the direct effects of HIV infection, or of the Tat protein, on the regulation of firing activity or excitability of dopamine neurons in the brain remain undetermined.

As shown in Figure 5, there are three primary clusters of DA neurons, two in the mid-brain and one in the hypothalamus. In the midbrain, cluster A9 is found in the substantia nigra pars compacta (SNc) and cluster A10 is in the ventral tegmental area (VTA). A third smaller cluster, A8, can be found in the retrorubral area (RR) (Bjorklund and Dunnett, 2007; Fu et al., 2012; Nestler, 2009; Zaborszky and Vadasz, 2001). Despite resembling each other in many respects, dopamine neurons of the SNc and VTA area mediate distinct functions and exhibit dissimilar responses to toxins and addictive agents (Choi et al., 2015; Teo et al., 2004). Since the discovery of dopamine as a neurotransmitter (Carlsson et al., 1962) and the observation that dopamine was significantly depleted in the SNc of patients with Parkinson's disease (Benazzouz et al., 2014; Hornykiewicz and Kish, 1987; Tremblay et al., 2015), the regionally selective vulnerability of dopamine neurons has been the focus of a large number of studies (Bernheimer et al., 1973; Braak and Braak, 1986; Braak et al., 2003; Burns et al., 1983; Damier et al., 1999; Double et al., 2010; Fearnley and Lees, 1991; German et al., 1992; Gibb and Lees, 1991; Greenfield and Bosanquet, 1953; Halliday and Tork, 1986; Hirsch et al., 1989; Poulin et al., 2014).

It is not clear whether HIV infection or the Tat protein differentially affect distinct clusters of dopamine neurons in the brain. This type of regional difference has been shown in the differential vulnerability of dopaminergic neurons in the VTA and SNc when exposed to neurotoxins such as MPTP (Elsworth et al., 1990; Rothblat and Schneider, 1994; Rothblat et al., 2001; Schneider et al., 1987). Some patients with HIV dementia develop acute onset Parkinsonism and dystonia when treated with dopamine receptor antagonists (Hriso et al., 1991), and patients on cART can also develop parkinsonism (Tisch and Brew, 2009). In methamphetamine-treated rodents, an intra-nigral infusion of 10 μg/μL (approximately 1 mM) Tat was shown to exacerbate Parkinson-like locomotor deficit (Liu et al., 2014). This is consistent with reports showing methamphetamine-induced behavioral sensitization were enhanced in HIV-1 Tg rats (Kass et al., 2010). These data suggest Tat might directly or indirectly affect the cluster of dopamine neurons involved in regulation of locomotor activity. Recent reports suggest VTA dopamine neurons might also be a target of the Tat protein. In transgenic mice with doxycycline-induced Tat protein expression in the brain (GT-tg bigenic mice), reward thresholds were elevated by 20% in Tat^{+} mice compared with Tat^{-} mice. Additionally, dopamine levels were increased in the caudate putamen and

decreased in the nucleus accumbens (Kesby et al., 2016b). Studies in this animal model have also shown an increased sensitivity to cocaine-induced psychomotor responses in the Tat^{+} GT-tg bigenic mice (Paris et al., 2014a). These studies suggest Tat expression, in the absence of active HIV replication, may target the dopaminergic neurons in the mesolimbic and mesocortical pathways, although the specific mechanism remains undetermined. However, a recent study by Fan and He, using a doxycycline-inducible, astrocyte-specific HIV-1 Tat transgenic mouse model, demonstrated that increased Tat expression led to aggregation of GFAP, and the induction of a UPR in astrocytes (Fan and He, 2016a). The induction of UPR causes increased lysosomal exocytosis from astrocytes, which leads to astrocyte-mediated neurotoxicity (Fan and He, 2016b). This data from the doxycycline-inducible animal model suggests that Tat mediated neurotoxic effects may not be specific to dopaminergic systems, and also reinforces the concerns noted above regarding the unknown effects of Tat expression in animal models.

Although several studies using total striatal tissue homogenates from rodents have examined the impact of Tat on DAT function, these are difficult to correlate with the precise dopaminergic neurons clusters being affected due to the lack of anatomical specificity in the homogenates. To address these concerns, future studies could examine the amount of Tat expressed in different dopaminergic compartments in the brains of Tat-expressing animal models. This could then be correlated with changes in the expression of dopaminergic proteins such as DAT, TH or dopamine receptors in these regions.

In the substantia nigra, studies showed a significant decrease in tyrosine hydroxylase (TH) and phosphorylated TH (pTH) in HIV-infected adult human tissues (Gelman et al., 2006; Silvers et al., 2006). This suggests an alteration in dopamine production, as TH phosphorylation at Ser40, and to a lesser degree at Ser31, increases TH activity and subsequently catecholamine synthesis (Dunkley et al., 2004; Salvatore et al., 2001). Additionally, in rodents stably transplanted with Tat-producing C6 glioma cells in the striatum, Tat is transported from the striatum to the substantia nigra, resulting in neurotoxicity and decreased TH expression in that region (Bruce-Keller et al., 2003). This is consistent with reports by Zauli and colleagues showing a Tat-mediated decrease in TH expression in rat neurons (Zauli et al., 2000). These data suggest dopaminergic neurons in the substantia nigra may be more susceptible to Tat-induced neurotoxicity, providing an alternate explanation for the reduction of TH staining in Tat exposed model systems. Although the underlying mechanism(s) is not understood, these and other studies suggest that HIV infection and/or Tat expression can result in a loss or dysfunction of dopamine neurons in the substantia nigra (Itoh et al., 2000; Obermann et al., 2009a; Reyes et al., 1991). Positron emission tomography studies have shown decreased DAT expression in the putamen and ventral striatum of infected patients with HIV-associated dementia (Wang et al., 2004); however, Gelman and colleagues found an increase in DAT expression in postmortem human striatal tissue homogenate (Gelman et al., 2006).

This discrepancy might be due to the differences in the development of the infection, as HIV infected patients who display dementia have decreased DAT levels as compared to those with HIV who do not have dementia (Itoh et al., 2000; Wang et al., 2004). The disparate conclusions might be due to methodological differences. For example, Itoh et al., examined

the size and density of pigmented and non-pigmented neurons in the SNc; whereas, Gelman et al., have used striatal tissue homogenate containing terminal regions. Overall, these and other studies showing HIV and/or Tat-associated neuropathology in dopaminergic regions may describe a potential mechanism for the clinical symptoms, such as Parkinson-like movement disorders, bradykinesia, tremor or postural instability in HIV patients (Arendt et al., 1994; Navia et al., 1986) even after antiretroviral therapy (Valcour et al., 2008). However, the conflicting results of these studies, the relatively small number of region specific studies and the relative difficulty of interrogating these questions *in vivo* have kept the precise mechanism(s) by which both HIV and/or Tat impact the dopaminergic system unclear. Importantly, the specificity of the untoward effect(s) of Tat on dopaminergic neurons in the SNc is unclear, as there is no information on the effects of Tat on other neuronal types in this brain region. Therefore, further studies specifically examining the effect of Tat and/or HIV infection on the activity of different clusters of dopaminergic neurons and terminal regions are necessary to better understand and potentially treat the various effects of Tat and/or HIV infection on dopamine neurotransmission.

V. Tat and Cognition: The Dopamine Link

Due to the success of combined antiretroviral therapy (cART), the prevalence of HIV-associated neurocognitive disorders (HAND) is growing as individuals infected with HIV live longer. While HIV infection of the CNS produces a variety of neurocognitive deficits, (Anderson et al., 2015; Berger et al., 1994; Byun et al., 2016; Heaton et al., 2014; Janssen et al., 2016; Plessis et al., 2015; Plessis et al., 2014), the mechanisms underlying these deficits are poorly understood. Currently, between 40 and 70% of HIV-infected individuals suffer from some form of HAND (Cysique et al., 2004; Heaton et al., 2010a; Heaton et al., 2011a; Simioni et al., 2010; Tozzi et al., 2005), although the frequency of the more severe pathologies and neurocognitive disorders such as encephalitis and HIV dementia has declined significantly in the cART era. Similarly, the frequency of individuals with HAND who are asymptomatic or have minor cognitive impairments has significantly increased (Ellis et al., 2007; Heaton et al., 2011a). While it is commonly accepted that neuroinflammation and the resultant neurotoxicity play a central role in the development of HAND, there are also a number of studies implicating alterations in neurotransmission in the development of these disorders. Dopaminergic, glutamatergic and cholinergic neurotransmission have all been studied as a central factor in the development of HIV-associated neurological disorders (Fitting et al., 2010; Hargus and Thayer, 2013; Koutsilieri et al., 2000; Ozdener, 2005).

Prior to cART, numerous studies found that patients with HIV Associated Dementia (HAD) exhibit many symptoms common to diseases involving dopaminergic dysfunction, such as damage to the basal ganglia and substantia nigra, psychomotor impairment, attention difficulties, obsessive ruminations and decreases in coordination (Aylward et al., 1994; Aylward et al., 1993; Czub et al., 2001; Itoh et al., 2000; Kieburtz et al., 1991; Koutsilieri et al., 2001; Maj, 1990; Nath et al., 1999; Navia and Price, 1987; Reyes et al., 1991; Sardar et al., 1996). Individuals with HAD on stable cART therapy also show decreased DAT availability in the putamen and ventral striatum, correlating with decreased neurocognitive performance (Chang et al., 2008; Wang et al., 2004). Similar results show association

between dopamine deficits, microglial activation and regulation of cAMP signaling in the brains of SIV-infected monkeys (Jenuwein et al., 2004; Scheller et al., 2005). Moreover, this and other studies have identified a direct correlation between the higher plasma viral load in patients with HIV dementia and lower DAT expression in the caudate and putamen (Berger et al., 1994; Kramer and Sanger, 1990; Wang et al., 2004). As discussed above, recent studies suggest Tat may influence dopamine neurotransmission by altering DAT function (Midde et al., 2012; Midde et al., 2015b; Yuan et al., 2015b; Yuan et al., 2016; Zhu et al., 2009), and therefore some portion of HIV-mediated cognitive impairment may be the result of impaired dopaminergic neurotransmission due to dysfunction in dopamine transporter proteins. This will be discussed in detail in the following section.

Supporting this idea, several studies treating animals with Tat alone have demonstrated cognitive and behavioral impacts similar to those seen in HIV-infected individuals. Studies using GT-tg bigenic mice have found that doxycycline induction of Tat produces deficits in working and spatial memory. Also, MRI studies in these mice have found a significant reduction in gray matter in areas associated with learning and memory including the entorhinal cortex, hippocampus and amygdala (Carey et al., 2013). Studies in this animal model also suggest the association of Tat with other psychiatric complications. One week of doxycycline-mediated Tat induction produced anhedonia, increased the animals' sensitivity to psychostimulant-induced reward enhancement (Kesby et al., 2016b), and also increased anxiety-like behaviors (Paris et al., 2014b). Similar symptoms can be found in HIV infected individuals, who also display an increased propensity for anxiety disorders and disruption of the reward system (Anderson et al., 2015). In a rat model, intra-hippocampal injection of Tat disrupts the acoustic startle response and pre-pulse inhibition (Fitting et al., 2006). Pre-pulse inhibition (PPI) is a neural mechanism is used to measure adaptive inhibition mechanisms, and has been shown to be decreased in patients with HAND, but not HIV-infected individuals without neurocognitive deficits (Minassian et al., 2013). It is important to note that while suggestive of a direct link with Tat, none of these studies have examined the amount or distribution of Tat in the brain region(s) relevant to the reported neurophysiological measures described above, therefore, the causal bearing of these effects requires further investigation.

Notably, these studies are all focused on the shorter-term impact(s) of Tat on cognition, with the longer-term neurological consequences of Tat exposure not being studied. However, the pivotal role of dopamine neurotransmission in synaptic plasticity and cognition are well established (Backman et al., 2010; Jay, 2003; Otani et al., 2003); therefore, Tat-mediated disruption of DAT function may also impact synaptic plasticity. Treatment of rat CA1 hippocampal slices with Tat suppresses long-term potentiation (LTP), which is representative of suppression of learning and memory (Behnisch et al., 2004; Li et al., 2004). Tat also affects synaptic plasticity by decreasing excitatory synapses and increasing inhibitory synapses (Fitting et al., 2013; Hargus and Thayer, 2013), by altering the expression of dendritic spines and distribution of synaptic proteins (Fitting et al., 2010; Hahn et al., 2015) and by modulating interaction between microglial-neuronal "synapse" interaction (Tremblay et al., 2013). Only one behavioral study has examined the long-term effect of Tat on cognition (Hahn et al., 2015). Hahn and colleagues found mice expressing Tat in the CNS for 3 months exhibited deficits in open-field ambulation, with male mice also demonstrating

motor memory deficits, both behaviors linked to dopaminergic damage (Hahn et al., 2015). It is essential to increase the number of long-term studies examining the prolonged effect(s) of Tat on cognition, because as antiretroviral therapies continue to improve, so will the number of long-lived HIV-infected individuals with expression of viral proteins in the CNS. Collectively these data strongly suggest HIV and Tat alone can impact the dopaminergic system and thus cognition. Therefore, it is critical to conduct further research addressing the medium and longer term impact of HIV infection and Tat on dopamine-driven cognitive processes, so that we are better prepared to treat the deficiencies resulting from living with HIV long-term.

VI. Tat and Dopamine Transporter Function

The dopamine transporter (DAT) plays a central role in dopaminergic neurotransmission as the primary regulator of extracellular dopamine concentrations. The DAT removes dopamine from the synapse by transporting it into the pre-synaptic neuron across the plasma membrane using the concentration gradient generated by Na^+/K^+ ATPase (Khoshbouei et al., 2003; Sonders et al., 1997). Dopamine returned to presynaptic neurons is then placed in synaptic vesicles for storage and reuse. The reuptake process is critical, as it controls the magnitude and duration of dopamine receptor activation on the pre- and postsynaptic neurons (Gainetdinov et al., 1999; Sulzer et al., 2016). Loss of DAT activity leads to decreased tissue dopamine levels (Jones et al., 1999a; Rocha et al., 1998; Salahpour et al., 2008; Zhuang et al., 2001) and has been implicated in several neurodegenerative diseases, attention deficit hyperactivity disorder (ADHD), and altered sensitivity to psychostimulants (Bowton et al., 2010; David et al., 2008; Mazei-Robison et al., 2008; Nakamura et al., 2010; Volkow et al., 2014). A significant number of studies over the last 20 years have led to the discovery of molecular and cellular mechanisms involved in DAT regulation and it availability at the plasma membrane of the dopamine neurons. A plethora of different kinases, scaffolding proteins, and receptors regulate DAT-mediated dopamine uptake, dopamine efflux, conformational state of DAT, oligomerization, and trafficking of the transporter (Aksenov et al., 2008; Bowton et al., 2014; Cartier et al., 2015; Fog et al., 2006; Guptaroy et al., 2009; Hamilton et al., 2014; Hansen et al., 2014; Kahlig et al., 2005; Khoshbouei et al., 2004; Lute et al., 2008; Reddy et al., 2016; Sakrikar et al., 2012; Speed et al., 2011; Wei et al., 2007). The cell specificity and complexity of DAT regulation highlight the potential perils of cursory approach when examining Tat modulation of DAT function. There are a number of studies in the field that have begun to describe the effect of HIV-1 Tat on the activity of DAT (Aksenova et al., 2006; Bucci, 2015; Ferris et al., 2009; Midde et al., 2012; Midde et al., 2013; Midde et al., 2015a; Zhu et al., 2016). While these and other recent studies suggest Tat may interact with DAT to modulate its functions, technical limitations such as the lack of available Tat specific antibodies and the large amount of Tat used in these studies limit interpretation (Midde et al., 2012; Midde et al., 2013; Midde et al., 2015a; Yuan et al., 2015a; Yuan et al., 2016; Zhu et al., 2011; Zhu et al., 2009; Zhu et al., 2015). Despite these limitations, these studies suggest the effects of HIV infection on the dopaminergic system may, at least in part, be mediated by Tat-specific changes in DAT function. (Chang et al., 2008; Maragos et al., 2003; Perry et al., 2010; Wang et al., 2004). In

order to build upon these results, future studies should focus on examining the molecular mechanisms in the biologically relevant model systems using Tat specific antibodies.

HIV-infected patients who display dementia have decreased DAT levels as compared to both controls and those with HIV who do not have dementia. Specifically, the loss of DAT molecules is most apparent in the caudate and putamen region, similar to Parkinson's disease and other frontal-striatal pathologies (Itoh et al., 2000; Wang et al., 2004). Though the loss of DAT has been implicated in HIV infection of the CNS, and the Tat protein has been shown to regulate DAT activity through decreased DAT expression, a correlation has not been fully established between the rate of HIV-mediated CNS disease progression, loss of neuronal activity and ultimately neuronal damage or death. Therefore, future studies are needed to measure decreased DAT activity at earlier stages of HIV infection using acutely infected individuals prior to the initiation of therapy, and to measure Tat production and loss of DAT at the later stages of HIV-mediated neurological disorders.

Several studies reported that Tat, in the absence of viral replication, may negatively affect dopamine transmission by targeting DAT activity, without affecting total DAT levels in striatal homogenates. In rat striatal synaptosomes, Tat reduced DAT mediated dopamine uptake without changing total DAT immunoreactivity (Aksenova et al., 2006; Wallace et al., 2006; Zhu et al., 2009), although changes in the distribution of DAT to the membrane and intracellular compartments were not examined. As functional DAT molecules are located at the plasma membrane (Bowton et al., 2010; Bowton et al., 2014; Cremona et al., 2011; Sakrikar et al., 2012), a decrease in DAT activity usually correlates with increased intracellular DAT, as internalization represents decreased activity of the transporter. However, it is possible that direct or indirect (via DAT's partner proteins) interaction between DAT and Tat reduces DAT activity by altering DAT conformation to obscure DA binding sites on DAT molecules without affecting its trafficking. Consistent with the latter hypothesis, DAT antagonists have shown to block both the activity and trafficking of the transporter. As the protein is readily detected in tissues or cell lysates, immunolabeling of membrane DAT should be used to more conclusively determine the mechanism(s) of Tat mediated changes in DAT function.

To date there is only one study that has directly examined the role of Tat in the highly regulated cellular processes controlling DAT. This study examined Tat regulation of cell surface redistribution of DAT, and indicated that Tat may induce DAT internalization via a PKC dependent mechanism (Midde et al., 2012). It is not known, however, whether Tat affects regulated DAT trafficking, i.e. amphetamine or methamphetamine regulation of DAT trafficking, or cocaine-induced increases in DAT at the plasma membrane (Daws et al., 2002). Recent studies by Blakley and colleagues have shown that PKC-regulation of the constitutive and regulated DAT trafficking is complex. Accelerated rates of constitutive endocytosis and recycling of DAT may show no change in the total or surface DAT, but significantly affect the kinetics of DAT trafficking (Mazei-Robison et al., 2008; Sakrikar et al., 2012). Given the relatively high percentage of HIV+ individuals who abuse psychostimulants (Beyrer et al., 2010; Crime, 2014; Mathers et al., 2008), it is important to determine whether and how Tat affects the kinetics of DAT at the plasma membrane following methamphetamine or cocaine exposure. For example, it has been shown that

amphetamines' regulation of DAT trafficking is two-fold; they cause DAT internalization (Guptaroy et al., 2009; Holton et al., 2005; Hong and Amara, 2013; Kahlig and Galli, 2003; Kahlig et al., 2006; Moron et al., 2003; Mortensen and Amara, 2003; Saunders et al., 2000; Wu et al., 2015) via CaMKII and PKC-dependent mechanisms as well as a DAT-dependent membrane depolarization (Boudanova et al., 2008; Hong and Amara, 2013; Mortensen et al., 2008; Navaroli et al., 2011; Richardson et al., 2016). This suggests DAT trafficks via a voltage-dependent mechanism in addition to PKC- and CaMKII-mediated DAT phosphorylation. On the contrary, cocaine has been shown to rapidly increase surface DAT level (Daws et al., 2002). Therefore, a careful examination of the Tat regulation of DAT trafficking will provide critical mechanistic information on how acute or prolonged exposure to Tat regulates dopamine neurotransmission.

Though the time-dependent and the precise level of Tat in the CNS of HIV-infected individuals are unknown, studies have shown that much higher concentrations of Tat, between 1 and 10 μM, decrease dopamine uptake through DAT (Aksenov et al., 2008; Zhu et al., 2009). But it is not clear whether Tat directly or indirectly regulates dopamine uptake by modulating the activity of other membrane proteins or intracellular targets known to modulate dopamine uptake via DAT. As an example, estrogen appears to reduce Tat enhancement of oxidative stress and protect against DAT loss (Wallace et al., 2006). This may explain why male mice exposed to Tat have more severe motor deficits and greater changes in striatal neuronal morphology as compared to their female counterparts (Hahn et al., 2015). Recent studies have generally focused on the outcome of the interaction of Tat and DAT, but the mechanism underlying this potential interaction remains unclear. Studies by Zhu et al. suggest Tat acts as an allosteric modulator of DAT, as opposed to a reuptake inhibitor or a substrate-type releaser (Zhu et al., 2011; Zhu et al., 2009).

Surface plasmon resonance analysis performed in rat striatal synaptosomes suggests Tat directly interacts with DAT in a concentration-dependent manner (Zhu et al., 2009). Additional studies from this group concluded that Tat binds to Tyr470 on the DAT, as mutation of this residue attenuated the effects of Tat on dopamine uptake in CHO cells transfected with human DAT (Midde et al., 2013). Interactions with the DAT residues Tyr88 and Lys92 have been shown to be required for Tat mediated inhibition of DAT, as mutation of these residues also altered the DAT response to Tat binding (Midde et al., 2015a; Yuan et al., 2015a). Studies by Yuan et al. (2015) suggest Tat may stabilize the inward facing conformation of DAT, which limits the availability of extracellular dopamine binding sites on the transporter molecule, thereby attenuating dopamine uptake (Midde et al., 2015a; Yuan et al., 2015a). However, it is not clear whether Tat regulation of dopamine uptake is a consequence of its binding to the external or internal domains of DAT molecules. Additionally, as the specificity of Tat/DAT interaction has not been examined, it is possible that Tat modulates DAT activity through indirect binding to different membrane proteins. Future studies in this area should address these possibilities, and also address the fact that dopamine uptake and efflux are independently regulated (Khoshbouei et al., 2004). This would enable determination of whether Tat simply increases the inward facing conformation of DAT that is expected to increase dopamine efflux, or if it acts as an antagonist to block both uptake and efflux.

Currently, there is no information about Tat regulation of DAT conductance and biophysical properties of the transporter. The molecular and biophysical mechanism by which the Tat/DAT interaction governs DAT function, the potential Tat-mediated alterations in Na^+/Cl^- coupling of DAT molecules, lipid rich versus lipid poor membrane distribution of the transporter, the kinetic of DAT trafficking, its interaction with partner proteins or its phosphorylation levels, all of which known to regulate DAT activity, are yet to be determined (Butler et al., 2016; Cervinski et al., 2010; Cremona et al., 2011; Erlendsson et al., 2014; Foster and Vaughan, 2011; Hong and Amara, 2010; Pizzo et al., 2013; Sakrikar et al., 2012; Sorkina et al., 2013). While further investigation is necessary to determine the mechanism(s)by which Tat regulates DAT activity and the firing activity of dopamine neurons, the existing literature suggest that Tat alters dopamine neurotransmission within the CNS. This is consistent with the susceptibility of HIV-1 infected patients to abuse of illicit drugs, such as cocaine and methamphetamine, that target monoaminergic systems such as midbrain dopamine neurons (Goodwin et al., 2009; Lin et al., 2016; Saha et al., 2014), and to the higher sensitivity of (GT-tg bigenic mice) mice to psychostimulants (Kesby et al., 2016a; Mediouni et al., 2015a; Paris et al., 2014a). Further developing our understanding of the precise mechanism(s) by which of Tat regulates DAT might be a key in the development of effective therapeutic approaches designed to ameliorate the damaging and disruptive effects of Tat and HIV infection on DAT activity and the dopaminergic system.

VII. Tat and Dopamine Receptors

The data described above suggest Tat is involved in at least some of the dopaminergic dysfunction described in HIV-infected individuals. While studies clearly show a link between Tat and DAT, the direct effect(s) of Tat on the dopamine receptors is unclear. Dopamine mediates its regulatory actions by means of G-protein coupled receptors (GPCR) called dopamine receptors, which can be separated into two subtypes: D1-like (D1 and D5) and D2-like (D2, D3 and D4) receptors (Figure 6). The D1-like receptors couple to $G\alpha_{s/olf}$, activating adenylyl cyclase and D2-like receptors couple to $G\alpha_{i/o}$, inhibiting it. The difference subtypes of dopamine receptors also activate a number of other distinct and overlapping signaling pathways. (Beaulieu and Gainetdinov, 2011; Missale et al., 1998).

There are few studies investigating the direct interaction of dopamine receptors and Tat. A number of studies by Booze and colleagues have found, in rat midbrain neurons, blockade of D1-like receptor by SCH23390 decreases the neurotoxic effects of Tat in the presence or absence of methamphetamine (Aksenova et al., 2006; Silvers et al., 2007). These data suggest that D1-like receptors play a role in Tat-mediated neurotoxicity, albeit with a less understood molecular mechanism. There are even fewer studies that have specifically examined the interaction of Tat with D2-like dopamine receptors, either on neurons or on cell types such as macrophages, which are infected with HIV and express D2-like receptors (Gaskill et al., 2009; Gaskill et al., 2012). In a recent study, Gaskill and colleagues proposed there might be a link between HIV entry and Ca^{2+} flux that is mediated by activation of both D1-like and D2-like receptors, but this study did not investigate the specific interaction of the Tat protein with either subtype of dopamine receptor (Gaskill et al., 2014).

This paucity of data suggests that there is a significant need for studies directly addressing the impact of Tat on dopamine receptor mediated signaling. To this end, other studies examining the impact of Tat on other drug-related GPCR, such as opioid and cannabinoid receptors, might provide a template for investigation of possible mechanisms for Tat regulation of dopamine receptors. For example, studies by Turchan-Cholewo et al. found that Tat prevented morphine-induced downregulation of opioid receptor expression on the plasma membrane of microglia and astrocytes (Turchan-Cholewo et al., 2008). A more recent study found that macrophage migration toward the Tat protein was significantly inhibited by endogenous cannabinoid agonists for the CB2 receptor (Raborn and Cabral, 2010). These reports suggest Tat could potentially influence multiple cellular processes, such as receptor expression and cell migration, potentially through interactions with GPCR. G_{α}-subtype coupled receptors are promiscuous, where the nature of host environment will determine their signaling outcomes. Thus, it is possible that Tat-GPCR interactions mediate diverse signaling cascade per the nature of host system and its level of activity. Future investigations will determine the specific molecular interaction(s) between the dopamine receptors and Tat, and the possible functional outcomes of this interaction.

VIII. Tat and Psychostimulant Abuse

Throughout the AIDS epidemic, drug abuse has been an important comorbidity in HIV infection (El-Bassel et al., 2014; Halkitis et al., 2001; Kumar et al., 2014; Vongsheree et al., 2001). Substance abuse is far more common among HIV-infected individuals than in the general population (Beyrer et al., 2010; Crime, 2014; Mathers et al., 2008), and increases the risk of acquiring HIV infection by engendering risky behaviors (El-Bassel et al., 2014; Halkitis et al., 2001; Huff, 2006), but the biological effects of drugs of abuse on HIV infection are less clear. While a number of studies have found that psychostimulant abuse accelerates the progression of HIV and related diseases, irrespective of its effects on adherence (Baum et al., 2009; Burbano et al., 2001; Kipp et al., 2011; Lucas et al., 2006; Moore et al., 2004; Webber et al., 1999), other reports contradict this finding. (Cofrancesco et al., 2008; Edelman et al., 2015; Milloy et al., 2016; Thames et al., 2016).

The effects of drugs of abuse on HIV neuropathogenesis are similarly unclear. A number of studies have found that the interaction of HIV and drug abuse accelerated neuropathology and/or neurocognitive dysfunction, compared with both non-HIV infected drug abusers (Gray et al., 1992; Makrigeorgi-Butera et al., 1996) or HIV-infected non-drug abusers (Carey et al., 2006; Kousik et al., 2012; Langford et al., 2003a; Meade et al., 2011b; Nath et al., 2002; Rippeth et al., 2004; Starace et al., 1998; Tomlinson et al., 1999). However, many of these studies examine therapy-naïve individuals, and several studies have also shown that drug abuse combined with HIV has little impact on cognition (Basso and Bornstein, 2003; Byrd et al., 2012; Byrd et al., 2011a). Therefore, the precise impact of drug abuse on the development of HIV-associated neurocognitive disorders, particularly in the era of cART remains undefined. Numerous studies have also examined specifically the effects of the Tat protein in conjunction with drugs of abuse, both as a surrogate for general HIV infection and as a stand-alone protein (Bokhari et al., 2009; Cass et al., 2003; El-Hage et al., 2008; El-Hage et al., 2005; Fitting et al., 2014; Flora et al., 2005). Much of this data is summarized in several excellent recent reviews (Fitting et al., 2015; Hauser and Knapp, 2014; Maubert et

al., 2015; Mediouni et al., 2015b), thus this section will focus on the direct impact of Tat specifically on the dopaminergic system.

In both the pre- and post-cART eras, research in infected individuals has shown high levels of HIV infection and associated neuropathology throughout the basal ganglia (Aylward et al., 1993; Becker et al., 2011; Fujimura et al., 1997; Gongvatana et al., 2013; Hestad et al., 1993; Vera et al., 2016; Wright et al., 2014; Yiannoutsos et al., 2004) where the highest density of dopaminergic terminals are located (Alexander et al., 1986; Haber, 2014; Lanciego et al., 2012). Therefore, the neurotoxic effects of psychostimulants, such as cocaine and methamphetamine, on the dopaminergic terminals are predicted to be exacerbated in during HIV infection. These drugs directly target dopamine neurons in the basal ganglia, and increase CNS dopamine by blocking dopamine reuptake (Ritz et al., 1987; Volkow et al., 1997) and inducing dopamine efflux (Branch and Beckstead, 2012; Goodwin et al., 2009; Sulzer et al., 2005).

Although the underlying mechanisms for the interaction between HIV and methamphetamine are not fully understood, methamphetamine seems to synergize with Tat to affect a number of neurocognitive processes (Mediouni et al., 2015a), including direct damage the dopaminergic system. Using proton magnetic resonance spectroscopy (^{1}H-MRS), Chang and colleagues have found additive effects of HIV and chronic methamphetamine abuse on brain metabolite abnormalities (Chang et al., 2005). In an *in vivo* rodent model, Tat and methamphetamine synergistically increase loss of striatal dopamine terminals (Cass et al., 2003; Maragos et al., 2002; Theodore et al., 2006a; Theodore et al., 2006b; Theodore et al., 2007). The cooperative effects of Tat and methamphetamine have also been shown to enhance the motor-stimulant response to a recurrent exposure to methamphetamine, a demonstration of behavioral sensitization (Liu et al., 2009). One possible mechanism by which methamphetamine could enhance the effects of Tat in humans is through an increase in extracellular dopamine by inhibition of dopamine uptake, which could increase HIV replication (Gaskill et al., 2009; Scheller et al., 2000). However, the synergy between methamphetamine and Tat seen in the studies described above cannot result from this mechanism because there is no HIV replication in rodents.

In vitro studies also show Tat and methamphetamine synergistically increase the neurotoxicity in human fetal cortical dopaminergic neurons (Maragos et al., 2002) and rodent midbrain neurons (Aksenov et al., 2012) relative to either substance alone. Similarly, in SH-SY5Y (neuroblastoma) cells, Tat and methamphetamine together induce a small but significant increase in apoptosis (Qi et al., 2011). In methamphetamine treated rats, where Tat was delivered directly to the substantia nigra, Tat potentiated methamphetamine induced dopamine deficits in the striatum and enhanced deficits in dopamine-driven behaviors such as the rotarod and open field tests (Liu et al., 2014). Rodents treated with both Tat and methamphetamine show 60% – 78% reductions in the basal ganglia dopamine levels, particularly striatal dopamine levels. These are accompanied by a severe loss of tyrosine hydroxylase (TH) immunoreactivity relative to animals treated with Tat or methamphetamine alone (Cass et al., 2003; Maragos et al., 2002; Theodore et al., 2006b). The loss of TH positive neurons in dopaminergic regions may also be the mechanism by

which Tat exaggerates methamphetamine-mediated disruption of pre-pulse inhibition (Moran et al., 2012).

Notably, serotonin levels in the CNS of these animals are unaffected (Maragos et al., 2002), suggesting that the interaction of Tat and methamphetamine uniquely impacts the dopaminergic system. Similar data are found in human HIV-infected methamphetamine abusers, who are at increased risk for basal ganglia dysfunction (Chang et al., 2005; Taylor et al., 2007) and show decreased levels of the brain metabolite *N*-acetylaspartate (NAA), a marker correlated with dementia and other neuropathological disorders (Ben Salem et al., 2003; Enzinger et al., 2004; Griffith et al., 2008).

Cocaine has also been shown to increase viral replication in macrophages (Swepson et al., 2016), as well as Tat-induced oxidative stress and neurotoxicity in rat hippocampal neurons (Aksenov et al., 2006). In mice treated with Tat, cocaine has been shown to induce a hyperdopaminergic tone suggesting a profound dysregulation of dopamine transmission in these animals (Ferris et al., 2010). These data suggest cocaine and methamphetamine may potentiate Tat-induced damage to dopaminergic terminals. Changes in the dopamine-regulated behavioral responses in rodents exposed to Tat and cocaine support this conclusion. Rats injected with Tat and treated with cocaine show a significant elevation in cocaine-induced locomotor behavior relative to control (Harrod et al., 2008). Expression of Tat in the CNS of animals treated with cocaine results in increased conditioned place preference to cocaine (Paris et al., 2014a), increased sensitivity to the reinforcing effects of cocaine and an increased abundance of low-affinity DAT binding sites in animals receiving chronic cocaine (McIntosh et al., 2015). Because HIV does not infect neurons directly, nor do rodent models involve HIV replication, it is not yet clear how well these data model the impact of Tat on the human dopaminergic system during HIV infection. However, there are a number of similarities between the neurobiological and behavioral effects seen in rodents and humans. Taken together with the data discussed in earlier sections, these data suggest the direct effects of Tat on the dopaminergic system could be amplified by the concurrent use of psychostimulants, resulting in a much broader impact on dopamine system that is induced by either Tat or drugs of abuse alone.

IX. Tat and Other Substances of Abuse

Unlike psychostimulants, other drugs of abuse such as opioids, as well as a number of legal abused substances, such as cannabinoids, nicotine and alcohol indirectly act on the dopaminergic system. Opioids, cannabinoids and nicotine act primarily through their cognate receptors (Dani et al., 2011; Iversen, 2003; Pathan and Williams, 2012), while alcohol has effects on multiple receptor systems including GABA, opioid and cannabinoid receptors (Cruz et al., 2008; Cui et al., 2013). While the use of these drugs does not directly increase CNS dopamine, they do increase extracellular dopamine concentrations through activation of the mesolimbic dopaminergic system, with the precise mechanism and release pattern varying with the substance used (Dani et al., 2011; Di Chiara, 1995; Fadda et al., 2005; Nestler, 2005; Vander Weele et al., 2014; Yorgason et al., 2014).

The neuropathological interactions of Tat with different drugs of abuse have been studied extensively, particularly in conjunction with opioids, but relatively little research has examined the direct effects of Tat and non-psychostimulant drugs on dopaminergic neurotransmission. Studies show that Tat in conjunction with morphine induces large reductions in dendritic spine density within the striatum (Fitting et al., 2010). This brain region has the highest number of DAT-positive terminals, and damage to this region may enhance LTD (Monfils and Teskey, 2004; Nagerl et al., 2004; Zhou et al., 2004). Further, dendritic spines aid in neurotransmission and plasticity (Chen et al., 2014), and alterations in dendritic spines in dopaminergic regions could accelerate the development of dopaminergic dysfunction in HAND. Indeed, both postmortem and fMRI studies of patients with HIV-1 have revealed extensive white matter and cortical damage along with large losses in neocortical dendrites (Archibald et al., 2004; Masliah et al., 1992). Additionally, increases in neuronal intracellular of Ca^{2+} induced by Tat and opioids in astrocytes and neurons (Haughey et al., 1999) could disrupt alternative dopamine receptor signaling through the PLC / $G_{\alpha q}$ pathway (Beaulieu and Gainetdinov, 2011; Bergson et al., 2003), as well as damage to dopaminergic neurons (Fitting et al., 2014).

In addition to opioids, a few studies also suggest that the substances nicotine, cannabinoids and ethanol may also synergize with Tat to impact the dopaminergic system. In rats, injection of Tat into the VTA alters nicotine-induced locomotor activity as well as cAMP and ERK1/2 signaling (Zhu et al., 2015). As nicotine can modulate dopamine release through nicotinic acetylcholine receptors expressed on dopaminergic neurons in the VTA (Zoli et al., 2002), these data suggest Tat may modulate the impact of nicotine on dopaminergic neurons in this region. Research on the synergistic effects of cannabinoids and Tat have shown that the injection of Tat into the pre-frontal cortex of rats induced a decrease in GABAergic neurotransmission, which could be blocked with a CB1R antagonist (Xu et al., 2016). Hyperpolarization of GABAergic neurons can result in excitation of dopaminergic neurons through disinhibition mechanism (Johnson et al., 1992). Therefore, these effects could also increase dopamine concentrations in the pre-frontal cortex. Moreover, in Gt-tg bigenic mice, there is a 3-fold increase in ethanol-induced conditioned place preference (McLaughlin et al., 2014), suggesting that Tat potentiates the rewarding effects of alcohol. The biological relevance of these effects is not clear; future research will reveal whether Tat directly or indirectly alters dopaminergic neurotransmission and behavioral sequelae. Nevertheless, together with the findings detailed in the previous section, these data suggest Tat could have a significant impact on the dopaminergic system in the CNS of drug abusers, albeit with less understood mechanism. Further studies specifically evaluating the impact of Tat on the dopaminergic effects induced by different types of drugs of abuse are needed to help develop drug-type specific therapies for HIV-infected substance abusers using those substances.

X. Concluding remarks

This review has examined recent investigations into the interactions between the Tat protein and dopaminergic neurotransmission. The studies described herein provide a large amount of information regarding the impact of HIV, and the Tat protein, on the brain, specifically regarding neurotransmission. Although we have seen correlations between HIV infection

and dopaminergic dysfunction for more than 20 years, understanding the causal mechanism(s) requires further investigation. The majority of the existing studies have examined the effects of Tat in the context of individual brain structures or heterologous systems *in vitro,* resulting in a great deal of information about the neurotoxic and immunomodulatory effects of Tat. Over the past decade there have also been a small but growing number of studies examining the effects of HIV and Tat on dopaminergic system proteins, using both *in vitro* systems and rodent models, and this is the area of research that has been and needs to continue to grow. However, as noted above, while data from model systems and *in vitro* studies are valuable, they come with significant caveats, and further efforts should be made to better correlate these research modalities with the hallmarks of HIV neuropathogenesis in the human brain.

Future studies warrant development of more sophisticated and relevant animal models that accommodate the current problems and lack of information regarding the expression, localization and concentration of Tat in the CNS. Animal models must also carefully account for the significant species specific differences between primate and rodent dopaminergic systems (Garcia-Cabezas et al., 2009; Garrick and Murphy, 1980; Raghanti et al., 2009). Additional investigation is needed to elucidate the possible differences in the mechanism(s) by which Tat alters neuronal circuits and affects communication in distinct brain regions. For instance, it is not clear if the untoward effects of Tat are similar between the dopamine neurons in the ventral tegmental area involved in motivated behavior and the more sensitive dopamine neurons in the substantia nigra involved in movement disorder, or if other regional differences exist. Technological advances in imaging and electrophysiology, as well as the development of more sophisticated rodent models, can further reveal how synaptic connectivity is altered in response to HIV-1 Tat.

Improving our understanding of the effect of HIV on dopamine transmission is of specific importance, because a substantial percentage of the HIV-infected population abuse illicit drugs that directly or indirectly target the dopamine system. Further, significant numbers of HIV infected individuals suffer from psychiatric disorders, such as major depressive disorder or generalized anxiety disorder (Brandt, 2009; Jallow et al., 2017; Nanni et al., 2015; Salters et al., 2016). HIV induced changes in dopaminergic neurotransmission could worsen the impact of drugs of abuse, or hinder the effectiveness of different treatments for mental illness. Overall, a better understanding of the mechanism(s) by which Tat interactions with and disrupts the dopaminergic system will provide better avenues for treatment of HIV-associated neurocognitive disorders, and perhaps a greater understanding of the overall mechanism of HIV neuropathogenesis.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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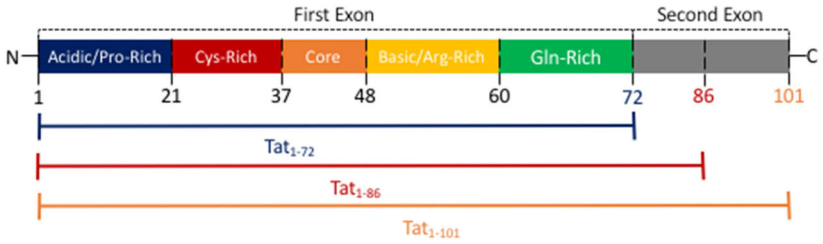

Figure 1. Illustration of the different regions of the HIV-1 Tat protein

The first exon of the HIV-1 Tat protein, which can be found is all three forms of the protein (e.g., Tat_{1-72}, Tat_{1-86}, and Tat_{1-101}), is composed of five distinct regions: an acidic or proline (Pro)-rich domain (the N-terminal), a cysteine (Cys)-rich domain, a core domain, a basic or arginine (Arg)-rich domain, and a glutamine (Gln)-rich domain (the C-terminal). The second exon of the HIV-1 Tat protein, which spans from amino acid residues 73–101, comprises the integrin binding modality and can be found in two forms of the protein (e.g., Tat_{1-86} and Tat_{1-101}). Note that the letters N and C represent the N-terminal and C-terminal of the protein, respectively.

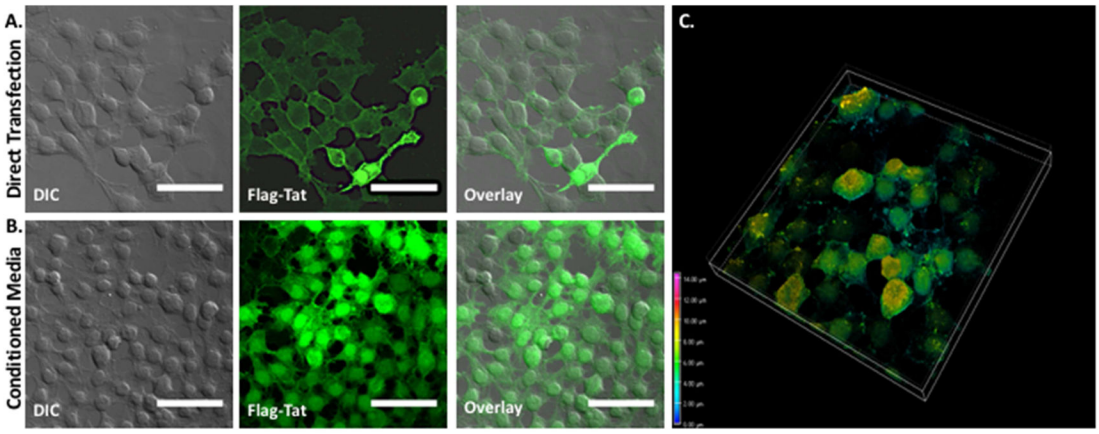

Figure 2. HIV-1 Flag-Tat$_{1\text{-}101}$ Uptake In HEK cells

A. HEK cells were transfected with 1 ng of a plasmid containing the HIV-1 FLAG-Tat$_{101}$ gene (pcDNA3.1+/Tat$_{101}$-flag(PEV280), NIH AIDS Reagent Cat. No. 10453), immunostained with the monoclonal ANTI-FLAG® M2 primary antibody (Sigma-Aldrich, St. Louis, MO, USA) and secondary antibody conjugated to Alexa 488, and imaged 72 hours post-transfection on a Nikon Multiphoton/Super Resolution Imaging System (Nikon A1RMPsi-STORM 4.0, 20X Magnification). N = 5 independent experiments. B. A separate set of HEK cells was incubated with conditioned media containing the HIV-1 Flag-Tat protein for 48 hours, immunostained as above, and imaged (20X Magnification). Flag-Tat is detected in virtually all cells under this experimental configuration. As shown in the image, almost all cells express Flag-Tat. N = 6 independent experiments. Scale bar = 50 μm. C. Depth-coded 3D Z-stack of HEK cells from panel B.

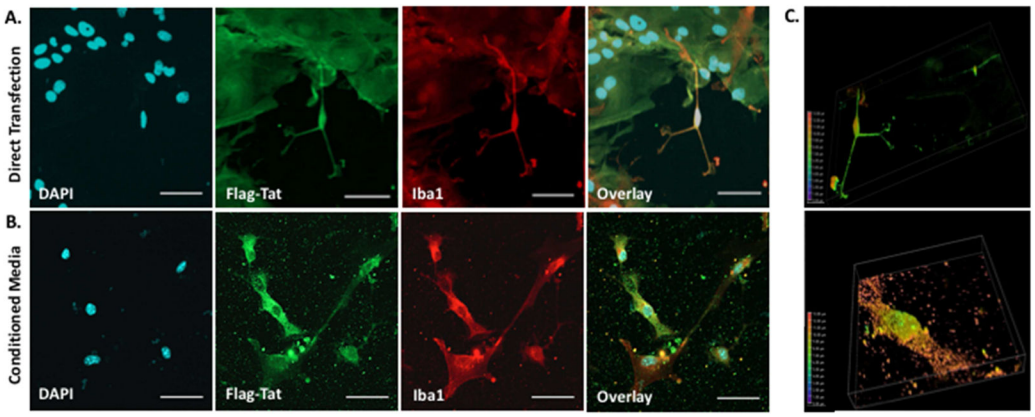

Figure 3. HIV Flag-Tat$_{101}$ Uptake in Midbrain Microglia

A. Mouse midbrain microglia in a mixed glia culture at postnatal day 2 were transfected with 1 μg of a plasmid containing the HIV-1 Flag-Tat$_{101}$ gene (pcDNA3.1+/Tat$_{101}$-flag(PEV280)), immunostained with the monoclonal ANTI-FLAG® M2 primary antibody (Sigma-Aldrich, St. Louis, MO, USA), polyclonal Iba1 primary antibody (Wako Pure Chemical Industries, Ltd., Richmond, VA, USA), and secondary antibody conjugated to Alexa 488 (Green) or 647 (Red), mounted with DAPI (Blue) Fluoromount-G (SouthernBiotech, Birmingham, AL, USA), and imaged 24 hours post-transfection on a Nikon Imaging System (Nikon A1RMPsi-STORM 4.0, 20X Magnification). N = 6 independent experiments (midbrain of 3–5 mice used for each experiment). **B.** Another set of mouse midbrain microglia in a mixed glia culture at postnatal day 2 was incubated with conditioned media containing the HIV-1 Flag-Tat protein, immunostained as described above, and imaged 24 hours later (20X Magnification). N = 5 independent experiments (midbrain of 3–5 mice used for each experiment). **C.** Images represent a depth coded 3D Z-stack of one microglia cell from the 60X magnified image in panel A (*top*) and panel B (*bottom*). Scale bar = 50 μm in 20X images and 25 μm in 60X images.

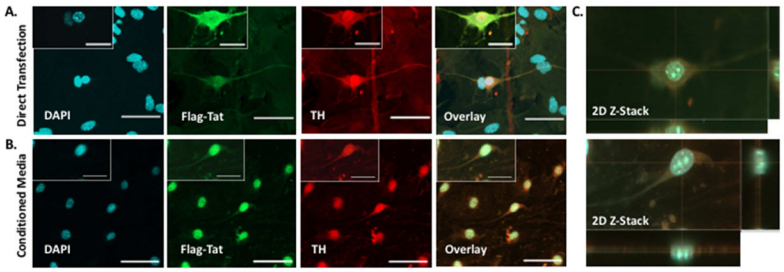

Figure 4. HIV Flag-Tat$_{101}$ Uptake in Midbrain Dopaminergic Neurons

A. Midbrain neuronal cultures were obtained from a mouse strain that contained the *TH*::RFP transgene, which labels neurons with the red fluorescent protein driven by the tyrosine hydroxylase (TH) promoter. The TH:RFP transgene was constructed by ligating a 4.5kb *Hind*III/*Eco*RI fragment of the rat tyrosine hydroxylase promoter with DsRed2-1 (Clontech, Palo Alto, CA, USA). Dopaminergic neurons (Red) at postnatal day 2 were grown on a monolayer of glia and transfected with 1 μg of a plasmid containing the HIV-1 Flag-Tat$_{101}$ gene (pcDNA3.1+/Tat$_{101}$-flag(PEV280)). The neurons were immunostained with the monoclonal ANTI-FLAG® M2 primary antibody (Sigma-Aldrich, St. Louis, MO, USA) and secondary antibody conjugated to Alexa 488 (Green), mounted with DAPI (Blue) Fluoromount-G (SouthernBiotech, Birmingham, AL, USA), and imaged 24 hours post-transfection (20X magnification and 60X magnification of one dopaminergic neuron from 20X image in corner). N = 6 independent experiments (midbrain of 3–5 mice used for each experiment). B. Another set of mouse midbrain neuronal cultures at postnatal day 2 was incubated with conditioned media containing the HIV-1 Flag-Tat protein, immunostained as previously described, and imaged 24 hours later (20X Magnification (large box) and 60X Magnification (small box in the corner of 20X image). N = 5 independent experiments (midbrain of 3–5 mice used for each experiment). C. Images represent an orthogonal XY, XZ, and YZ projection of a Z-stack of one neuron from the 60X magnified image in panel A (*top*) and panel B (*bottom*). Scale bar = 50 μm in 20X images and 25 μm in 60X images.

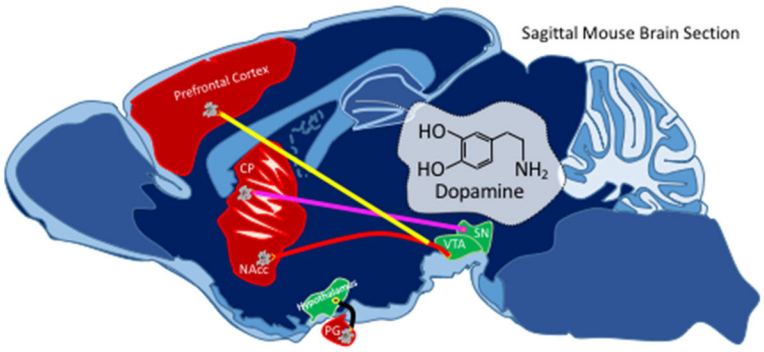

Figure 5. Diagram of the Dopamine Pathways in the Brain

In both animals and humans, the neurotransmitter, dopamine, is transmitted from neurons in the substantia nigra (SN) pars compacta to cells in the caudate putamen (CP) through the nigrostriatal pathway (pink). Dopamine can also be transmitted from neurons in the ventral tegmental area (VTA) to cells in the nucleus accumbens (NAcc) through the mesolimbic pathway (red), from neurons in the VTA to cells in the prefrontal cortex through the mesocortical pathway (yellow), and from neurons in the infundibular nucleus of the hypothalamus to cells in the pituitary gland (PG) through the tuberoinfundibular pathway (orange).

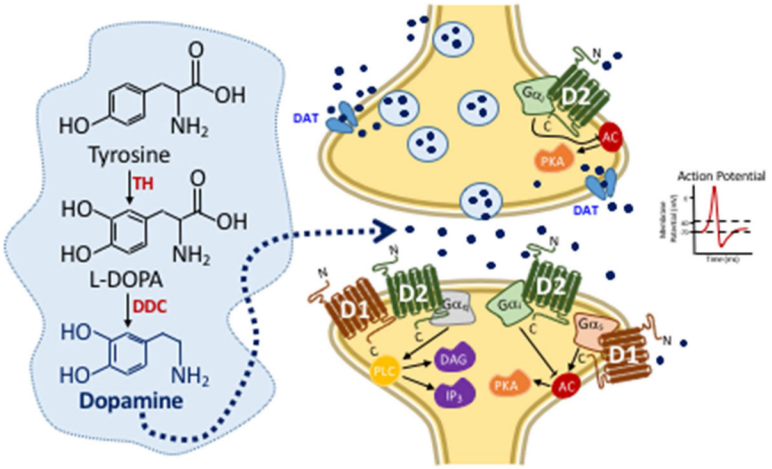

Figure 6. Illustration of Dopamine Neurotransmission

In neurons, the amino acid, tyrosine, is converted to dopamine by two enzymatic reactions. First tyrosine is converted into L-dihydroxyphenylalanine (L-DOPA) by the rate-limiting enzyme, tyrosine hydroxylase (TH), which is then converted into dopamine by the enzyme, DOPA decarboxylase (DDC). Dopamine can be released by neurons into the synaptic cleft via two distinct mechanisms, which are labeled 1 and 2. First, after an action potential has been generated (1) or through the dopamine transporter (DAT) via efflux mechanism (2). Upon release of dopamine into the synaptic cleft, dopamine can bind to G protein-coupled dopamine D_1-like or D_2-like receptors to regulate downstream signaling mechanisms involving protein kinase A (PKA), diacylglycerol, or inositol triphosphate (IP_3). $G\alpha_{i/s}$, the alpha subunit of the stimulatory (s) or inhibitory (i) G protein. PLC, phospholipase C. AC, adenylyl cyclase.

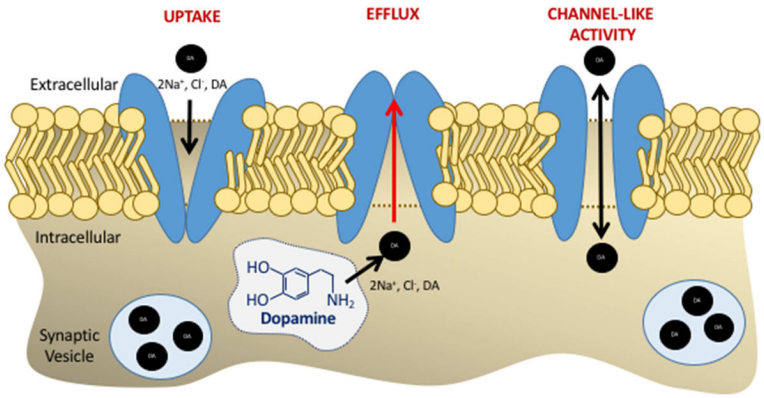

Figure 7. Dopamine Transporter has three distinct modes of activity in dopamine neurons

Independent of dopamine neuron firing, the dopamine transporter, DAT, an integral membrane protein, transports the neurotransmitter, dopamine (DA), along with two sodium ions (Na^+) and one chloride ion (Cl^-) across the plasma membrane by three mechanisms: (1) uptake which involves a conformational change in DAT that is induced by the sequential binding of the ions and dopamine to the transporter and the subsequent release of the ions and dopamine into the cytosol (2) reverse transport or efflux mechanism which involves reverse transport of cytosolic dopamine to the extracellular space. The reverse transport of dopamine via DAT occurs via multiple mechanisms. These include but not limited to, conditions when the transporter is in an inward facing conformation, as occurs following exposure to psychostimulants such as amphetamine, when there is excess intra-neuronal DA, or when there is phosphorylation of the N-terminal domain of DAT. The third mechanism is a channel-like mechanism (3) where dopamine is transported via the DAT across its electrochemical gradient.

Table 1

Tat Models Referenced in Review

First Author	Year	Model System	Experimental Details	Methods	Key Results
Kao	1987	Cell Line	COS-7 African green monkey kidney cells exposed to Tat. Amount or variant of Tat not stated.	Radiolabelling, nuclear run-on transcription analysis, Rnase protection assay	Tat enables full-length HIV to be transcribed by circumventing a block to elongation present in the TAR RNA sequence.
Green	1989	Cell Line	HeLa cells exposed to 100 nM Tat 1-86	In situ hybridization, radiolabelling,	The transactivation function of Tat resides in the cysteine-rich, core and basic domains of the Tat peptide
Ensoli *	1990	Cell Line	KS Kaposi Sarcoma (KS) primary cell culture, human umbilical vein endotheial (H-UVE), and human newborn aortic smooth muscle (H-ASM) cells exposed to conditioned media from COS-1 and H9 HIV-1 infected T-cells. Tat variant not stated.	Cell counting, DNA radiolabelling	Tat is produced and released by cells infected or transfected with HIV
Feinberg	1991	Cell Line	CEM, H938 cells treated with 10 ug/ml Tat 1-72	RNA radiolabelling, Northern blotting	Tat acts early in the viral replication cycle, increasing the efficiency of transcriptional elongation to induce large increases in viral replication
Mann	1991	Cell Line	HL3T1, H938, U38 cells exposed to TRITC conjugated or iodine-125 labeled Tat 1-86 or 1-72 1 ug	Radiolabeled Tat uptake, transactivation assay	Tat binds non-specifically to the plasma membrane and can be taken up by bound cells
Ensoli **	1993	Cell Line	H9, Jurkat, COS-1, HeLA-CD4+, KS cells exposed to Tat derived from COS-1 cells transfected with plasmid containing Tat or from E. Coli purified by HPLC and serially diluted from 10 to 0.01 ug/ml. Tat variant not stated	Immunoblotting, radioimmunoprecipitation, immunocytochemistry, cell counting, DNA radiolabelling	Tat is released extracellularly and in this form Tat can be taken up into the nucleus of infected cells where it can stimulate viral gene expression
Hofman	1994	Primary Human Cell Culture	CNS-derived endothelial cell culture, HUVE cell culture treated with 100 ng/ml of Tat. Tat variant not stated.	Trypan blue, ICC, IHC	Treatment with extracellular Tat can stimulate cytokine production in human endothelial cells
Westendorp **	1995	In vitro cell culture	Jurkat, S13, ATC cells exposed to 1 ng/mL to 10 ug/mL Tat. Tat variant not stated.	Propium iodide uptake, DNA fragmentation, northern blotting, immunoblotting	HIV Tat accelerates CD95 mediated T-cell apoptosis. Notably, sera from HIV-infected individuals and supernatant from infected cells were shown to contain 0.1 – 1 nM extracellular Tat

First Author	Year	Model System	Experimental Details	Methods	Key Results
Chang **	1997	Cell Line	COS-1 fibroblast-like cells expressing Tat 1-86	Trypan blue dye exlcusion, pulse-chase, autoradiogram, SDS-PAGE	Tat protein is released from transfected cells expressing this protein in the absence of cell death or changes in membrane permeability.
Ma *	1997	Primary Human Cell Culture	Human fetal astrocytes, neuroblastoma cells, human fetal neruons, HL3t1 cells exposed to iodine-125 labeled Tat 1-86 or 1-72 (10 nM)	Radiolabeled Tat uptake, transactivation assay	Tat is taken up by human neurons and astrocytes. Uptake of Tat may be charge dependent and region of Tat comprising amino acids 73 – 86 is important to the uptake process.
Albini	1998	Cell Line	T53 adenocarcinoma cell line, PC12 pheochromocytom a cell line, human peripheral monocytes exposed to Tat 1-86 (1 nM–100 nM)	Immunoblotting, chemotaxis microchamber, radiometric ligand-binding	Tat modulates monocyte chemotaxis through the cysteine-rich and core regions. Notably cells from a Tat-transgenic mouse were found to excrete 4.4 nM Tat into supernatant over 24 hr
Bonwetsch **	1999	Human Tissue	HIV-positive human tissue.	Hematoxylin and eosin staining, IHC	In the brains of HIV-infected individuals with encephilitis, Tat can be seen within astrocytes and microglia
Haughey	1999	Primary Human Cell Culture	Primary human neuronal culture exposed to 100 nM to 100 uM (4 fmol to 4 pmol total) of Tat 1-72	Fura-2/AM, trypan blue, IHC, radiolabelling	Tat mediated changes in calcium release are important to Tat-induced neurotoxicity
Nath	1999	(1) Primary Human Cell Culture (2) Cell Line	Peripheral blood monocytes, human fetal astrocytic culture, U373, THP-1 cells exposed to 100ng/ml Tat 1-72	ELISA, reverse-transcriptase PCR, Southern blotting,	Tat treatment of monocytes and astrocytes can modulate inflammatory cytokine production
Bansal	2000	Rat injected with Tat	3-4 month old sprague dawley rats injected with Tat 1-72 (1-50 mM, 1 to 50 ug) into dorsal striatum	IHC, Nissl staining	Striatal Tat injections of 5 ug/ul or higher produce significant loss of tissue with significantly increased GFAP+ cells. Combined injections of Tat with gp120 further increased this effect.
Zauli	2000	(1) Cell Line (2) Rat Injected with Tat	PC12 cells transfected with plasmid containing Tat, Wistar rats injected with 10–100 ng/ml (1-10 nM) Tat into striatum or substantia nigra	Immunoblotting, ICC, ELISA, northern blotting, trypan blue, IHC	Extracellular Tat inhibits the expression of tyrosine hydroxylase in rat neuronal cells and a loss of TH+ neurons in the substantia nigra of rats
Maragos *	2002	(1) Primary Rodent Cell Culture (2) Rat Injected with Tat	Hippocampal slice culture exposed to 100 nM Tat 1-72, injection of 5 ug of Tat 1-72 into hippocampus	IHC, cresyl violet	Methamphetamine and Tat act synergistically to significantly and specifically decrease striatal dopamine

First Author	Year	Model System	Experimental Details	Methods	Key Results
Aksenov	2003	Rat injected with Tat	3-4 month old sprague dawley rats injected with 50 ug Tat 1-72 into dorsal striatum	IHC, fluoro-jade staining	Tat treatment of the striatum leads to rapid and progressive neurodegeneration which may be linked to oxidative stress
Bruce-Keller	2003	Rat injected with cell line containing Tat	1 ul of 7.5x10^4 C6 rat glioma cells transfected with plamsid containing Tat 1-86 injected into neostriatum or hilar area of dentate gyrus	Rotorod, Nissl staining, IHC	In rat brains infused with Tat producing cells, Tat was seen to move between adjacent neuronal populations along anatomical pathways
Cass	2003	Rat injected with Tat	Male Fischer-344 rats injected with 10-25 ug Tat 1-72	In-vivo microdialysis, HPLC	Tat alone does not significantly alter striatal dopamine, but with methamphetamine it synergistically induces reductions in striatal dopamine
Eugenin	2003	In vitro cuture of primary human cells	Human primary cortical neural and astrocytic culture exposed to 10 ng/ml of Tat 1-72.	Immunocytochemistry, TUNEL, immunoblotting	Tat increases glutamate and NMDAR1 expression in cultures of human neurons and astrocytes, inducing apopotosis that can be inhibited by CCL2
Feligioni	2003	In vitro primary culture of human cells	Synaptosomal preparations from human or rat frontal or temporal tissue exposed to 0.1, 0.3, 1, or 3 nM of Tat 1-72	Neurotransmitter radiolabelling	Tat ellicits calcium-dependent achetylcholine released via an intraterminal mechanism
Kim *	2003	Transgenic Mouse	Transgenic mice tetracycline conditional Tat 1-86 expression (dox 6 mg/ml in drinking water for 7 days)	reverse transcriptase-PCR, IHC, cell countaing, ELISA, TUNEL	Generation of first transgenic mice expressing Tat 1-86
Maragos	2003	Rat injected with Tat	Sprague-Dawley rats striatally injected 20 ug Tat 1-72, primary human neuronal culture exposed to 80 nM Tat 1-72	Core body temperature, HPLC, trypan blue, JC-1, radiolabelled binding	Found a unique pattern of Tat-induced hippocampal injury. Simialr pattern of hippocampaldamaged was found in HIV-positve human samples.
Behnisch	2004	Primary Rodent Cell Culture	Organotypic hippocampal slices 25-30 day old male Wistar rats exposed to 100 nM Tat 1-86	Electrophysiology (field potential)	LTP induction was reduced in organotypic hippocampal slices following Tat exposure.
Campbell	2004	Cell Line	Jurkat T-cell exposed to 50 or 100 nM Tat (1-86 synthesized from two subtype D patients)	Immunoblotting, real-time PCR, flow cytometry, circular dichroism	Different subtypes of Tat can have distinct effects on the same function
Li	2004	(1) Primary Rodent Cell Culture (2) Rat Injected with Tat	C57BL/6 mice stereotaxically injected into right ventrical with 200 uM Tat 1-86 (Cy3 conjugated), hippocampal slice incubated with 1uM Tat 1-86 (FITC conjugated), primary neuronal culture from C57BL/6 mice exposed to Tat (Variant and amount not stated)	Radial maze, electrophysiology (patch clamp, LFP), cresyl violet, fura-2 AM	Tat decreased hippocampal LTP and spatial memory

First Author	Year	Model System	Experimental Details	Methods	Key Results
Campbell	2005	(1) Primary Human Cell Culture (2) Cell Line	HeLa P4, human CD4+ cells purified from blood, Jurkat clone I9.2 cells exposed to Tat 1-86 ot Tat 1-101 (50nM-2uM)	Mass spectrometry (MALDI-TOF), B-galactosidase enzyme-linked immunosorbent assay, immunoblotting, IETD-FMK, FITC-LEHD-FMK, real-time PCR	Tat upragulates CD178 to induce apoptosis. Tat-induced apoptisis in T-cells is dependent on Tat c-terminus.
El-Hage	2005	Primary Rodent Cell Culture	Primary striatal astrocyte cultures exposed to 100 nM Tat 1-72	Fura-2/AM, TranSignal Cytokine Antibody Array, reverse-transcriptase PCR	Opioids and Tat synegistically increase Cymokines release
Aksenov *	2006	Primary Rodent Cell Culture	Primary hippocampal cell culture from 18 day old Sprague Dawley rats treated with Tat 1-72 (10–250nM)	ICC, calcein AM	Blockade of D1 receptors decreased cocaine-mediated potntialtion of Tat-induced toxicity
Aksenova	2006	Primary Rodent Cell Culture	Primary midbrain cell culture from 18 day old Sprague Dawley rats treated with Tat 1-72 (50nM)	Calcein AM, radiometric ligand-binding	Tat-mediated toxicity in primary cullture associate with decreased DAT binding to its tritiated ligand, WIN35428
Fitting	2006	Rat injected with Tat	Sprague-Dawley rats bilaterally injected with 50 μg of Tat	Behavior analysis, IHC	Hippocampal Tat induced neuronal damage and a lesion in the dentate gyrus, causing interference with sensorimotor gating ability
Theodore	2006a	Rats and Mice Injected with Tat	Sprague-Dawley rats, C57BL/6 mice, MCP-KO mice intrastriatal injected with 20 ug Tat 1-72	Dot blot, HPLC, immunoblotting	Tat and methapmphetamine synergistic increase toxicity to the striatal dopamine neurons. Tat and methamphetamine synergistically increase the levels of some (but not all) of the cytokines in this brain region.
Theodore	2006b	Rat injected with Tat	Sprague-Dawley rats striatally injected 20 ug Tat 1-72	HPLC, silver staining, IHC, immunoblotting, dot blot	Tat and methapmphetamine decrease TH immunoreactivity in the striatum, but not in the substantia nigra.
Wallace	2006	(1) Cell Line (2) Primary Rodent Cell Culture	SK-N-SH cells, striatal synaptosomes from Sprague-Dawley rats exposed to 10–250 nM Tat 1-72	DCFH, radiolabeled uptake	Estreogen attaneuates Tat-indcued oxidative stress an prevents loss of dopamine transporter fucntion.
Eugenin *	2007	Primary Human Cell Culture	Human primary cortical neural and astrocytic culture exposed to 10 ng/ml of Tat 1-72.	TUNEL, immunocytochemistry, co-immunoprecipitation/blotting , nitrate/nitrite assay kit	Defines complex mechanism (formation of PSD95-NMDAR-nNOS complex) by which Tat promotes apoptosis in neurons and astrocytes
Silvers	2007	Primary Rodent Cell Culture	Primary hippocampal or midbrain neuronal culture from Sprague-Dawley rats exposed to Tat 1-72 50 nM	Calcein/Ethidium bromide Live/Dead ratio, ICC, Hoechst staining, radiolabeled binding, immunoblotting,	D1 receptor blockade attenuates Tat induced cells death in the primary midbrain neuronal culture, but not in the primary hippocampal culture

First Author	Year	Model System	Experimental Details	Methods	Key Results
Aksenov	2008	Primary Rodent Cell Culture	Primary hippocampal cell culture from 18 day old Sprague Dawley rats treated with Tat 1-72 (10–250nM)	ICC, calcein AM, radiometric ligand-binding	Validated the importance of dopamine transporter and pscyhostimualnts in Tat toxixicty.
El-Hage	2008	Primary Rodent Cell Culture	Primary striatal astrocyte cultures exposed to 100 nM Tat 1-72	TranSignal Protein/DNA array, real-time PCR, electrophoretic mobility shift assay, immunoblotting, immunocytochemistry, ELISA, Bio-Plex Kinas Assay	Morphine increases Tat-induced cytokine production in primary astrocytes culture via calcium and NF-kB mechanisms
Harrod	2008	Rat injected with Tat	Injection of 15 ug/ul Tat 1-72 into nucleus accumbens core of ovariectomized female Sprague-Dawley rats	Locomotor activity	Bilateral microinjection of Tat into the nucleous accombense acultey enhanced cocaine-induced total activity, but attenuated the cocaine-induced locomotor sensitiozation following repeated IV cocaine.
Mishra	2008	Primary Human Cell Culture	Human CNS progenitor derived astrocytes and neurons exposed to Tat (B and C strains) 10, 25, 50, 100ng/ml	ELISA, TUNEL, MTT assay, JC-1, DCFDA, immunoblotting,	Clade-sepcificificity determines Tat-induced apoptosis. C-Tat is less neurotoxic than B-Tat, potentially due to dicysteine motif of the protein.
Turchan-Cholewo	2008	(1) Cell Line (2) Primary Rodent Cell Culture	N9 microglial cells, primary microglia and astrocytes from Sprague-Dawley rats exposed to 50 nM Tat 1-72	ICC, quantitative real time PCR, DAPI	Tat increases morphine-induced receptor (M, K, D) trafficking, and reduces stuface membrane levels of these receptors.
Aksenova	2009	Primary Rodent Cell Culture	Primary midbrain cell culture from 18 day old Sprague Dawley rats treated with Tat 1-86 (50nM)	Calcein AM, ELISA, immunoblotting, fluorochrome inhibitor of caspases (FLICA) caspase 9, Poly-Caspase apoptosis detection kit, ICC,	Tat toxicity is time dependent, and lower NR2A expression represents a potential mechansim for decreased Tat toxicity in primary neuronal culture.
Bokhari	2009	(1) Cell Line (2) Primary Rodent Cell Culture	Primary murine microglial-enriched cultures from 1 to 2 day old C57BL/6 mice, BV-2 immortal microglial cell line exposed to 20nM Tat 1-72	Flow cytometry, ICC, reverese transcription, real-time PCR, immunology bead-based multiplex	Morphine enhances Tat-induced microglial activation as measured by increased CD11b protein expression and mRNA levels of iNOS, TNFa, IL6.
Ferris	2009	Rat injected with Tat	Male Sprague-Dawley rats administerd Tat 1-86 via intraccumbal infusion	No-net-flux microdialysis, HPLC	The microdialysis data suggest Tat-induced dyregualtion of dopamine transporter activity preceeds nerve terminal dysfunction.
Zhu **	2009	Primary Rodent Cell Culture	N2A cells and striatal synaptosomes from Sprague-Dawley rats exposed to 0.1 nM to 10 uM Tat 1-86	Radiolabeled uptake, radiolabeled binding, immunoblotting, surface plasmon resonance	Tat decreases DAT-mediated dopamine uptake. Tat interacts with the dopamine transporter.
Ferris	2010	Rat injected with Tat	Male Sprague-Dawley rats administerd Tat 1-86 via intraccumbal infusion	Locomotor activity, microdialysis, HPLC	Using an animal model of cociane exposure, it was found that Tat induces a hypodopaminergic state and

First Author	Year	Model System	Experimental Details	Methods	Key Results
					decresases behavioral sensitization to cocaine.
Fitting	2010	Transgenic Mouse (GT-gt bigenic)	Transgenic mice conditional Tat 1-86 expressed in GFAP positive cells in the presence of a tetracycline (dox 6 mg/kg chow 2, 7, or 10 days)	ELISA, quantitative real-time PCR, immunoblotting, IHC, Golgi-Kopsch	Tat decreaes spine density, and dendritic morphology in the striatum, cortex, hippocampus of low and high expressing Tat mice. Morphine increased these effects of Tat via M, K, D receptors and enkephalinergic signaling mechanisms.
King	2010	Primary Human Cell Culture, cortex and hippocampal tissue obtaiend form HIV infected	Primary human neuronal culture exposed to 10 to 300 ng/ml (1.2 to 35.6 nM) of Tat 1-72	Coimmunoprecipitation, immunoblotting, in vitro kinase phosphorylation, ICC, IHC	There is an increased phosphoryalton of NR2A in the cortext and hippocampal tissue obtaiend form HIV infected human samples as well as in the primary human cortical neurons
Musante	2010	(1) Primary Human Cell Culture (2) Primary Rodent Cell Culture	Synaptosomes from human cerebral cortex, synaptosomes or slices from male Swiss mice, mGlu1R KO mice, mGlu5R KO mice exposed to 0.1, 0.3, 1, 3 nM Tat 1-86	Immunoprecipitation, immunoblotting, radiolabeled neurotransmitter release,	Tat increaes glutamate and decreases GABA release from human and mouse cortical primary culture
Perry	2010	Primary Rodent Cell Culture,	Primary midbrain neuronal culture from Spague-Dawley rats and PC12 cells exposed to Tat 1-72 120nM, Transgenic mice tetracycline condition Tat 1-86 (8-mg/kg/day for 7 days)	Radiolabeled uptake, fluorescent uptake, immunoblotting, ICC, fluorescent reporter labeling	Tat activate calpain proteases to increase cell sruface dopamine transporter levels in two model system midbrain culture and PC12-expressing hDAT cells
Rayne **	2010a	Cell Line	Jurkat cells transfected with plasmid containing Tat 1-86, N-glycosylated Tat 1-86, or Tat 1-86 eGFP labeled	ELISA, luciferase, ICC, fluorescent staining, immunoblotting	Tat intracellualr trafficking and compartmental exchange do not follow the conventional glogi-ER pathway. It is difficult to accuraltey detemine Tat relseare form the host cells.
Rayne **	2010 b	(1) Primary Human Cell Culture (2) Cell Line	Primary CD4+ T-cells, Jurkat cells transfected with plasmid containing Tat 1-86.	ELISA, luciferase, ICC, transactivation assay, liposome sedimentation assay	In CD4+ cells Tat interacts with the PIP2 within the membrane, which facilitates its release from these cells. Tat monoplizes PIP2 at the membrane, leasding to decreased recrutiment of other PIP2 interacting partner proteins.
Qi	2011	SH-SY5Y Cell Line	SH-SY5Y cells exposed to 50 ng/mL Tat. Variant not stated.	Flow cytometry, TEM	combined Tat and methamphetamine induces apotosis.
Zhu	2011	Primary Rodent Cell Culture	Sprague-Dawley rat striatal synaptosomes and HEK cells exposed to 5 uM Tat 1-86	Radiolabeled uptake, radiolabeled binding	Suggest Potential alosteric modualtion of hDAT by exagenous Tat in the HEK cells

First Author	Year	Model System	Experimental Details	Methods	Key Results
Agrawal	2012	Rat injected with Tat	Female Sprague Dawley Rats injected during diestrus stage (lowest estrogen stage) with 10 ng recombinant Tat (acute) or SV40-derived vector Tat (chronic) into the caudate-putamen. Tat variant not stated.	IHC, TUNEL, NeuroTrace, malondialdehyde (MDA)	One of the few studies that have examined the effect of Tat on lipid persoxidation. Genetic delivery of antioxidants attenuated lipid persoxidation follwing both acute and chronic Tat exposure.
Aksenov	2012	Primary Rodent Cell Culture	Primary midbrain and hippocampal cell culture from 18 day old Sprague Dawley rats treated with recombinant Tat 1-86 (10nM) 18–21 DIV	ICC, calcein AM	This work again has shown that combined Tat and methamphetamine is toxic in clutured dopamine but not hippocampal neurons, and it is decreased by blockade of D1 receptor. MK801 inhibition of NMDA receptor also blocks the above the effect.
Midde	2012	Primary Rodent Cell Culture	Striatal synaptosomes from Sprague-Dawley rats incubated with Tat 1-86 1uM	Radiolabeled uptake, radiolabeled binding,immublotting,	Tat decreases dopamine transporter cell surface expression and VMAT2 fucntion.
Bertrand	2013	Primary Rodent Cell Culture	Primary hippocampal cell culture from 18 day old Sprague Dawley rats treated with Tat 1-72 (10–250nM)	Fluorescent staining, IHC, calcein AM	Mutation in the cytstine-rich doamine of Tat decreases its ability to induce synapto-dendritic injury.
Carey *	2013	Transgenic Mouse (GT-gt bigenic)	Transgenic mice conditional Tat 1-86 expressed in glial fibrilary acidic protein positive cells in the presence of a tetracycline (5-7 days of 100 mg/kg/day doxycycline i.p. injection)	MRI	Conditional tat expression reduces gray matter density in mulitple brian regions.
Fitting *	2013	Transgenic Mouse (GT-gt bigenic)	Transgenic mice conditional Tat 1-86 expressed in glial fibrilary acidic protein positive cells in the presence of a tetracycline (dox 6 mg/kg chow 1-3 weeks)	Golgi-Kopsch, TUNEL, transmission electron microscopy, immunohistochemistry, slice electrophysiology, Morris water maze, contextual fear conditioning	Although Tat expression in the brain produces modest structural change and induces minimal pathology, the alterations in the hippocampal synaptic tranmission and consequent behavioral responses are significant.
Hargus	2013	Primary Rodent Cell Culture	Primary rat hippocampal neurons exposed to 50 ng/ml Tat. Tat variant not stated.	Electrophysiology (patch clamp), fluorescent counting	In hippcampal neuronal culture Tat treatment alters the balance between excitatory and inhibitory synaptic responses leading to increased GABAergic inhibitory tone.
Midde	2013	(1) Primary Rodent Cell Culture)2) Cell Line	Synaptosomes from rat spleen, cerebellum, striatum incubated with Tat 1-86 350 nM, CHO DAT expressing cells exposed to Tat 1-72,	Coimmunoprecipitation, GST-pull-down, radiolabeled uptake/ efflux, immunodepletion, radiolabeled binding, immunoblotting	Mutational analysis examines the potenail Tat binding sites on dopamine transporter. Examination of specificity is future direction of this group.

First Author	Year	Model System	Experimental Details	Methods	Key Results
			Tat 1-86, Tat 1-101 (amount not stated).		
Tremblay **	2013	Mice Injected with Tat	Mice intracortically injected with Tat 1-72. Amount of Tat not stated.	ICC	Tat alters microglial-neuronal contact sites that could be the prerequist step for the Tat-induced structural change.
Zucchini *	2013	Transgenic Mouse	TT (BDF) mice expressing constitutively expressing Tat. Tat variant not stated. Synaptosomes of BDF mice (wild-type control) exposed to Tat 1-86 0.03, 0.1, 0.3, 1, or 3 nM	PCR, reverse-transcriptase PCR, immunoblotting, HPLC, seizure, H&E stain,Fluoro-Jade B, NeuroTrace 594	Constitutive Tat expression alters the balance between excitatroy and inhibitory synaptic tranmission in the brain leading to increase sensitivity to Kainate-induced sizure.
Fitting	2014	Primary Rodent Cell Culture	Primary neuronal culture from outbred or mu-opioid receptor knock-out mice exposed to 10-100 nM Tat 1-86	Immunocytochemistry, SBFI-AM, fura1-AM, rhod123,	Morphine and Tat interact to disrupt intracellular Ca2+ levels, coinciding with onset of synaptodendritic injuries.
Liu	2014	Rat injected with Tat	Male Wistar rats intranigrally infused with 10ug of Tat 1-86	ELISA, locomotor activity, HPLC, rotarod	Tat and methamphetamine synergistically act to inccrease inflammatory cytokine levels such as IL-1B and TNFa, as well as enhancing striatal dopamine defecits
McLaughlin	2014	Transgenic Mouse	Transgenic mice conditional Tat 1-86 (25, 50, or 100 mg/kg i.p for 1, 3, 5 or 7 days)	Conditioned place preference	Tat increases ethanol reward and reinstates extinguished conditioned place preference.
Moran	2014	Rat injected with Tat	Neonatal Sprague-Dawley rats Tat 1-86 stereotaxically injected with Tat 1-86 25ug in 1 uL into hippocampus	Bodyweight, eye opening, righting reflex, negative geotaxis, acoustic startle reflex, locomotor activity, reverse-transcriptase PCR	Injection of Tat hindered normal development milestones such as delayed eye-opening and reflex development. Direct injection, however, did not increase inflammatory cytokine (IL-1B, NF-kB,IkB), but did induce neurotoxicity.
Paris	2014a	Transgenic Mouse (GT-gt bigenic)	Transgenic mice tetracycline conditional Tat 1-86 (doxycycline 25, 50, or 100 mg/kg i.p for 1, 3, 5 or 7 days)	Locomotor activity, CPP	Tat potentiates cocaine-induced loccomotor behavior.
Paris	2014 b	Transgenic Mouse (GT-gt bigenic)	Transgenic mice conditional Tat 1-86 (25, 50, 100, or 125 mg/kg i.p for 1, 3, 5, 7 or 14 days)	Open field, social interaction, marble burying, immunoblotting	Conditional Tat expression induces dose dependent anxiety-like behavior.
Fields	2015	Transgenic Mouse (GT-gt bigenic)	Transgenic mice conditional Tat 1-86 expressed in glial fibrilary acidic protein positive cells in the presence of a tetracycline (14 days of 80 mg/kg/day doxycycline i.p. injection), B103 rat neuroblastoma	Immunocytochemistry, immunoblotting, immunohistochemistry	Tat interferes with CDK5 nuclear transport, causing prolonged cytoplasmic CDK5 levels, resulting in irregular phosphylation of cytoplasmic

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First Author	Year	Model System	Experimental Details	Methods	Key Results
			treated with conditioned media containing Tat 101 with HA tag		proteins such as Tau, CRMP2, DCX
Flora	2015	Mice Injected with Tat	Stereotaxic injection of 25ug/ul Tat 1-72 into the right hippocampus of C57 BL/6 mice	2′,7′ dichlorofluorescene assay, immunoblotting, reverse-transcriptase PCR	Tat and ethanol potentiate reactive oxygen species production in hippocampus and corpus straitum, as well as IL-1B, MCP-1, NF-kB, CREB activity.
Hahn	2015	Transgenic Mouse (GT-gt bigenic)	Transgenic mice tetracycline conditional Tat 1-86 expressed in GFAP positive cells in the presence of a tetracycline (dox 6 mg/kg chow 12 weeks)	Rotorod, forelimb grip strength, open-field, light/dark box, stereology, IHC,immunoblotting, transmission electron microscopy,TUNEL	Compared to female counterparts, male mice exposed to Tat show increased anxiety-like behavior, motor memory deficits, TUNEL+-NeuN+ cells, and reduced grip strength but with equivalent astro/microgliosis.
Midde	2015	Cell Line	CHO, PC12 incubated with 500 nM Tat 1-86	Radiolabeled uptake/efflux, radiolabeled binding, immublotting	Computational modelling and radiolabelled DA transport suggest the Y470 residue of DAT is critical for Tat-dependent alterations in DA transport.
Mediouni	2015a	(1) Cell Line (2) Transgenic Mouse (GT-tg bigenic)	HeLa-CD4-LTR-Luc cells exposed to Tat 1-86 1.25 ug or 0.6 ug, U937 microglia like cells, U87MG astrocyte cells exposed to 500 ng FLAG-Tat 1-86 in 1 mL or 500 uL serum free DMEM. Transgenic mice conditional Tat 1-86 (100 mg/kg/day for 7 days)	ICC, MTT assay, transactivation assay, immunoblotting, dot blot, CPP	Didehydro-Cortistatin A crosses the blood-brain-barrier and inhibits Tat-dependent alterations in IL-1B, TNF-a, MCP-1 levels, reduces glial uptake, and reverses Tat-potentiated cocaine reward.
Yuan	2015	Cell Line	PC12 and ATCC cells exposed to 500 nM Tat 1-86	Radiolabeled uptake	Provides supporting evidence for data published in Midde et. al., 2015 in different cell line, again suggesting the importance of Y470 residue of DAT being critical to Tat-dependent alterations of DA transport.
Zhu	2015	Rat injected with Tat	Sprague-Dawley rats intra-VTA injected with 25ug Tat 1-86	Locomotor activity, radiolabeled binding, immunoblotting, body weight,	Direct injection of Tat into the ventral tegmental area enhances pERK1/2 levesl in the VTA and nucleus accumbens with reduced locomotor behavior and blunts behavioral sensitization to nicotine.
Kesby *	2016	Transgenic Mouse (GT-gt bigenic)	Transgenic mice tetracycline conditional Tat 1-86 expression (dox 100 mg/kg i.p. injection for 7 days)	ICSS, HPLC, delayed nonmatch-to-position	Tat elevated baseline reward thresholds, enhanced methamphetamine-induced threshold lowering, increased

First Author	Year	Model System	Experimental Details	Methods	Key Results
					striatal dopamine, trendwise reduced mesolimbic dopamine levels and significantly increased serotonin in nucleus accumbens.
Xu	2016	Primary Rodent Cell Culture	PFC slices from C57BL/6 mice exposed to 5, 10, or 50 nM Tat 1-86	IHC, Hoechst, electrophysiology (patch clamp)	Tat induces decreases frequency and amplitude of miniature inhibitory postsynaptic currents which are reversed by CB1R, but not CB2R, antagonism.
Yuan	2016	Cell Line	PC12 cells exposed to 140 nM Tat 1-86	Radiolabeled uptake	H547 of dopamine transporter is crucial for Tat binding and alterations of dopamine transport.

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- denotes article of particular interest to this review

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- denotes article of substantial importance to this review