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Modulatory Effects of Nicotine on neuroHIV/neuroAIDS

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Abstract

Nicotine, one of the key active ingredients in tobacco smoke, exerts its effects via binding to nicotinic acetylcholine receptors (nAChRs). Although both negative and positive pharmacological effects of nicotine have been shown in numerous animals and human studies, its interaction with human immunodeficiency virus-1 (HIV-1) have not been fully elucidated. Even though combined anti-retroviral therapy (cART) limits the progression of HIV-1 to acquired immune deficiency syndrome (AIDS), HIV-associated neurocognitive disorders (HAND) remain prevalent. There is thus a compelling need to enhance our understanding of HAND-related neurologic dysfunction. Some biochemical pathways and physiological dysfunctions have been found to be shared by HAND and Alzheimer's (AD) or Parkinson's (PD) diseases, and nicotine may exert the same neuroprotection in HAND that has been observed in both AD and PD. In the past dozen years, various potential therapeutic effects of nicotine such as neuroprotection have been revealed in both *in vivo* and *in vitro* studies, including using HIV-1 transgenic (HIV-1Tg) rat model, which mimics HIV-infected patients receiving cART. In the current review, we describe recent progress in the prevalence of HIV/AIDS with and without cigarette smoking, some animal models for studying neural dysfunction associated with HIV-1 infection, elucidating the modulatory effects of cigarette smoking/nicotine on HIV/AIDS, the anti-inflammatory effects of nicotine, and the neuroprotective effects observed in HIV-1Tg rat model. Taken together, these findings suggest the following: although tobacco smoking does cause deleterious effects in both health and disease conditions such as HIV infection, nicotine, the significant component of tobacco smoke, has been shown to possess some neuroprotective effects in HIV patients, possible via its anti-inflammatory activities. It is therefore necessary to study nicotine's dual effects on neuroHIV/neuroAIDS in hope of better defining the potential medical uses of nicotine or its analogues, and to make them available in a purer and less dangerous form.

Summary

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Cigarette smoking is a challenging comorbidity to HIV/AIDS. Nicotine, as a key component of tobacco smoke, has some modulatory effects on both the immune system and cognition. Nicotine's neuroprotective effects have been characterized in both AD and PD, and it may be involved similarly in protecting HIV-1–infected individuals, especially against HAND. Neuroprotective effects of nicotine have been well demonstrated using some HIV-1 animal models, particularly the HIV-1Tg rats, further studies are therefore needed to delineate the potential medical uses of nicotine, to study molecular and cellular mechanisms underlying nicotine's protective effects against HAND, and finally to provide clinical strategies to reduce the rate of cigarette smoking among the PLWHA.

Keywords

HIV/AIDS; HIV-associated neurocognitive disorders; Anti-inflammation; Nicotine; Neuroprotection

Introduction

Nicotine is a significant component of tobacco smoke. Although many studies have shown that nicotine causes dependence (ND) through binding to nicotinic receptors (Markou 2008; Benowitz 2009, 2010), it also has been found to be potentially protective against neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), and human immunodeficiency virus- and acquired immune deficiency syndrome (HIV/AIDS)-induced neurocognitive disorders (HIV-associated neurocognitive disorders; HAND) (Fratiglioni and Wang 2000; Nordberg et al. 2002; Wojna et al. 2007; Quik et al. 2012). HIV/AIDS is still a leading cause of disease and death globally (Wang et al. 2016). Although combined anti-retroviral therapy (cART) averts the immune deficiency syndrome, lifelong HIV-1 infection causes various medical dysfunctions, including neuropsychiatric disorders (Saylor et al. 2016).

There are a large number of studies on the effects of nicotine on people living with HIV/AIDS (PLWHA), but nicotine's modulatory effects in health and disease have been controversial. In the present communication, we review the recent developments on the epidemiology of HIV/AIDS, animal models used for investigating neural dysfunctions in the presence of viral proteins, the prevalence of cigarette smoking and its detrimental effects on HIV/AIDS, and the anti-inflammatory and neuroprotective effects of nicotine possibly helpful in the health of PLWHA.

Epidemiology of HIV-1 Infection and AIDS

HIV-1 infection is a pandemic disease, and there is no effective vaccine to control it (Steinbrook 2016). In 2015, more than 36 million people in the world lived with HIV infection, and there was an estimated 2.1 million new HIV-1 infections (UNAIDS 2015). The number of AIDS-related deaths was about 1.1 million, which has decreased in recent years although it remains high (UNAIDS 2015). Multiple measures for reducing the morbidity and mortality rate of AIDS have been implemented, which include more sensitive diagnostic tests, early antiretroviral therapy, and public health education (Laboratories 2014;

Frieden et al. 2015; Lundgren et al. 2015). The cART is the most commonly used form of HIV-1 treatment, which can prevent viral replication and stop the virus from invading the immune system (McArthur et al. 2003; Gonzalez-Scarano and Martin-Garcia 2005). The lifespan of HIV-1-infected patients has been greatly prolonged, yet the gap in life expectancy between HIV-infected and -uninfected individuals is still 8 years even with early treatment (Marcus et al. 2016). Thus, HIV infection is currently considered a chronic disease (Fauci and Folkers 2012). However, because of the coexistence of HIV viral proteins and other factors, such as illnesses, drug abuse, and aging, central nervous system (CNS) impairment is still common in infected patients (Valcour et al. 2011). Many neurologic problems occur, including gliosis, motor dysfunction, striatal pathology, progressive cognitive decline, and HAND (Yoshioka and Itoyama 1997; Krebs et al. 2000; Xu and Ikezu 2009; Joseph et al. 2016). Thus, a better understanding of the neurologic disorders induced by HIV-1, as well as effective therapies, is greatly needed. Although current cART is capable of reducing the viral load, the mortality rate, and the incidence of AIDS and HIV-associated neurological diseases, the prevalence of peripheral neuropathy still is increasing, probably because of the continued presence of viral proteins in infected persons (Sacktor 2002; Barbaro et al. 2005; Vigano et al. 2006).

Animal Models of HIV-1 Infection-Related Neurodysfunction

To better understand HIV infection-related neurodysfunction and its mechanisms, animal models mimicking patients infected with HIV and receiving cART are necessary. During the past few decades, a number of animal models have been developed that mimic PLWHA (Table 1), which enable research projects for different purposes, such as discovery of a cure for HIV infection (Micci et al. 2015; Policicchio et al. 2016), co-infection study (Guo and Ho 2014), anti-HIV drug discovery (Sliva 2015), and so on. At first, researchers were looking for animal models relying on a natural virus similar to HIV-1 that can cause immunodeficiencies; e.g., those found in monkeys, cows, and cats (Olmsted et al. 1989; Gonda et al. 1994; Schmitz et al. 1999). Although these models are appropriate for HIV study, the high cost of the animals and their care prevents researchers from using them frequently.

HIV-1 infection, replication, and progression to AIDS are possible only in humans. However, species-specific mouse models have been developed that incorporate human cells or tissue, and these models can be used to study human immunobiology (Ito et al. 2012; Brehm et al. 2013). The discovery of severe combined immunodeficiency (SCID) mice was a key advance in infectious disease and xenotransplantation (Bosma et al. 1983; Ito et al. 2012). Humanized HIV-infection models have been used widely in studies related to anti-HIV-1 drug development, HIV-1 mucosal transmission and prevention, the pathogenesis of HIV-1 infection, immune responses, gene therapy for HIV-1, and CNS invasion (Nischang et al. 2012; Akkina 2013). However, some issues remain, such as immature differentiation, insufficient intercellular relations of certain cell lines, and lack of any capacity to generate an effective human immune response in these humanized mouse models (Ito et al. 2012; Nischang et al. 2012; Akkina 2013).

During recent years, new transgenic rodent models that express the HIV genome and develop AIDS-like diseases have been applied to HIV-1-related diseases such as neuroAIDS (Maung et al. 2012). Two important HIV-encoded proteins, glycoprotein 120 (gp120) and Tat, are toxic to neurons (Nath 2002). In 1994, a transgenic mouse model was generated by (Toggas et al. 1994) that produces gp120 in the brain. The abnormal neuronal and glial changes in this model are similar to those in HIV-1-infected humans. Further, several transgenic models were created in which Tat is expressed constitutively in most tissues throughout the lifespan (Vellutini et al. 1995; Choi et al. 2000; Jaeger and Nath 2012). Although several studies were conducted using this model to identify the mechanisms of HIV-1-associated neuropathology (Krucker et al. 1998; Kim et al. 2003; Chang et al. 2011; Lee et al. 2011), there are some limitations (Jaeger and Nath 2012), such as the low replication capacity of HIV and the inability of the virus to interact with key proteins. Macrophages are the main cell type supporting HIV brain infection, but both the gp120 and Tat transgenic mice express the respective transgene only in astrocytes, so they are not ideal for the study of HIV-1-associated neurologic symptoms.

The HIV-1 transgenic (HIV-1Tg) rat was developed as a noninfectious model that expresses seven of the nine HIV-1 genes, the exceptions being *gag* and *pol*, which are regulated by the viral promoter (Reid et al. 2001). Although there is no viral replication, the HIV proteins can be detected in various organs, including blood (Reid et al. 2001). This model has been demonstrated to mimic HIV-1-infected patients receiving cART, who have suppressed viral replication (Peng et al. 2010). A number of reports have shown abnormal changes in the HIV-1Tg rats, for instance, lower body weight (Peng et al. 2010), immune-response alterations (Reid et al. 2001), T-cell abnormalities (Reid et al. 2004), kidney failure (Ray et al. 2003), neurobehavioral and spatial learning and memory changes (Vigorito et al. 2007; Lashomb et al. 2009; Moran et al. 2013), neuronal dysfunction (Reid et al. 2016), immunophenotype and cellular response alterations (Abbondanzo and Chang 2014), neurocognitive deficits in pediatric HIV-1 (McLaurin et al. 2016, 2017), and gene expression alterations in various brain regions (Li et al. 2013). Therefore, this rat is a more suitable animal model, without expensive high-level biosafety demands, for studying the mechanisms of HIV-associated disease in the post-cART era.

In addition, HIV-1Tg rats show different sensitivities to various addictive substances commonly abused by HIV-infected patients, such as nicotine, alcohol, morphine and its derivatives, and methamphetamine (METH) (Chang et al. 2014; Vigorito et al. 2015). In HIV-1Tg rats that have received alcohol, significantly decreased locomotor activity, accentuated skeletal muscle atrophy, exacerbated lung liquid clearance and alveolar epithelial paracellular permeability, and enhanced novelty-seeking behavior are observed (Clary et al. 2011; Fan et al. 2011; Sarkar et al. 2013; Wingo et al. 2016). After the treatment of HIV-1Tg rats with binge drinking, there exist significantly different molecular effects in a concentration-dependent manner (Sarkar and Chang 2013). There is a more sensitive conditioned place preference (CPP) in these animals after they receive morphine (Chang and Connaghan 2012; Homji et al. 2012). HIV-infected humans present greater behavioral sensitization and are more vulnerable to METH (Liu et al. 2009; Kass et al. 2010; Moran et al. 2012). We will discuss the studies on nicotine in HIV-1Tg rats in more detail below.

Cigarette Smoking Prevalence and Interactions with HIV-1 Infection

Cigarette smoking is a world-wide epidemic and a leading cause of preventable disease and death. In 2015, about 15.1% of adults (age 18 or older) in the U.S. were cigarette smokers, but this was a 27.7% decline from 2005 (Jamal et al. 2016). Tobacco smoking leads to the development of various diseases and health risks, including cardiovascular disease, bacterial pneumonia, respiratory diseases, reproductive diseases, diabetes, renal failure, several kinds of cancer, HIV-associated infections, and death (Stampfli and Anderson 2009; Lifson and Lando 2012). Compared with persons who have never smoked, the mortality rate is two to three times higher among current smokers (Carter et al. 2015). Moreover, the rate of serious psychological distress is 40.6% higher in smokers (14.0%) (Jamal et al. 2016).

Cigarette smoking is one of the leading killers of PLWHA. The prevalence of cigarette smoking among PLWHA is nearly twice as high as in uninfected persons, and they are less likely to quit than the general adult population (Mdodo et al. 2015). Tobacco smoking as an independent risk factor has been shown to accelerate acquisition of HIV infection and its progression to AIDS, or to increase the mortality rate of HIV-infected patients (Marshall et al. 2009). The mortality rate of PLWHA who smoke is nearly twice that of smokers without HIV infection (Helleberg et al. 2013). In addition, smokers with HIV-1 infection have a greater risk of virological rebound, more frequent immunologic failure, and poorer responses to antiretroviral therapy (Feldman et al. 2006). The introduction of cART results in reduction of some AIDS-related co-morbidities, such as the prevalence of cardiovascular disease, pulmonary disease, cancers, and opportunistic infections. Not unexpectedly, smoking further increases the risk for occurrence of these diseases among HIV-positive patients (Petrosillo and Cicalini 2013).

At the molecular level, HIV-1 protein gp120 binds to nicotinic acetylcholine receptors (nAChRs) (Bracci et al. 1992), and nicotine inhibits the activation of microglia induced by HIV-1 gp120 (Giunta et al. 2004). Pretreatment of microglia with nicotine, on the other hand, increases HIV-1 expression in a concentration-dependent manner (Rock et al. 2008). Cytochrome P450 (CYP)-mediated oxidative stress is a novel pathway that may be involved in smoking-mediated HIV-1 pathogenesis (Ande et al. 2013). Epidemiologically, male smokers with HIV are more likely than women to become heavy smokers and to use other psychoactive substances (Shuter et al. 2016). In contrast to the above-mentioned studies, following their findings that women have a greater risk of HIV-associated cognitive impairment (Wojna et al. 2006), Wojna and colleagues further investigated the effects of smoking on neurocognitive impairment among 56 HIV-positive and HIV-negative females, which revealed no significant differences in cognitive impairment between HIV-positive and HIV-negative smokers. However, the authors found that HIV-positive women with a smoking history exhibited significantly better frontal/executive performance than those without a smoking history (Wojna et al. 2007). These studies showed that tobacco smoking, possibly via the activities of its key components such as nicotine, could reduce harm from HIV to PLWHA.

Nicotine's Anti-Inflammatory Effects

There are approximately 4,500 compounds in smoke during different phases of tobacco burning. These compounds include several known direct carcinogens (e.g., methylcholanthrene, benzo- α -pyrenes, and acrolein), toxic agents (e.g., nicotine, carbon monoxide, ammonia, acetone, and hydroquinone), and oxidants (e.g., superoxide and nitrogen oxides) (Jaakkola and Jaakkola 1997; Stampfli and Anderson 2009). Typically, nicotine is available only in tobacco. Most diseases commonly associated with smoking are a result of the tar found in tobacco in addition to nicotine (Centers for Disease et al. 2010). Although the health risks of tobacco smoking are well documented, increasing evidence testifies that nicotine is of benefit for many diseases. In addition to its pro-inflammatory effects, smoking has been shown to exert both immunosuppressive and anti-inflammatory effects (Sopori 2002; Stampfli and Anderson 2009). Nicotine plays specific roles in cell proliferation, apoptosis, migration, invasion, and angiogenesis in a variety of cells (Cardinale et al. 2012). Some case reports suggest that nicotine is of benefit in several skin diseases, such as pyoderma gangrenosum, Behçet's disease, and oral aphthous ulcers (Ingram 2009). Nicotine also dose-dependently reduces the severity of viral myocarditis (Li-Sha et al. 2015) and the risk of developing multiple sclerosis (Hedstrom et al. 2013). In brain disorders, nicotine plays a neuroprotective role, examples being AD, PD, and major depression (Tizabi et al. 1999; McClernon et al. 2006; Picciotto and Zoli 2008; Quik et al. 2012). Nicotine exerts its functions in the brain mainly through binding directly to and activating nAChRs, which are located on the cytoplasmic membrane. So far, 17 types of nAChR subunits have been identified in humans. Different subunits are involved in various conditions (Albuquerque et al. 2009). During AD development, for example, nicotine protects against the neuropathology via activation of nAChR, and both $\alpha 4\beta 2$ and $\alpha 7$ nAChR subtypes participate (Durazzo et al. 2014). Similarly, $\alpha 4\beta 2$, $\alpha 6\beta 2$, and $\alpha 7$ nAChR are involved in neuroprotection during PD development (Kawamata et al. 2012; Quik et al. 2012).

Almost every CNS disorder, including AD, PD, neurotropic viral infections, stroke, paraneoplastic disorders, traumatic brain injury, and multiple sclerosis, has an inflammatory component (Lucas et al. 2006; Amor et al. 2010). Accumulating evidence indicates that a neuroinflammation mechanism is involved, and anti-inflammatory immunotherapeutics may slow the progress of these diseases and provide other benefits (Weiner and Selkoe 2002; Hirsch and Hunot 2009). Nicotine exerts an anti-inflammation effect, which could delay or attenuate CNS inflammatory and immune responses (Shi et al. 2009). The potential molecular signaling mechanisms involved in nicotine-mediated anti-inflammatory and neuroprotective effects have been investigated extensively (Fig. 1) (Rosas-Ballina and Tracey 2009; Quik et al. 2012; Baez-Pagan et al. 2015; Kalkman and Feuerbach 2016). A change in calcium signaling is most likely the first step in nicotine's neuroprotective actions, although calcium-independent mechanisms also have been described (Cui and Li 2010; Quik et al. 2012; Kalkman and Feuerbach 2016). Higher intracellular free calcium concentrations are triggered by calcium release from intracellular stores through the receptor channels (Sharma and Vijayaraghavan 2001). This leads to activation of downstream signaling molecules mediated mainly via binding to $\alpha 7$ nAChR, which is the subunit most involved in

this process. Activated $\alpha 7$ nAChR binds directly to Janus kinase 2 (JAK2) and triggers the JAK2/STAT3 (signal transducer and activator of transcription 3) pathway to interfere with activation of nuclear factor- κ B (NF- κ B), which is responsible for pro-inflammatory cytokine gene transcription (Tracey 2009; Andersson and Tracey 2012). Activation of $\alpha 7$ nAChR also can suppress inhibition of κ B (I κ B) phosphorylation, interfering with nuclear translocation of NF- κ B (Yoshikawa et al. 2006). Hence, NF- κ B nuclear translocation is prevented; at the same time, the secretion of high-mobility group box 1 (HMGB1), an important pro-inflammatory cytokine, is also inhibited (Wang et al. 2004). Another signal transduction pathway activated by nicotine is Akt, which is phosphorylated through phosphatidylinositol 3-kinase (PI3K) activation. Subsequently, expression of B-cell lymphoma 2 (Bcl-2) and Bcl-x anti-apoptotic proteins is upregulated, which will decrease apoptosis and enhance neuronal survival (Shimohama 2009). In addition, activation of $\alpha 7$ nAChRs stimulates protein kinase A (PKA), which activates glycogen synthase kinase 3 (GSK3) inhibition and cAMP response element binding protein (CREB) (Kalkman and Feuerbach 2016).

Nicotine's Neuroprotective Effects against HIV/AIDS

Inflammation also is associated with HIV replication, both in the periphery and within the CNS, an effect which has been recognized as a key driver of HIV pathogenesis (Gannon et al. 2011). In HAND, immune activation and neuroinflammation are involved. The neuroinflammatory response in HIV-1 infection may contribute to cognitive and behavior changes (Minagar et al. 2002; Hong and Banks 2015). Alzheimer's disease, PD, and HAND are common neurodegenerative diseases and have some shared pathways and dysfunctions (Tables 2 and 3). Very recently, it was discovered that neuroAIDS shares a convergent gene network with seven major neurological disorders, namely AD, PD, multiple sclerosis, age-related macular degeneration, amyotrophic lateral sclerosis, vascular dementia, and restless leg syndrome (Sagar et al. 2017). Innate immunity signaling pathways are involved in all of these disorders, which suggests a commonality exists among different forms of neuropathogenesis. Moreover, oxidative stress, neuronal death or survival, neurotransmitter release, cytokines and the inflammatory response, interleukin-5 (IL-5), IL-10, hypoxia-inducible factor 1 (HIF-1), NOD-like receptor, NF- κ B, Toll-like receptor, tumor necrosis factor (TNF), mitogen-activated protein kinase (MAPK), PI3K/Akt, JAK2/STAT3, extracellular signal-regulated kinase (ERK), and calcium signaling pathways are active in both AD and PD (Nunomura et al. 2007; Kawamata and Shimohama 2011; Jiang et al. 2016; Kori et al. 2016; Hu et al. 2017a; Hu et al. 2017b). Between HAND and AD, multiple-gene enriched pathways or categories are shared; for example, functions related to cell growth and communication, regulation of transcription, immune response, defense response, response to stimuli, antigen presentation, immune cell activation, and synapsis transmission (Borjabad and Volsky 2012; Levine et al. 2013; Sagar et al. 2017). Some structural, functional, and metabolic brain abnormalities and neuropathology are shared by AD and HAND (Cohen et al. 2015). Some manifestations, such as bradykinesia, postural instability, gait abnormalities, and hypomimetic facies, are shared by HAND and PD (Koutsilieri et al. 2002). Motor, cognitive, attention, and executive-function deficits also exist among HAND and PD patients (DeVaughn et al. 2015). Signaling pathways related to the immune response, cell activation,

and antigen processing and presentation are shared in AIDS and PD (Sagar et al. 2017). Given these many existing similarities among HAND and other neural disorders, nicotine may play similar roles in HAND, which will attenuate the effects of HIV infection on neurocognitive disorders. A recent study showed that $\alpha 7$ nAChR is upregulated in HIV-seropositive individuals (Delgado-Velez et al. 2015). Bupropion, an $\alpha 7$ nAChR antagonist, partially mitigates inflammation in HIV infection, suggesting that $\alpha 7$ nAChR is an attractive anti-inflammatory therapeutic target to counteract the chronic inflammation suffered by HIV-infected patients (Delgado-Velez et al. 2015). However, to our knowledge, there are few studies on the protective effects of nicotine in the presence of HIV-1 infection, for which the underlying mechanism remains to be determined.

Recently, some models have been applied to study the neuroprotective effects of nicotine in HIV infection. Previous study showed that the HIV-1Tg rat is a valid model for studying HIV-related neurological dysfunction (Vigorito et al. 2015). Midde et al. (2011) reported that HIV-1Tg rats exhibit diminished locomotor activity during habituation to a novel context, and behavioral sensitization is attenuated, after repeated nicotine administration. Further investigation showed that nicotine significantly attenuates working and contextual memories in HIV-1Tg rats with a brain region- and strain-specific effect, which is modulated by the calcium-signaling pathways (Nesil et al. 2015). Most recently, Yang et al. (2017) found that novelty-seeking behavior is greater among HIV-1Tg rats with abnormal expression of dopamine and GABA receptors in the prefrontal cortex–ventral tegmental area–nucleus accumbens (PFC-VTA-NAc) neural circuits. Nicotine differentially affects the transcription of excitatory and inhibitory neurotransmitter receptors in these animals.

Because the cholinergic system is an essential part of the central reward circuitry (Tuesta et al. 2011), nine nAChR subunit genes in the CNS of HIV-1Tg rats were evaluated during nicotine treatment (Cao et al. 2016). The expression of nAChR subunits $\alpha 6$, $\beta 3$, and $\beta 4$ mRNA in the VTA is decreased, whereas the expression of the $\alpha 4$ and $\alpha 6$ subunits in the NAc is increased. These findings indicate that expression of nAChRs can be altered by HIV-1 proteins or nicotine, which is one of the key mechanisms underlying nicotine's modulatory effects in the presence of HIV proteins. Furthermore, the effects of nicotine on genome-wide RNA expression in the prefrontal cortex (PFC), striatum (STR), and hippocampus (HIP) of HIV-1Tg rats revealed that 20%, 23%, and 14% of the abnormally expressed genes were restored in the PFC, HIP, and STR, respectively (Cao et al. 2013). This suggests that nicotine restores distinct signaling pathways in different brain regions. It also might be able to attenuate the pathologies associated with HIV-1 infection and HIV-associated CNS complications such as neurological/cognitive disorders and abuse of addictive substances.

Immune responses are important in the CNS (Waisman et al. 2015). Nicotine and nicotinic receptors are involved in the modulation of innate immune pathways (Cui and Li 2010). To understand nicotine's immunomodulation effects in HIV-1Tg rats, 52 immune-related genes were examined in three brain regions (PFC, NAc, and VTA) with or without nicotine treatment (Yang et al. 2016). The pharmacological effect of nicotine on the expression of immune-related genes differed in the presence (HIV-1Tg rats) and absence (control F344 rats) of HIV-1 viral proteins. Of the differentially expressed genes, interleukin 1 α (*IL-1 α*)

and interferon regulatory factor 7 (*Irf7*) are two representative genes that are dramatically changed when nicotine and HIV-1 coexist. Both genes are important mediators of the innate immune response (Colina et al. 2008; Garlanda et al. 2013). Thus, HIV-1 viral proteins may greatly affect immune function, especially innate immunity, and alter responsiveness to nicotine in certain immune-related genes. In contrast, a recent study using HIV-1Tg rat model detected the deleterious effects from those rats which were exposed to cigarette smoke or nicotine (Royal et al. 2018). Such an inconsistency might be related to different doses and durations of nicotine treatment among these studies.

Some other model animals also have been applied in nicotine neuroprotective studies. As we know, HIV-1 gp120 has an important role in the pathogenesis of HIV-associated dementia (HAD). The administration of nicotine prevents HIV-1 gp120-induced electrophysiological and motor alterations in rats (Gonzalez-Lira et al. 2006). *In vitro* studies also showed nicotine's anti-inflammatory effects. Cui et al. (2012, 2013) reported that 14 biological pathways are altered after nicotine treatment of SH-SY5Y cells. Of these pathways, the Toll-like receptor (TLR) pathway, which is a key regulator of innate immunity and responsible for inflammatory responses, is significantly modulated by nicotine. Besides, a model mimicking HAD-like microglial activation after introduction of HIV-1 gp120 was established by Giunta et al. (2004), who showed that nicotine treatment suppresses immunological cytokine release through the $\alpha 7$ nAChR and p44/42 MAPK system.

While the above-mentioned animal studies showed the presence of nicotine's neuroprotective effects, epidemiologic studies in human yielded some contradictory findings. For example, Bryant *et al.* reported that current smoking was negatively associated with learning, memory and global cognitive functioning (Bryant et al. 2013). It has been suggested that these differences were likely due to the lower education and higher rate of hepatitis C viral infection in the smokers. Thus, it is difficult to dissect if smoking was the main effect on the poor cognitive function in PLWHA in this study (Bryant et al. 2013). Another recent cross-sectional study showed that HIV-infection and tobacco smoking consistently showed additive deleterious effects on psychopathological symptoms, impulsivity and cognitive dysfunction (Chang et al. 2017). In this study, the authors indicated that the lack of nicotine's benefits might be due to the adverse effect of chronic tobacco use on cardio-neurovascular system (Chang et al. 2017). However, in another study, Wojna *et al.* found that HIV-seropositive women with a smoking history showed a significant better performance on the frontal/executive domain than those without a smoking history although no differences were detected among HIV-seropositive women with either history or current smoker when adjusted for age, education, and annual income (Wojna et al. 2007). Although there was a concern on relative small sample size of this study, their results still suggest that nicotine may have some beneficial effects on cognition in HIV-seropositive women.

HIV/AIDS is a multifactorial disease, which is more complicated in HIV patients. The animal model studies have provided evidence of nicotine's neuroprotective effects on HIV and of improved cognitive effects on the neurodegenerative diseases (Rezvani and Levin 2001; Swan and Lessov-Schlaggar 2007; Piao et al. 2009), but there were a few reported human studies showing the similar effects on cognitive function in PLWHA right now. The

balance between the neuroprotection and toxicity of nicotine or tobacco smoking depends on the dose, developmental stage, and/or regimen of administration. Therefore, it is necessary to conduct more mechanistic studies using animal models in order to clarify the modulatory effects of nicotine on neuroHIV/neuroAIDS.

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Fig. 1.

Potential molecular signaling mechanisms of nicotine mediated anti-inflammatory effects. Nicotine binds to nicotinic acetylcholine receptor (nAChR) on the membrane activating the downstream signaling molecules. Stimulation of nAChR triggers signaling pathways such as janus kinase 2/signal transducer and activator of transcription 3 (JAK2/STAT3), which interferes nuclear factor- κ B (NF- κ B) nuclear translocation and attenuates proinflammatory cytokine release. Phosphoinositol-3-kinase/Akt (PI3K/Akt) is another pathway activated by nicotine, which will decrease cell apoptosis and enhance neuronal survival. Activation of $\alpha 7$ nAChRs leads to increase in cAMP levels and stimulates protein kinase A (PKA), further result in cAMP response element binding protein (CREB) activation and glycogen synthase kinase 3 (GSK3) inhibition.

Table 1

Animal models of HIV-1 infection-related neurodysfunction

Model	Type(s) of Animal	Advantages	Disadvantages
Virus in nature	Monkey, cow, cat	Naturally occurring virus	High cost High risk to laboratory personnel
Humanized mouse	SCID mouse	Used in drug development, HIV-1 mucosal transmission and prevention, pathogenesis of HIV-1 infection, immune-response gene therapy for HIV-1, and CNS invasion studies Immune dysfunction can be observed	Need for special techniques Inability to generate an effective human immune response Lack of consistent results using different sources of cells Brain cells not susceptible to infection
Transgenic mouse	Mouse	Noninfectious Express HIV genome Develop AIDS-like disease	Replication capacity of HIV is limited Virus cannot interact with key proteins Not ideal for the study of HIV-1-associated neurologic symptoms
HIV-1 transgenic rat	Rat	Noninfectious Expresses 7 of the 9 HIV-1 genes Viral proteins can be detected in various organs Mimics HIV-1-infected patients receiving cART	No viral replication

Table 2

Pathways and dysfunctions shared by neurodegenerative diseases

Neurodegenerative Disease(s)	Shared Signaling Pathways	References
AD and PD	<ul style="list-style-type: none">• Oxidative stress• Neuronal death and survival• Neurotransmitter release• Cytokines and inflammatory response• NOD-like receptor• Calcium• NF-κB• Toll-like receptor	(Nunomura et al. 2007; Kawamata and Shimohama 2011; Jiang et al. 2016; Kori et al. 2016; Hu et al. 2017a; Hu et al. 2017b)
AD and HAND	<ul style="list-style-type: none">• Cell growth and communication• Regulation of transcription• Immune cell activation• Innate immunity response	<ul style="list-style-type: none">• TNF• ERK• MAPK• PI3K-Akt• JAK2/STAT3• IL-5• IL-10• HIF-1 (Borjabad and Volsky 2012; Levine et al. 2013; Sagar et al. 2017)
PD and HAND	<ul style="list-style-type: none">• Antigen processing and presentation• Immune cell activation• MAPK	<ul style="list-style-type: none">• Response to stimulus• Antigen presentation• Synapsis transmission• Defense response• Immune response• Immune response• Innate immunity (Koutsilieris et al. 2002; DeVaughn et al. 2015; Sagar et al. 2017)

Table 3

List of abbreviations

Abbreviations	Full name
AD	Alzheimer's disease
AIDS	Acquired immune deficiency syndrome
Bcl-2	B-cell lymphoma 2
cART	Combined anti-retroviral therapy
CNS	Central nervous system
CPP	Conditioned place preference
CREB	cAMP response element binding protein
ERK	Extracellular signal-regulated kinase
gp120	Glycoprotein 120
GSK3	Glycogen synthase kinase 3
HAD	HIV-associated dementia
HAND	HIV-associated neurocognitive disorders
HIF-1	Hypoxia-inducible factor 1
HIP	Hippocampus
HMGB1	High-mobility group box 1
HIV-1	Human immunodeficiency virus-1
HIV-1Tg	HIV-1 transgenic
IL	Interleukin
IRF7	Interferon regulatory factor 7
JAK2	Janus kinase 2
MAPK	Mitogen-activated protein kinase
METH	Methamphetamine
NAc	Nucleus accumbens
nAChRs	Nicotinic acetylcholine receptors
ND	Nicotine dependence
NF- κ B	Nuclear factor- κ B
PD	Parkinson's disease
PFC	Prefrontal cortex
PI3K	Phosphatidylinositol 3-kinase
PKA	Protein kinase A
PLWHA	People living with HIV/AIDS
SCID	Severe combined immunodeficiency
STAT3	Signal transducer and activator of transcription 3
STR	Striatum
TLR	Toll-like receptor
TNF	Tumor necrosis factor
VTA	Ventral tegmental area