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Anti-inflammatory Function of *Phyllostachys Edulis* Extract in the Hippocampus of HIV-1 Transgenic Rats

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Abstract

HIV induces neuroinflammation. We evaluated the anti-inflammatory effect of an extract from bamboo *Phyllostachys edulis* in the hippocampus of HIV-1 transgenic (TG) rats. Five (5) one-month-old TG rats and 5 Fisher 344 (F344) rats were fed a control diet, another 5 TG rats were fed the control diet supplemented with bamboo extract (BEX, 11 grams dry mass per 4057 Kcal). After 9 months of dietary treatment, the gene and protein expression of interleukin 1 beta (IL-1β), glial fibrillary acidic protein (GFAP), and ionized calcium-binding adapter molecule 1 (Iba1), and the protein expression p65 and c-Jun were analyzed in the hippocampus. Compared to the F344 rats, the TG rats fed control diet showed significantly higher protein expression of GFAP and c-Jun, and mRNA and protein levels of IL-1β. BEX supplement to the TG rats significantly lowered protein expressions of GFAP, p65, and c-Jun, and showed a trend to decrease the protein expression of IL-1β. Compared to the TG rats, TG+BEX rats also downregulated the mRNA levels of IL-1β and TNFα. In summary, neuroinflammation mediated by the NFκB and AP-1 pathways in the hippocampus of the TG rats was effectively abolished by dietary supplement of BEX.

Keywords: HIV; Hippocampus; Neuroinflammation; Bamboo *Phyllostachys edulis* extract; NFκB; AP-1

Introduction

Neuroinflammation is a pathogenic factor of neurological disorders, such as HIV-associated dementia [1], Alzheimer's disease [2], and Parkinson'sdisease [3]. Such inflammation is usually a result of prolonged activation of microglia and astrocytes, and the subsequent release of pro-inflammatory cytokines and reactive oxidative species (ROS). Both microglia and astrocytes can be infected by HIV and serve as reservoirs for the virus [4]. During HIV and SIV infection, acute inflammatory response in the central nervous system (CNS) was observed several days after the infection [5], and severer neuroinflammation was found in patients with HIV-associated neurocognitive disorders (HAND) than patients without HAND [6]. In HIV-infected brain, the hippocampus hosts higher HIV viral load than the cerebellar cortex and mid-frontal cortical gray matter [7], expresses high levels of HIV chemokine co-receptors which facilitates neuronal loss and gliosis [8], and suffers greater immunoreactive neuronal loss compared to the frontal cortex [9]. The hippocampus is also a major inflammation site in the brain with antiviral treatments [10], as the inflammation (indicated by CD68 expression) did not seem to be alleviated by HAART as seen in the basal ganglia [4].

NFκB is a pro-inflammatory transcription factor that regulates the expression of more than 400 genes, and can be activated by many stimuli, such as proinflammatory cytokines, virus and viral proteins [11]. Abnormal NFκB activity is involved in the pathogeneses of chronic inflammation and neurodegenerative diseases. NFκB consists five subunits: RelA (p65), RelB, c-Rel, NFκB1 (p50/105) and NFκB2 (p52/p100), and the p50-p65 heterodimer is the most abundant functional NFκB complex [12].

AP-1 is another inducible pro-inflammatory transcription factor, composed of the Fos family, Jun family and ATF family. c-Jun is the major component of AP-1 and its basal expression is detected in many cell types and compartments in the brain [13]. Increased c-Jun expression-induced cell death in the CNS has been found in Alzheimer's disease and cerebral ischemia [14].

Inflammatory cytokines interleukin 1 beta (IL-1β) and tumor necrotic factor alpha (TNFα) can be transactivated by NFκB and AP-1, and once secreted, they further stimulate NFκB and AP-1 activation through their receptors to form a positive feedback circle. Both astrocytes and microglia can release IL-1β and TNFα [15], and increased IL-1β has been reported in the brain of HIV patients [16]. Chronic release of these cytokines results in neuronal damage through ROS generation and calcium influx, as well as through increasing monocyte infiltration in the brain [17].

Varied extracts derived from bamboo plants have been used in Traditional Chinese Medicine to treat diseases, including inflammation. *Phyllostachys edulis*, also known as Maozhu or Moso, is one of the fastest growing plants in the world. The leaves of *P. edulis* is a by-product of the bamboo timber industry, and a patented procedure has been developed in China to utilize this "industrial waste" to produce a bamboo extract (BEX). In our previous studies, we have shown that BEX as a dietary supplement decreased inflammation in the peripheral circulation, as well as decreased anxiety in obese mice [18,19], and the anti-inflammatory effect of BEX was partially mediated by inhibiting the activation of NFκB and AP-1 [20].

HIV-1 transgenic (TG) rat is an animal model used in HIV-neuro AIDS studies. These rats constitutively express 7 HIV viral proteins (vpr, env, nef, vif, vpu, rev, and tat), and neuroinflammation, as evidenced by upregulated IL-1β, TNFα, and NFκB, has been reported in homogenized brain hemisphere [21]. In this study, we specifically examined the inflammatory status in the hippocampus of the TG rats, and evaluated the anti-inflammatory effect of BEX.

Materials and Methods

Bamboo extract (BEX)

BEX used in this study was provided by Golden Basin LLC (Honolulu, HI). It was produced by Golden Basin Bio-Tech (Hunan, China) through a patented procedure (Chinese invention patent, CN 1287848A). This BEX is commercially available in the United States as a dietary supplement. To produce BEX, twigs of *Phyllostachys edulis* no longer than 2 feet were washed in water and air dried, ground and infused with 70-90% ethanol twice. The ethanolic extract was concentrated by vacuuming. The final product contains 46% moisture, and the dry mass contains 53 mg/g polyphenols, 3 mg/g fat, 67 mg/g total sugar, and 233 mg/g protein.

Animal and dietary treatment

Ten (10) one-month-old HIV-1 NL4-3 gag/pol transgenic (TG) rats and 5 genetic background control Fisher 344 (F344) rats were purchased from Harlan Inc. (Indianapolis, IN) and housed at the Laboratory Animal Service facility of the University of Hawaii. The rats were maintained on a 12-hour light/dark schedule. Food and water were accessible *ad libitum*. Body weight and food consumption were monitored weekly. The experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of the University of Hawaii.

After one week of acclimation, 5 F344 rats and 5 TG rats were fed a standard (control) diet, and the other 5 TG rats were fed the standard diet supplemented with BEX at a dose of 11 grams dry mass per 4057 Kcal, or 1% w/w. Both diets were purchased from Research Diets (New Brunswick, NJ). The dietary composition has been reported in our previous publication [18].

Sample preparation

The rats were euthanized in a CO_2 induction chamber when they were 10-month old. The whole brain weight was measured and hippocampus was dissected on ice and stored at -80°C. The hippocampal tissue was then powderized on dry ice. An aliquot of the powder was sonicated in PBS (except for samples prepared for western blot, as described below), centrifuged at 18,000 × g for 10 min at 4°C, and the supernatant was collected. The protein concentration of the supernatant was measured using Bradford assay (BioRad, catalog No. 500-0205). The samples were stored at -80°C until assayed.

Chemicals and instruments

All chemicals used in this study were purchased from Sigma (St. Louis, MO) unless otherwise noted. A SpectraMax 340 from Molecular Devices (Sunnyvale, CA) was used for HNE-His ELISA assay. A protein electrophoresis system from BioRad (Hercules, CA), and an Odyssey Infrared Imaging System and an Odyssey Application Software Version 3.0 (Li-Cor Biosciences, Lincoln, NE) were used in western blot. A Light cycler 480 II (Roche Applied Science, Indianapolis, IN) was used in Real-time PCR.

Western blot

Hippocampal tissue powder was sonicated in 1M Tris (pH 7.5) membrane lysis buffer containing 1M NaCl, 1% Trition X-100, 5 mM EDTA, proteinase inhibitor, and phosphatase inhibitor. Supernatant was collected after 10 min centrifugation at 18,000 × g, 4°C. Protein concentration was measured by Bradford assay. Primary antibodies goat anti-Iba1 (sc-28528), rabbit anti-c-Jun (sc-1694) and rabbit anti-IL-1β (sc-7884) were purchased from Santa Cruz (Dallas, TX), rabbit anti-GFAP (ab7260) and rabbit anti-NFκB p65 (ab7970) were purchased from Abcam (Cambridge, MA); Secondary antibodies were purchased from Li-Cor (Lincoln, NE). Other western blot procedures have been reported in details in our previous publication [22].

Quantitative real-time PCR

Total RNA was extracted from hippocampus using Trizol (Invitrogin, Grand Island, NY) and cleaned up using RNeasy mini kit (Qiagen, Valencia, CA). The reverse transcription kit for cDNA synthesis was from Applied Biosystems (Foster City, CA). SABiosciences SYBR® Green (PA-010-24) kits were used for quantitative PCR. Sequences of the following primers were obtained from the Universal Probe Library of Roche Applied Science and synthesized by Integrated DNA Technologies (Coralville, IA): β-actin (actin) forward: cccgcgagtacaaccttct, reverse: cgtcatccatggcgaact; GFAP forward: tttctccaacctccagatcc, reverse: gaggtggccttctgacacag; ionized calcium-binding adapter molecule 1 (Iba1) forward: ccgaggagacgttcagttactc, reverse: tggcttctggtgttctttgtt; interleukin 1 beta (IL1β) forward: tgtgatgaaagacggcacac, reverse: cttcttctttgggtattgtttgg; tumor necrosis factor α (TNFα) forward: tgaacttcggggtgatcg, reverse: gggcttgtcactcgagtttt.The reactions were carried out in quadruplicates.

Statistical analysis

Prism 5 (GraphPad Software Inc., La Jolla, CA) was used for statistical analysis. Differences among the means were analyzed using one-way ANOVA and Bonferroni's multiple comparison test in figure 1, Mann Whitney test, Kruskal Wallis test, and Dunn's post-hoc test in figures 2-4. Correlation in figure 2 was analyzed using linear regression. $p<0.05$ was considered statistically significant.

Results

Energy consumption, body and brain weight

The energy consumption and body weight were recorded weekly for 30 weeks. No difference of energy intake was observed among the 3 groups when the weekly records were averaged (Figure 1A). At the end of the study (when the rats were 42-week-old), the average body weights of the 3 groups were different (p=0.0053, one-way ANOVA, Figure 1B), i.e. TG and TG+BEX rats were significantly lighter than the F344 rats (-12.6%, TG vs. F344, -12.4%, TG+BEX vs. F344, p<0.05, Bonferroni's post-hoc). Neither wet brain weight nor the ratio of brain weight over body weight showed differences among the 3 groups (Figures 1C and D).

HIV-1 transgenesis-induced glial activation and itsattenuation by BEX

To study HIV-1 transgenesis-induced inflammation in the hippocampus, the expression of astrocyte marker (GFAP) and microglia marker (Iba1) were measured. TG rats fed control diet showed almost 7 folds increase of GFAP protein level compared to F344 rats (Figures 2A and 2B, p=0.0079, Kruskal-Wallis test). This increment was significantly inhibited by BEX supplement (p<0.05, Dunn's post hoc test), and as a result, the protein levels of GFAP in the F344 rats and TG+BEX rats were similar. Conversely, the mRNA levels of GFAP did not show difference among the 3 groups (Figure 2E).

The protein expression of Iba1 was significantly decreased in the TG rats fed control diet compared to that in the F344 rats (-92.5%, p=0.003), but BEX supplement in the TG rats increased Iba1 protein by almost 40 folds (p=0.016), as shown in Figures 2A and 2C. Interestingly, the protein expression of GFAP and Iba1 showed strong negative correlation when data from all samples were pooled (Figure 2D, r=-0.92, p<0.0001). No difference of the Iba1 mRNA expression was found among the 3 groups (Figure 2F).

HIV-1 transgenesis-induced upregulation of cytokines and its reduction and normalization by BEX

As shown in Figures 3A and 3B, the protein level of IL-1β in the TG rats fed control diet was 1.4 folds higher than that in the F344 rats

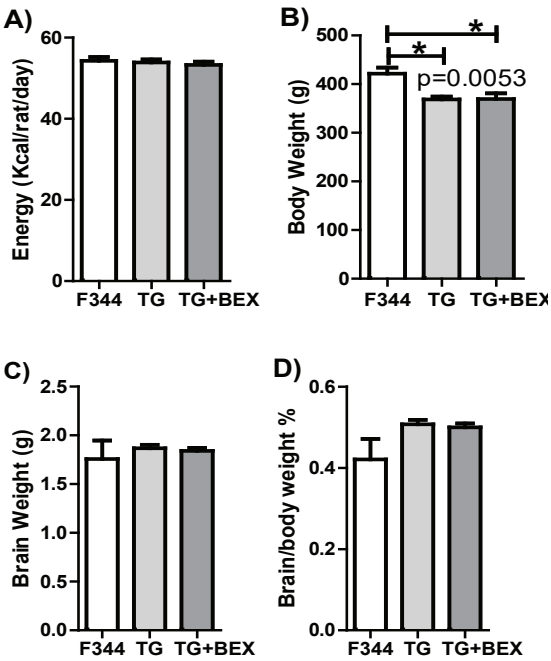

Figure 1: Energy consumption, body and brain weight of F344 rats fed control diet (F344), HIV-1 transgenic rats fed control diet (TG), and HIV-1 transgenic rats supplemented with BEX (TG+BEX). A: Energy consumption over 9 months. B: Bodyweight before decapitation. C: Wet brain weight. D: Percentage of brain weight over body weight. Average and SD are shown, n=5 per group. The P value labeled in panel B was from one-way ANOVA.*p<0.05, Bonferroni's multiple comparison

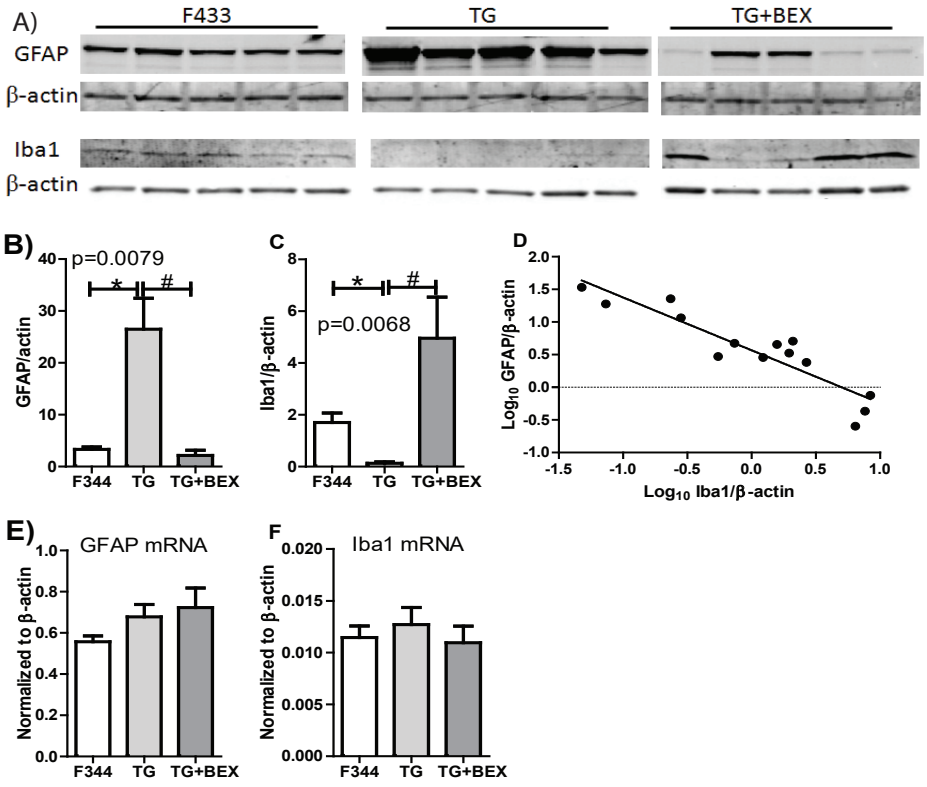

Figure 2: Protein and gene expression of glial fibrillary acidic protein (GFAP) and ionized calcium-binding adapter molecule 1 (Iba1)in the hippocampus of F344 rats fed control diet (F344), HIV-1 transgenic rats fed control diet (TG), and HIV-1 TG rats supplemented with BEX (TG+BEX). A: Western blot image of GFAP, Iba1, and loading control β-actin. B: Relative quantification of GFAP protein expression. C: Relative quantification of Iba1 protein expression. D: Correlation between the protein levels of GFAP and Iba1. E: Relative mRNA expression of GFAP.F, Relative mRNA expression of Iba1. Average and SD are shown, n=5 per group. P values labeled in panels B and C were from Kruskal-Wallis test; and that in panel D was from linear regression. #p<0.05, Dunn's multiple comparison test; *p<0.05, Mann Whitney test. For western blot, all samples were run on the same gel.

(p<0.05, Dunn's post-hoc), and this increment was normalized by BEX supplement, as indicated by a 37% decrease of IL-1β expression in the TG+BEX rats compared to the TG rats fed control diet (p=0.056, Mann-Whitney test). The IL-1β levels in the F344 and TG+BEX groups were comparable. Similar changes were also observed on the mRNA level of IL-1β (Figure 3C), i.e., the highest IL-1β mRNA level was found in the TG rats fed control diet, which was 90% higher than the F344 group (p=0.016, Mann-Whitney test) and 170% higher than the TG+BEX group (p<0.01, Dunn's post-hoc). The TG+BEX rats also showed lower IL-1β mRNA level than the F344 rats (-38.4%, p=0.03, Mann Whitney test). When mRNA expression of TNFα was tested (Figure 3D), higher TNFα mRNA level was found in the TG rats fed control diet compared to the TG+BEX rats (+113%, p=0.03, MannWhitney's test, Figure 3D).

HIV-1 transgenesis-induced upregulation of transcription factors and its normalization by BEX

To understand the transcriptional regulation of the cytokines, the protein expression of p65 (a subunit of NFκB) and c-Jun (a subunit of AP-1) were measured (Figure 4). The p65 protein expression level was different among the three groups (p=0.038, Kruskal Wallis test), and it was significantly lower in the TG+BEX rats compared with the TG rats fed control diet (-42.6%, p<0.05, Dunn's post-hoc, Figure 4B). The protein expression of c-Jun was also different among the three groups (p=0.02, Kruskal Wallis test, Figure 4C), with significantly higher c-Jun expression in the TG rats fed control diet than the F344 rats (+40.4%, p=0.016, Mann-Whitney test) and the TG+BEX rats (+113%, p<0.05, Dunn's post-hoc). While the F344 and TG+BEX groups showed similar protein levels for both p65 and c-Jun.

Discussion

Astrogliosis has been reported in both HIV-infected patients [4] and animal models [23,24]. We showed increased GFAP protein expression in the hippocampus of the TG rats, which is consistent with the hippocampal inflammation observed in HIV patients [4]. However, using the same animal model, Rao et al. [21] reported no changes on mRNA and protein levels of GFAP in the left hemisphere of the TG rats. This difference may be due to the following reasons: (1) age difference, the rats in the study of Rao et al. [21] were 1-3 months younger than those used in our study; (2) Rao et al. [21] used the cytosolic fraction for western blot, while we extracted proteins using a membrane lysis buffer, which could have released compartmentalized proteins; and (3) Rao et al. [21] studied the combined effect in multiple brain regions, while we focused on a defined region. Rao et al. [21] reported increased mRNA and protein levels of IL-1β, TNFα and protein level of NF-κB subunit p50, which were inline with our observations. A different research group also used this animal model for inflammation study, and they reported upregulated protein levels of TNFα, IL-1β, and GFAP in the frontal cortex and subcortical white matter, implicating neuroinflammation in other brain regions besides the hippocampus [24].

As a commonly used microglial activation marker, Iba1 expression has been found increased in the CNS of patients with HIV encephalitis [25], as well as in the spinal cord [26] and caudate-putamens [27] of rats treated with gp120. In 4-to-5-month-old HIV-1 TG rats, increased abundance of Iba1 positive microglial cells were found in both hippocampus and neocortex, and the change was more prominent in the hippocampus compared to the neocortex; these cells also displayed abundant branches and processes and distended cytoplasm, suggesting the possibility of an activated state [28]. However, our study showed decreased Iba1 expression in the hippocampus of the TG rats. In line with our finding, Rao et al. [21] also reported that in the hippocampus of 7-month old HIV-1 TG rats, the Iba1-positive microglia showed decreased arbor complexity and ~50% shortened processes compared to control [21]. Therefore the decrease of hippocampal Iba1 expression found in our study may be associated with the morphology changes of the Iba-positive microglia in the HIV-

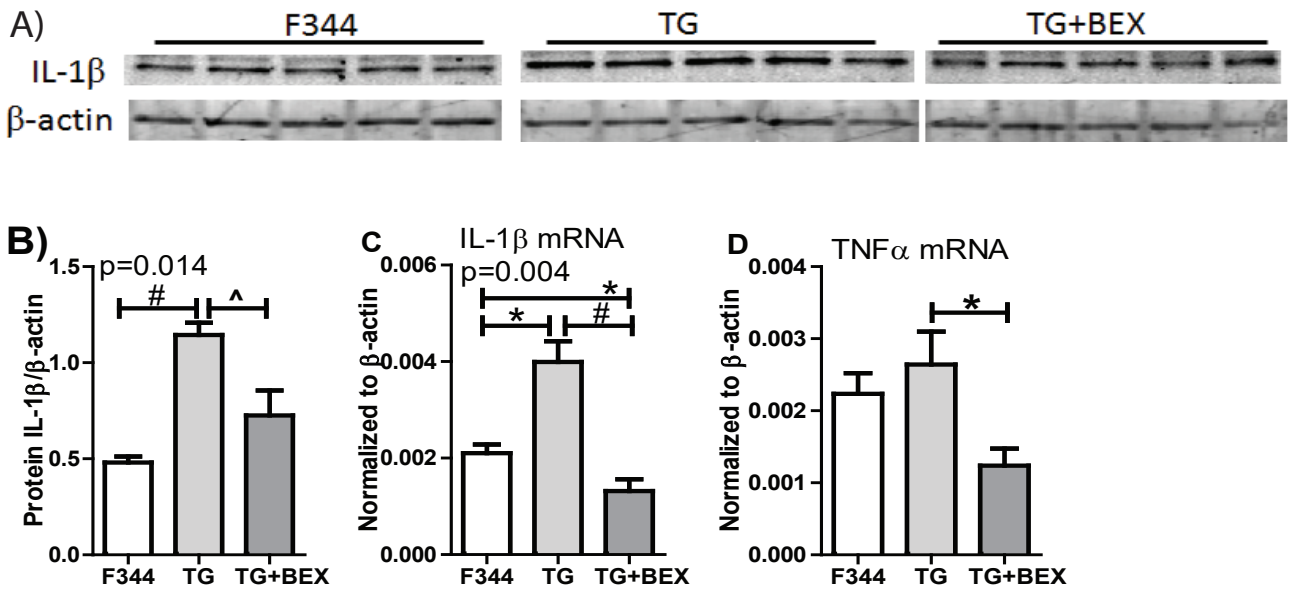

Figure 3: Protein and gene expression of interleukin-1β (IL-1β) and tumor necrosis factor α (TNFα) in the hippocampus of F344 rat fed control diet (F344), HIV-1 transgenic rats fed control diet (TG), and HIV-1 transgenic rats supplemented with BEX (TG+BEX). A: Western blot image of IL-1β and loading control β-actin. B: Relative quantification of IL-1β protein expression. C: Relative quantification of IL-1β mRNA expression. D: Relative quantification of TNFα mRNA expression. Average and SD are shown, n=5 per group. P values in panels B and C were from Kruskal-Wallis test. #p<0.05, Dunn's multiple comparison test; *p<0.05, Mann Whitney test; ^p=0.056, Mann Whitney test. For western blot, all samples were run on the same gel.

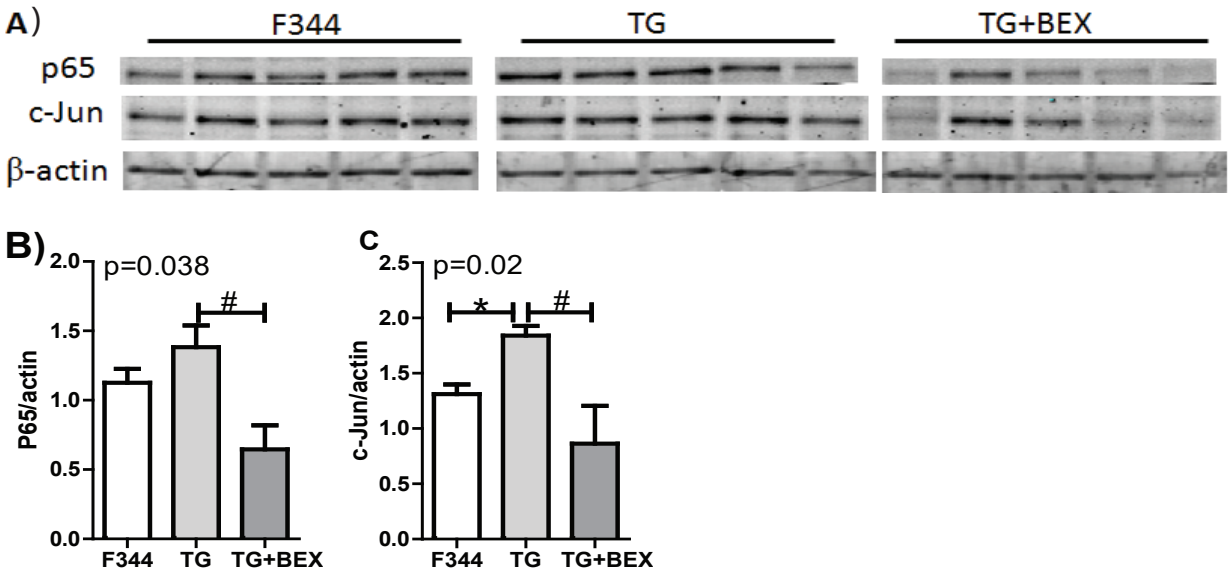

Figure 4: Protein expression of p65 and c-Jun in the hippocampus of F344 rat fed control diet (F344), HIV-1 transgenic rats fed control diet (TG), and HIV-1 transgenic rats supplemented with BEX (TG+BEX). A: Western blot image of p65, c-Jun and loading control β-actin. B: Relative quantification of p65 protein expression. C: Relative quantification of c-Jun protein expression. Average and SD are shown, n=5 per group. P values in panels B and C were from Kruskal-Wallis test. #p<0.05, Dunn's multiple comparison test; *p<0.05, Mann Whitney test. For western blot, all samples were run on the same gel.

1 TG rats. Furthermore, a study of Cerbai et al. [29] showed that the number of Iba1-positive reactive microglia significantly decreased in the CA1 Stratum radiatum of the hippocampus of aged (22-month) rats compared to adult (3-month) rats, while the number of resting microglia remained the same [29], implicating that microglial activation is age-dependent. The HIV-1 TG rats in our study were 10 months, and potential premature aging in these rats may have at least partially caused the decrease of Iba1 in the hippocampus. Interestingly, Cerbai et al. [29] also showed spatial reciprocal interaction of microglia and astrocytes around apoptotic neurons [29], which might be a potential explanation for the inverse correlation between the protein levels of GFAP and Iba1 found in our study.

Our previous studies showed that BEX inhibited NFκB and AP-1 activation under lipotoxic conditions [20], and prevented obesity-induced inflammation in peripheral circulation [19]. Bioactivity-guided fractionation revealed that flavonoids such as tricin and 7-O-methyltricin were among the anti-inflammatory compounds in BEX [30]. In the present study, BEX inhibited the increases of both mRNA and protein levels of IL1β in the hippocampus of the HIV-1 TG rats, and meanwhile lowered the protein levels of p65 and c-Jun, implicating the inhibition of both NFκB and AP-1 pathways. PPARγ upregulation has been reported to attenuate NFκB and AP-1 signaling [31], and interestingly our unpublished *in vitro* data suggested that BEX was able to enhance the gene expression of PPARγ. NFκB activation is also linked to the upregulation of GFAP [32], which provides an explanation to the GFAP over expression in the hippocampus of the HIV-1 TG rats, and the protective effect of BEX. Lastly, NF-κB is needed for HIV viral gene transcriptional activation through the binding of p50/p65 and c-Jun at the long terminal repeat (LTR) [33], whether BEX can reduce HIV replication through inhibiting NF-κB activity is to be further studied.

It is arguable that since BEX inhibited multiple protein expressions in the hippocampus of the TG rats, it is possible that BEX might have caused hippocampal atrophy. To exclude this possibility, we also evaluated the spatial learning ability (which is closely related to hippocampal function) of the rats 2 months before the endpoint using a modified Morris water maze [34]. We found that after 2 weeks of training, it took the TG rats 2.4 folds longer time to find the hidden platform than the F344 rats did, and BEX supplement shortened this latency in the TG rats by 36% (Supplemental Figure 1). This result showed that BEX supplement seemingly improved the hippocampal function, and therefore should not have caused hippocampal atrophy.

In conclusion, this study demonstrated neuroinflammation in the hippocampus of the HIV-1 TG rats, as evidenced by higher expression levels of GFAP and IL1β, and this inflammatory status was effectively abolished by dietary supplement of BEX through inhibiting the NF-κB and AP-1 signaling.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Author's Contributions

XP carried out experiments, analyzed and interpreted data, and drafted and revised the manuscript. JP designed the study, interpreted data and critically revised the manuscript.

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