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ORIGINAL ARTICLE

Neurotrophin Receptor p75 mRNA Level in Peripheral Blood Cells of Patients with Alzheimer's Disease

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Abstract

The neurotrophin receptor p75 (p75NTR) plays important roles in regulating amyloid-beta (Aβ) metabolism in the brain. The expression of p75NTR is altered in the brain of patients with Alzheimer's disease (AD). In this study, we aimed to evaluate whether p75NTR mRNA level in the peripheral blood cells is changed among AD patients and its potential to be a biomarker for AD. The study subjects included 26 patients with AD (PiB-PET positive) and 28 cognitively normal controls (PiB-PET negative). RNA was extracted from peripheral blood cells of fast blood. p75NTR mRNA was measured using quantitative real-time PCR assay. p75NTR mRNA levels in blood cells were comparable between AD patients and controls. p75NTR mRNA levels in blood cells were not correlated with MMSE scores, ApoE genotypes, gender, and age. p75NTR mRNA expression in blood cells is not changed in AD patients and is unlikely to be a biomarker for AD.

Keywords Alzheimer's disease (AD) · mRNA · Pittsburgh compound B (PiB) · p75 neurotrophin receptor (p75NTR)

Introduction

Alzheimer's disease (AD) is the most common form of dementia among the elderly and has become a major challenge for global health care (Alzheimer's Disease International and World Health Organization 2012; Wang et al. 2017b). However, no disease-modifying therapeutics are currently available. All previous efforts to treat AD patients at advanced stage failed to reverse the cognitive impairment in phase III clinical trials, suggesting that intervention at the early stage of the disease is the key to halt the progress of the disease. Thus, identification of biomarkers, particularly the peripheral biomarkers, is of great significance for the early detection of AD and disease intervention (Hampel et al. 2018; Sun et al. 2018).

Brain senile plaques consisting of amyloid-beta (Aβ) deposition is one of the hallmarks for pathological diagnosis of AD (Braak and Del Trecidi 2015). It is suggested that accumulation and aggregation of Aβ peptides result in neuronal death, leading to cognitive dysfunction in AD (Hardy and Higgins 1992; Xin et al. 2018). Thus, a promising strategy of early diagnosis is to screen the potential biomarkers from the molecules which regulate the metabolism of Aβ (Jack et al. 2018).

The neurotrophin receptor p75 (p75NTR) is a receptor for Aβ and mediates Aβ-induced neurodegenerative signals (Knowles et al. 2009; Sotthibundhu et al. 2008; Yaar et al. 1997). Our previous studies suggest that p75NTR plays an important role in regulating Aβ production, deposition, and clearance in the brain of AD patients (Wang et al. 2011; Yao et al. 2015), and mediating tau hyperphosphorylation (Shen et al. 2018). These findings indicate that p75NTR is involved in the pathogenesis of AD (Zeng et al. 2011). p75NTR is mainly expressed on the cholinergic neurons in the basal forebrain which are most affected in AD (Yeo et al. 1997). The brain expression of p75NTR is increased during aging and in AD patients (Chakravarthy et al. 2012; Costantini et al. 2005; Hu et al. 2002; Perez et al. 2011; Salehi et al. 2000; Wang et al.

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2011), suggesting that p75NTR might be a potential biomarker of AD (Chao 2016; Jiao et al. 2015).

It is recently suggested that peripheral Aβ metabolism is also involved in the pathogenesis of AD (Bu et al. 2018) and might be a source of AD biomarkers (Wang et al. 2017a). p75NTR is also expressed in white blood cells (Berzi et al. 2008; Ralainirina et al. 2010; Rogers et al. 2010). In the present study, we tried to investigate whether and to what extent the p75NTR mRNA level in blood cells changes in patients with AD, furthermore, whether p75NTR expression level in the peripheral blood cells can serve as a surrogate biomarker for AD.

Methods and Materials

Study Participants

The subjects with different ApoE genotypes were selected from the registry of AD patients in the neurology department of Daping Hospital. The eligibility of AD patients included (1) who were clinically diagnosed with AD; (2) who received the amyloid PET imaging examination; (3) who were willing to participate in the study. Age, gender, and ApoE genotype-matched cognitively normal subjects, whose amyloid PET imaging examinations were negative for brain amyloid deposition, were also enrolled as controls. A total of 26 AD (PiB-positive) and 28 cognitively controls (PiB-negative) were enrolled. This study was approved by the Ethics Committee of Daping Hospital affiliated to Third Military Medical University.

Clinical Assessment

The clinical evaluations were performed by neurologists who were experienced in dementia diagnosis following our previous protocols (Bu et al. 2015). In brief, the demographic data, medical history, and cognitive and functional status were assessed and collected based on formal questionnaires. Patients were also subjected to several blood tests and brain magnetic resonance imaging (MRI) or computed tomography (CT) and a neuropsychological battery, including Mini-Mental State Examination (MMSE), Montreal Cognitive Assessment (MoCA), and the Activities of Daily Living Scale (ADL) which were initially administered to screen and assess the overall cognitive and functional status. The subjects who were abnormal in MMSE or MoCA assessments were further administered with another battery of neuropsychological tests, including Hachinski Ischemic Score (HIS), Pfeiffer Outpatient Disability Questionnaire (POD), and Clinical Dementia Rating (CDR).

Diagnosis of AD

Dementia was diagnosed based on the criteria of DSM-IV. Subjects underwent Pittsburgh compound B (PiB)-positron emission tomography (PET) to illustrate brain Aβ deposition if they were diagnosed with probable AD dementia according to the criteria of National Institute of Neurological and Communicative Diseases and Stroke/AD and Related Disorders Association (McKhann et al. 1984). According to the NIA-AA criteria (McKhann et al. 2011), diagnosis of AD was made if patients with probable AD were positive in brain PiB-PET tests. Moreover, the cognitive normal controls were also administrated with PiB-PET tests to confirm their amyloid deposition status.

RNA Extraction

Fast blood was collected using PAXgene Blood RNA Tube (QIAGEN) and stored at − 80 °C until analysis. The total RNA was extracted with the PAXgene Blood RNA Kit (QIAGEN) according to the manufacturer's instructions.

Quantitative Real-Time PCR

For each RNA sample from an EDTA tube or a PAXgene tube, an equal amount of total RNA (1 μg) was reverse-transcribed into cDNA with random-hexamer primer mix using M-MLV Reverse Transcriptase (Promega) according to the manufacturer's instructions. The qRT-PCR was performed on Bio-Rad Real-Time PCR System with SYBR Green Master Mix (Bio-Rad). The p75NTR fragment was amplified by PCR using human full-length p75NTR as the template and p75NTR specific primers, including forward primer: CCTACGGCTACTAC CAGGATG, and reverse primer: CACACGGTGTTCTG CTTGT (Shen et al. 2018). The β-actin primers were forward CATGTACGTTGCTATCCAGGC and reverse CTCCTTAA TGTCACGCACGAT. This set of primers were validated to specifically measure p75NTR mRNA levels in human brain tissues in our previous study (Shen et al. 2018).

The value was calculated and repeated three times for each sample. The melting curve and real-time PCR amplification chart for the amplicons of p75NTR gene in AD and control groups are shown in Fig. 1.

Statistics

For qRT-PCR analysis, β-actin was used as a reference gene and the relative levels of target genes were calculated with the comparative Ct method. One blood sample was randomly chosen as the reference sample and it was amplified in each PCR run. The level of the target gene in the reference sample was set as 1 and the relative levels of all

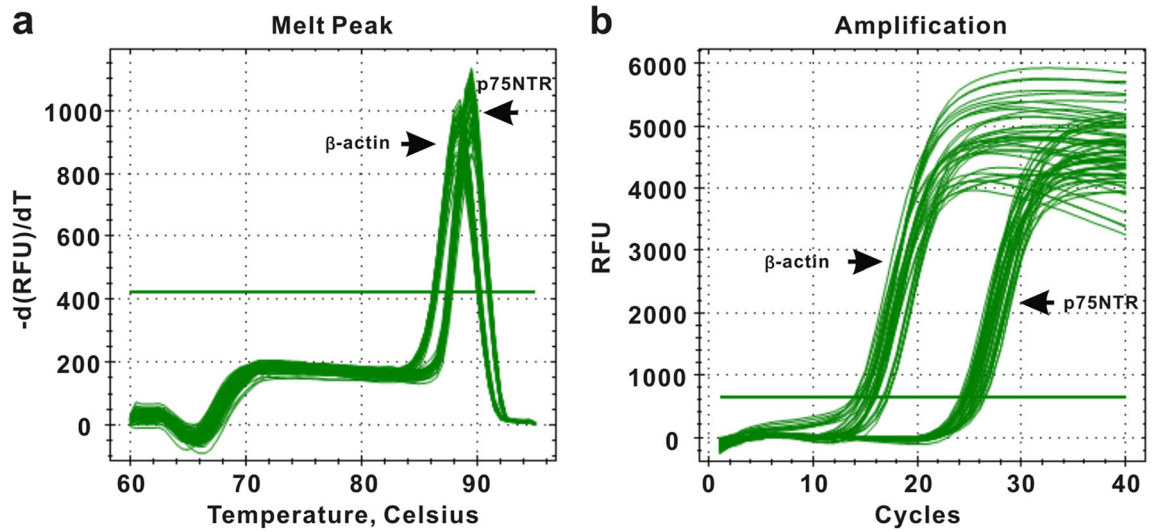

Fig. 1 Real-time PCR of p75NTR in AD and control groups. **a** Melting curve analysis of p75NTR and β-actin genes: the melting curves for all amplicons presented only one peak for each gene (melting temperature: p75NTR, 89.5 °C; β-actin, 88.5 °C). **b** The amplification plot: the amplification plot screen displays post-run amplification of each sample, and the PCR cycle number at which the fluorescence meets the threshold in the amplification plot (Ct value) of p75NTR and β-actin genes in AD and control groups

samples were normalized according to the reference sample. Data were presented as median (range). All the analyses were performed on actual data. The normality of data distribution was evaluated by the Kolmogorov-Smirnov test. Difference in the target gene level was analyzed by nonparametric Mann–Whitney *U* test for two groups or Kruskal–Wallis test followed by post hoc Dunn's multiple comparison tests for more than two groups. The $P < 0.05$ was considered statistically significant. All statistical analysis was performed using SPSS statistical package 15.0.

Results

Subject Demographic Characteristics

The study consists of AD set (Aβ-positive set) in the Chinese population. Baseline characteristics of the participants are displayed in Table 1. There were no significant differences in ages, ApoE genotypes, and gender between the two groups.

p75NTR mRNA Level between AD Patients and Controls

The mRNA levels of p75NTR were 1.50 ± 1.37 in AD group and 1.35 ± 1.10 in the control group (Fig. 2). No significant difference was detected between AD group and control group.

Correlation between p75NTR mRNA Levels and MMSE Scores

The association of p75NTR mRNA levels and MMSE scores was analyzed and revealed that there was no significant correlation between p75NTR mRNA level and MMSE score in the total cohort ($r = 0.044$, $p = 0.752$) (Fig. 3).

Table 1 Comparison of clinical data in the AD and controls

Clinical variable	AD *n* = 26	Control *n* = 28	*P* value
Age (years) (range)	71.85 ± 8.27 (52–87)	69.75 ± 8.98 (53–86)	0.377
PIB (pos/neg)	26/0	0/28	NA
ApoE4/Non-ApoE4	16/10	9/19	0.055
Male/female	13/13	12/16	0.785
MMSE (range)	13.58 ± 7.73 (0–27)	27.18 ± 3.76 (14–30)	0.000

Data are expressed as mean ± S.D. values. *P*-values were computed using independent samples *t* test (age, MMSE) or χ^2 test (ApoE4/Non-ApoE4, female/male). *P* values < 0.05 were considered significant. NA = not applicable

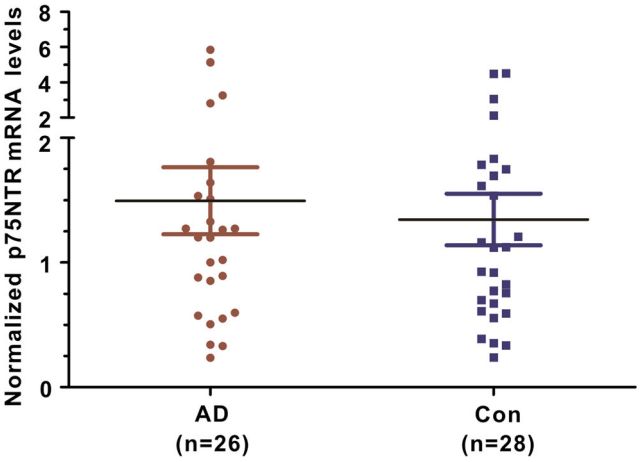

Fig. 2 Comparison of normalized p75NTR mRNA levels between AD group and control group ($P > 0.05$)

p75NTR mRNA Level by Age, Gender, and ApoE Genotypes

Levels of p75NTR mRNA were not found to significantly differ by ApoE genotypes. The p75NTR mRNA in ApoE e4 group was (1.58 ± 1.20) and 1.27 ± 1.25 in non-ApoE-e4 group (Fig. 4a). There were also no significant differences in p75NTR mRNA levels among each ApoE genotype subgroups ($p > 0.05$) (Fig. 4b, c). The p75NTR mRNA levels were also not significantly different between the male group (1.48 ± 1.28) and female group (1.37 ± 1.20) ($p > 0.05$) (Fig. 5a, b). We also valued the association of p75NTR mRNA level and age and no significant correlation was found ($r = -0.120$, $p = 0.387$, Fig. 5c).

Discussion

In the present study, the expression of p75NTR mRNA was detected in the peripheral blood cells from sporadic AD patients. We found that p75NTR mRNA level in blood cells was comparable between AD patients and controls, and was not correlated with MMSE scores, ApoE genotypes, gender, or age.

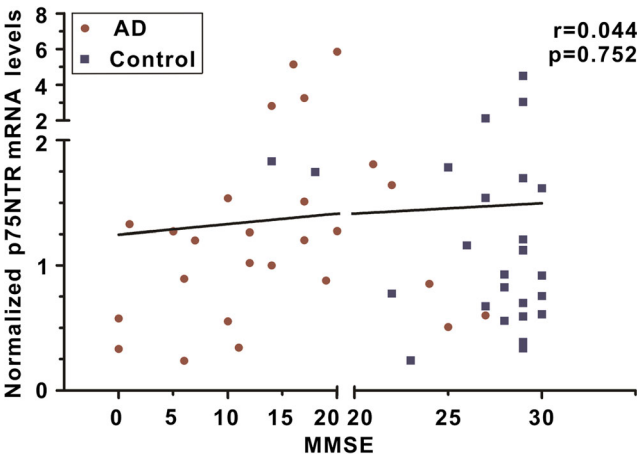

Fig. 3 Correlation of normalized p75NTR mRNA levels and MMSE scores

Identification of peripheral blood biomarkers is an important strategy for early and easier detection of AD patients. Recent studies suggested that molecules regulating Aβ metabolism in peripheral blood cells may be able to serve as a biomarker for AD. For example, the expression of transient receptor potential canonical 6 (TRPC6) in blood cells changed in peripheral blood cells in a pattern that is similar to its increased expression in the brain of AD patients. Moreover, using TRPC6 as a biomarker can substantially differentiate AD dementia patients from those with MCI or cognitively normal controls (Lu et al. 2018). In the brain, p75NTR plays an important role in AD pathogenesis. It is known that p75NTR could mediate Aβ-induced neural damage (Perini et al. 2002) and it is involved in Aβ-induced inflammation (Yaar et al. 2008) and neurodegeneration (Knowles et al. 2009; Sotthibundhu et al. 2008; Yaar et al. 1997). p75NTR also mediates proneurotrophins and Aβ-induced Tau-phosphorylation (Saez et al. 2006; Shen et al. 2018; Yao et al. 2015). As p75NTR has been proven to be involved in the pathogenesis of AD, we tried to explore whether p75NTR mRNA level in peripheral blood cells could be a potential biomarker for AD in the present study.

p75NTR is mainly expressed in the cholinergic neurons of the basal forebrain. Previous studies revealed that p75NTR is also expressed in the peripheral neurons and tissues such as NK and B cells (Berzi et al. 2008; Ralainirina et al. 2010; Rogers et al. 2010). The expression of p75NTR is increased under pathological conditions such as trauma and ischemia (Kokaia et al. 1998; Skup et al. 1996). In the present study, we found that p75NTR expression was not changed in AD patients in relative to age- and gender-matched controls, suggesting that the p75NTR expression in blood cells may not participate in the pathogenesis of AD.

p75NTR was found to be subjected to the proteolysis by tumor necrosis factor-alpha-converting enzyme (TACE) under physiological conditions and release soluble ectodomain of p75NTR (p75ECD) (Weskamp et al. 2004). Our previous study revealed that p75ECD may be an endogenous protective molecule against Aβ neurotoxicity and deposition (Wang et al. 2011). p75ECD release is suppressed specifically in AD brains with decreased expression in parenchymal and cerebrospinal fluid (Yao et al. 2015). However, we also found that p75ECD levels were increased in the blood of AD patients and were able to differentiate AD patients from cognitively normal controls (Jiao et al. 2015). While we speculate that p75NTR expression would be increased in the periphery, thus leading to the release of more p75ECD into blood in AD patients (Jiao et al. 2015), p75NTR expression in peripheral blood cells was not altered. The source of elevated p75ECD in

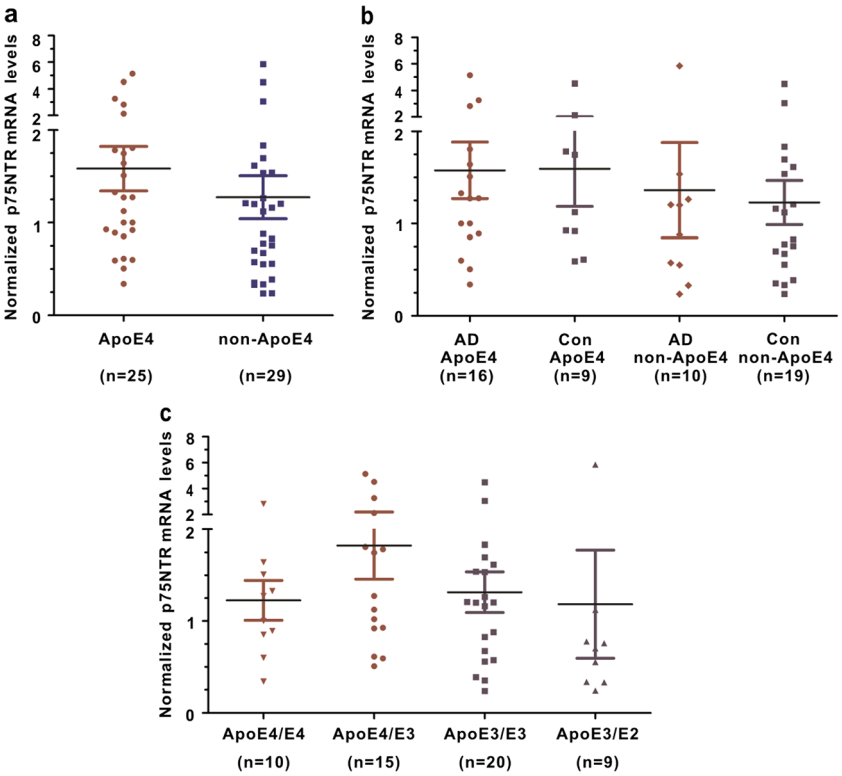

Fig. 4 Normalized p75NTR mRNA levels in different ApoE genotypes groups. **a** Comparison of p75NTR mRNA levels between ApoE4 group and non-ApoE4 group ($p > 0.05$). **b** Comparison of p75NTR mRNA levels among ApoE4 subgroups and non-ApoE4 subgroups in AD group and control group ($p > 0.05$). **c** Comparison of p75NTR mRNA levels among different ApoE genotype groups ($p > 0.05$)

the blood of AD patients remains to be elucidated in further investigation.

The strength of the present study is that the AD patients and cognitively normal controls we enrolled were all confirmed by brain amyloid PET. The recruitment of AD cases in most previous studies was mainly based on clinical manifestation without pathological evidence, resulting in around 25% of enrolled subjects showing no brain amyloid deposition and

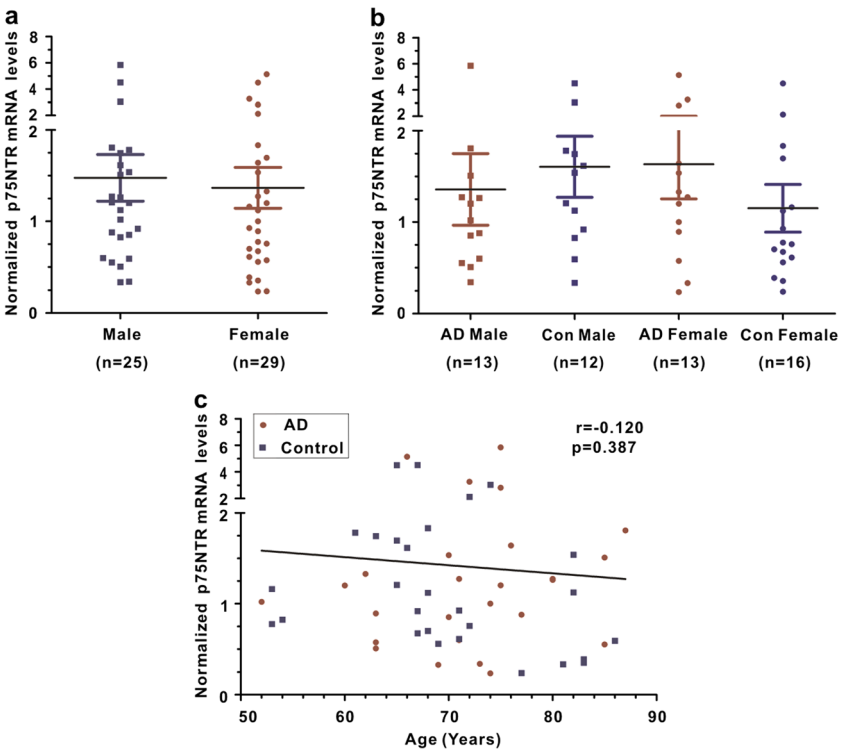

Fig. 5 Normalized p75NTR mRNA levels in different gender groups and correlation between normalized p75NTR mRNA levels and age. **a** Comparison of p75NTR mRNA levels between male group and female group ($p > 0.05$). **b** Comparison of p75NTR mRNA levels among male subgroup and female subgroup in AD group and control group ($p > 0.05$). **c** Correlation between normalized p75NTR mRNA levels and age ($r = -0.120$, $p > 0.05$)

thus they are not actual AD cases (Beach et al. 2012; de Wilde et al. 2018). Therefore, the findings of our present study are relatively more reliable. One limitation of our study is the enrolment of a relatively small number of cases, which may restrict interpretation of our data. Despite that, the p75NTR mRNA level in blood cells may not be a suitable biomarker for AD, the mRNA levels of some other AD-related molecules are suggested to be altered in blood cells (Lu et al. 2018; Manzine et al. 2015; Poulopoulou et al. 2008; Zhang et al. 2012). Thus, identifying biomarkers from the periphery is still a promising way to understand the AD pathogenesis and improve early diagnosis in the future (Wang et al. 2017a).

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