International Congress Series 1304 (2007) 357–361

www.ics-elsevier.com

Up-regulation of the brain indoleamine 2,3-dioxygenase activity in a mouse model of Alzheimer's disease by systemic endotoxin challenge

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Abstract. Inflammation is suspected to be a critical component of the progression and severity of neurodegeneration in Alzheimer's disease (AD). The kynurenine pathway (KP), which is the major route for tryptophan degradation, is activated in central nervous system (CNS) inflammation. The activation of KP, which is caused by the up-regulation of indoleamine 2,3-dioxygenase (IDO), leads to the production of some neurotoxic metabolites (e.g., quinolinic acid). To address the hypothesis that the KP may play a role in the pathogenesis of the AD brain, we examined the IDO activity in the brain of the Tg2576 transgenic mouse model of AD. The IDO activity was detected in the brain of the mouse model of AD, but the level was not significantly different from that of the age-matched nontransgenic control mice. In contrast, when CNS inflammation was induced in this mouse model by a single intraperitoneal injection of lipopolysaccharide (LPS), a marked (3-fold) increase in the IDO activity was observed, but not in the control mice with the same treatment. These results suggest that peripheral inflammation activates the CNS KP in the AD brain, leading to the production of neurotoxic metabolites and thereby inducing neuronal death.

Keywords: Alzheimer's disease; Indoleamine 2,3-dioxygenase; Inflammation; Lipopolysaccharide; Activated microglia

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0531-5131/
doi:10.1016/j.ics.2007.07.026

1. Introduction

Alzheimer's disease (AD), a progressive neurodegenerative disease, is the most prevalent cause of dementia in humans. Characteristic pathologies develop in the brain of AD patients, including senile plaques composed of amyloid β-peptides (Aβ), neurofibrillary tangles, as well as dystrophic neurites, diminished synaptic densities, and the loss of neuronal function [1]. Senile plaques are considered to be the foci of local inflammatory responses in the AD brain, as demonstrated by the presence of increased levels in acute phase proteins, pro-inflammatory cytokines, complement components, and proteases [2,3]. It is well established that senile plaques are surrounded by activated microglia and/or infiltrating macrophages [4]. These cells in AD are therefore thought to be major producers of proinflammatory mediators and neurotoxins [5,6].

The kynurenine pathway (KP) is a major route of the L-tryptophan (Trp) metabolism, which results in the production of NAD and various neuroactive intermediates [7]. Its production in the brain is probably controlled by the first and rate-limiting enzymes, indoleamine 2,3-dioxygenase (IDO). Of the neuroactive metabolites, much attention has been focused on the *N*-methyl D-aspartate receptor agonist and neurotoxin, quinolinic acid (QUIN), because it causes neural death either by direct intracerebral injection [8] or when it is applied to neurons in culture *in vitro* [9]. There is both direct and indirect evidence demonstrating that the KP is involved in AD [10,11]. The Trp concentrations in the blood of AD patients correlate inversely with the degree of cognitive deficit but not with the duration of the disease, and elevated serum concentrations of kynurenine have been also found in AD [12–14]. Although an earlier study did not find any significant changes in the QUIN levels in the brain or CSF from AD patients [15], in the AD hippocampus, QUIN has recently been reported to exist in cortical microglia, astrocytes and neurons, with the highest microglial and astrocytic expression of QUIN and IDO in the perimeter of senile plaques [10], suggesting the neurodegeneration in AD by local, and highly concentrated QUIN.

In the current study, we measured the IDO activity in the brain of a Tg2576 transgenic mouse model of AD to investigate whether the CNS KP showed any alterations by accumulating Aβ *in vivo*. We also used LPS to mimic the aspects of systemic infection to address the hypothesis that IDO in the brain of AD patients is up-regulated with the neuronal inflammation by peripheral infection.

2. Materials and Methods

2.1. Animals and LPS challenge

Tg2576 transgenic mouse models of AD (Tg2576) harboring a chimeric mouse/human β-amyloid precursor protein (APPswe) were obtained from Taconic Farms, Inc. (Germantown, NY). LPS (Salmonella equine abortus, Sigma, Poole, UK) in sterile saline was administrated intraperitoneally to 8 to 11-month-old Tg2576 mice (males, $n=9$) or nontransgenic (nonTg) littermates (male, $n=7$) at a dose of 500 μg/kg body weight, and returned to their cages. The control groups of both Tg2576 and nonTg mice (males, $n=7$ and $n=6$) received an injection in the same manner with saline only. All experiments were performed in compliance with existing laws and our Institute's guidelines.