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Effect of quinolinic acid on gene expression in human astrocytes: Implications for Alzheimer's disease

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Abstract. Activated microglia and astrocytes play a key role in the neuroinflammatory response during Alzheimer's disease (AD). The kynurenine pathway (KP) of tryptophan degradation is activated and production of the excitotoxin quinolinic acid (QUIN) by monocytic cells is increased. We studied here the effects of QUIN in pathophysiological concentrations on the expression of genes including IL-1β, IL-6, S100β, Glutamate synthetase (GS) glial fibrillary acidic protein (GFAP) that are commonly associated with astrocytes in the development of neuroinflammation in AD. We found that IL-6, S100β and GS genes were constitutively expressed in human adult astrocytes (HAA) and only with TNFα, but not QUIN, IL-6 and S100β expression were increased compared with controls in HAA. IL-1β expression was increased by IFN-γ, TNFα and QUIN in HAA. These preliminary results suggest that QUIN's role in astroglial inflammatory response is mediated by increase of IL-1β expression. Therefore, QUIN is likely to play a role in astroglial inflammatory response that may contribute to the pathogenesis of AD. © 2007 Published by Elsevier B.V.

Keywords: Alzheimer's disease; Inflammation; Quinolinic acid; Human adult astrocytes; Kynurenine pathway; IL1β; IL-6; S100β; GFAP; GS; TNFα; IFNγ

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1. Introduction

Alzheimer's disease (AD) is a progressive degenerative disease that affects cognition, behaviour, and the ability to perform activities of daily living [1]]. AD is associated with the dysfunction and degeneration of select populations of vulnerable neurons in the hippocampus and other cortical brain regions [2]. There is increasing evidence that quinolinic acid (QUIN) is involved in the pathogenesis of AD [14, #6558]. QUIN is the end-metabolite of the kynurenine pathway (KP), which is involved in the catabolism of L-tryptophan. However, this pathway is different between species and even between cell types. For example, both human macrophages and microglia have complete KP whereas human astrocytes lack one central enzyme and are unable to produce QUIN [3].

To date, little is known about the role of QUIN on astrocytes, which make up the brain's largest resident cells. Studies have found that QUIN could contribute and amplify brain inflammation by increasing production of chemokines and chemokine receptors by astrocytes [4]. However, that may not be the sole effect on astrocytes. There is also evidence that QUIN can increase GFAP, an astrocyte specific protein [5]. The effect of QUIN on other astrocyte specific proteins are unknown, particularly those associated with AD. Glutamate synthetase (GS) and S100β are two such proteins. GS is an important enzyme for glutamate–glutamine cycle and was found to be reduced in the vicinity of astrocyte endfeet and perisynaptic regions of neurons. This reduction in GS may implicate the astrocyte in glutamate excitotoxicity that may lead to AD [6]. S100β is a neurotrophic cytokine at normal concentrations but when overexpressed, S100β can lead to neuronal death [7]. IL-1β is a major driving force in AD pathogenesis and has been known to be overproduced in neuritic plaques found in AD. Moreover, it has been discovered that IL-1β can activate astrocytes and up-regulate S100β production [8]. Astrocytes are a major inducible source of IL-6 which can be a neurotrophic cytokine. However, overexpression could lead to neuroinflammation adding to the pathophysiology of AD. Many factors particularly, IL-1β and TNFα have been shown to induce IL-6 expression in rodent astrocytes [9,10]. Thus, it would be useful to investigate the effect of QUIN on IL-1β and IL-6 expression in human adult astrocytes. Since IFN-γ can increase the production of QUIN via the KP [11] and TNFα can induce IL-6 expression in astrocytes, these cytokines will be included in this study in order to simulate inflammation.

2. Materials and method

2.1. Preparation of purified primary cultures of human adult astrocytes (HAA)

Human adult brain tissues were obtained from the Neurosurgery Department of St. Vincent's Hospital from patients who had brain surgery following informed consent. AA were prepared using a previously described method by Guillemin et al. [12].

2.2. Stimulation of purified cultures of human astrocytes

Equal numbers of astrocytes were seeded into 6-well plates in 2 ml of RPMI 1640 medium. The cells were left to grow until 90% confluence. Then, astrocytes were treated