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FUNCTIONAL ROLE OF ACETYLCHOLINE IN THE IMMUNE SYSTEM

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1. ABSTRACT

Increasing evidence indicates that the central nervous system (CNS) can operate certain immune functions. There is a bidirectional regulation system between the brain and peripheral immune system during infection and inflammation. Furthermore, autopsy brain preparations in Alzheimer's disease patients show the up-regulated expression of proinflammatory cytokines, suggesting an important role of cytokines in disease progression. Recently, acetylcholine has been suggested to inhibit lipopolysaccharide (LPS)- induced inflammation in macrophages. In this paper, we review the important aspects of several cytokines under the pathologic conditions of CNS. Furthermore, we discuss recent views on the nonneuronal action of acetylcholine in the cross talk between acetylcholine and the immune system.

2. INTRODUCTION

Cytokine has a variety of roles in the brain (neuronal and glial cells) as well as the immune system (e.g. lymphocytes and macrophage). Infection and inflammation induce sickness responses such as anorexia, fever and depressed activity and these effects are mediated through cytokine production in the brain and immune tissues. Moreover, up-regulation of proinflammatory cytokine expression in an Alzheimer's disease suggests that proinflammatory cytokines are involved in disease progression. On the other hand, acetylcholine (ACh), the principal neurotransmitter, is reported to play an anti-inflammatory role in LPS-induced cytokine production (1). The purpose of this review is to summarize and discuss the role of cytokine in the brain during the bacterial infection or pathogenesis of Alzheimer's disease, in particular, the nonneuronal action of ACh-the role of ACh in the immune system.

3. CYTOKINE ACTION IN THE CENTRAL NERVOUS SYSTEM

The central nervous system (CNS) has been regarded as an immunologically privileged site. However, recent evidence indicates that the CNS can operate certain immune functions (2-4). Interleukin (IL)-1β, IL-6, and TNF-α are proinflammatory cytokines produced not only in the immune system but also in the brain. In addition to these cytokines, other cytokines or their receptors have been found to express in CNS cells, such as IL-11 (5), IL-12 (6), IL-15 (7) and IL-18 (8). There is a bidirectional regulation system between the brain and peripheral immune system. CNS can affect the peripheral immune system through endocrine, paracrine and neuronal mechanisms. On the other hand, the peripheral immune system communicates with the CNS. For example, inflammatory cytokine can activate the hypothalamic-pituitary-adrenal (HPA) axis and glucocorticoids in turn suppress further cytokine synthesis. Peripheral or central application of proinflammatory cytokines such as IL-1β_can affect various brain functions such as fever (9), inhibition of food intake (10) and gastric acid secretion (11, 12), and activation of the sympathetic (13) and HPA axis (14, 15) (Figure 1). Treatment with IL-1 receptor antagonist, which is known to block biological effects of IL-1, has shown to reduce endotoxin- or IL-1β- induced fever, indicating the importance of the physiological level of IL-1β in fever response (16, 17). Moreover, the importance of IL-6 expression in the CNS for lipopolysaccharide (LPS)- or IL-1-induced fever has been demonstrated in IL-6 deficient mice (18). In addition to such cytokines, many other cytokines have been reported to affect brain biological functions (9, 19, 20). Furthermore, in an Alzheimer's disease brain, expression of proinflammatory cytokines is up-regulated and has been suggested to play an important role in the disease progression (21, 22).

On the other hand, there are bidirectional interactions between nervous and immune systems via neurotransmitters and cytokines (Figure 1). Neurotransmitters including substance P (23, 24), norepinephrine (NA) (25) and serotonin (5HT) (26) increase IL-1 or IL-6 expression in astrocytes. Conversely, cytokines have been reported to modulate the release of ACh (27), NA, dopamine (DA) and 5HT (28) in the brain. Thus, cytokine play diverse and important roles in the CNS as well as peripheral immune functions.

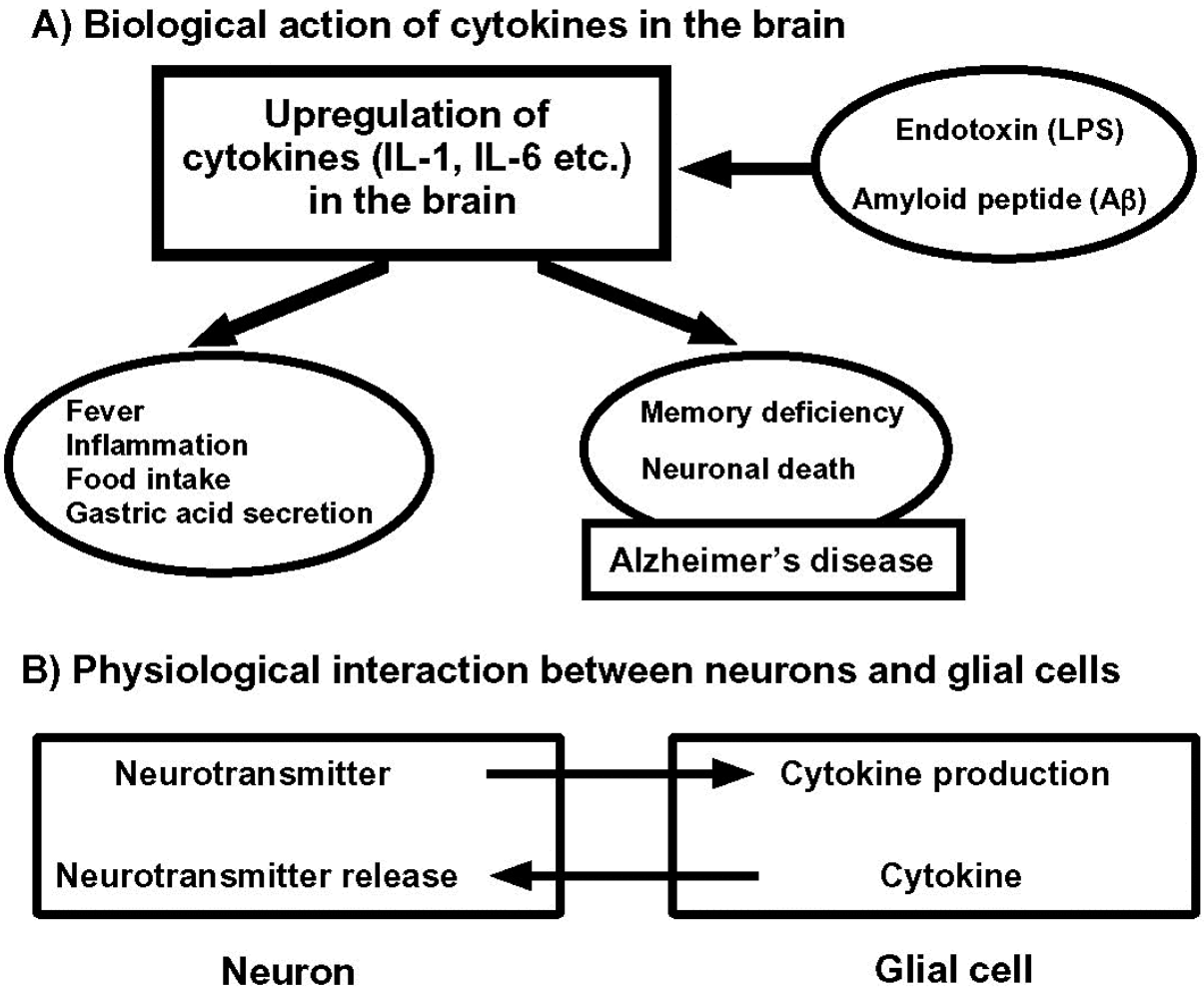

Figure 1. Cytokine action in the brain and neuro-glial interaction.

4. ALZHEIMER'S DISEASE AND NEURONAL CELL DEATH

In an Alzheimer's disease brain, massive neuronal loss is observed in the vulnerable brain regions (29, 30). Nuerofibrillary tangles and senile plaques are typical hallmarks of an Alzheimer's disease brain (31). The amyloid core of senile plaques are composed primary of 40- and 42-aminoacid peptides-$A\beta_{40}$ and $A\beta_{42}$, respectively. Aβ peptide is produced from a larger precursor, the amyloid precursor protein (APP) (32). The three proteases, α-, β-, and γ-secretases, which cleave APP, have been implicated in the development of Alzheimer's disease. The first cleavage occurs in the luminal domain of APP (β-cleavage) to generate a 10-kDa fragment. Then, it is further cleaved within the transmembrane domain (γ-cleavage) to produce Aβ. The generation of APPsec by α-cleavage in the luminal domain leaves an 8-kDa transmembrane fragment in the cell membrane, which subsequently generates nonamyloidogenic p3 by γ-cleavage. Among these products, Aβ is presumed to accumulate in the brain lesions and to cause the disease (33). The reactive astrocytes or microglia participate in the inflammatory response observed in Alzheimer's disease by their production of proinflammatory cytokines such as IL-1 (34), TNF-α (35, 36) or inducible nitric oxide synthase (iNOS) (37, 38). As shown in Figures 1 and 2, extracellular Aβ is known to act in the glial cell to produce proinflammatory cytokine such as TNF-α or iNOS via nuclear factor-κB (NF-κB) or mitogen-activated protein kinase (MAP Kinase)-dependent mechanisms (36, 39-41). The resulting products such as proinflammatory cytokine or excess NO act on neurons to elicit apoptosis. Moreover, Aβ is known to elicit endoplasmic reticulum stress (ER stress) in neurons, which subsequently activates caspase-12 and results in cell death (42). Thus, in the Alzheimer's disease brain, in addition to the direct action of Aβ to induce neuronal cell death, it is presumed possible indirect actions such as glial cytokine- and NO-mediated pathways to induce neuronal cell death.

5. ACETYLCHOLINE AND IMMUNE SYSTEM

Infection and inflammation induce sickness responses such as anorexia, fever and depressed activity.

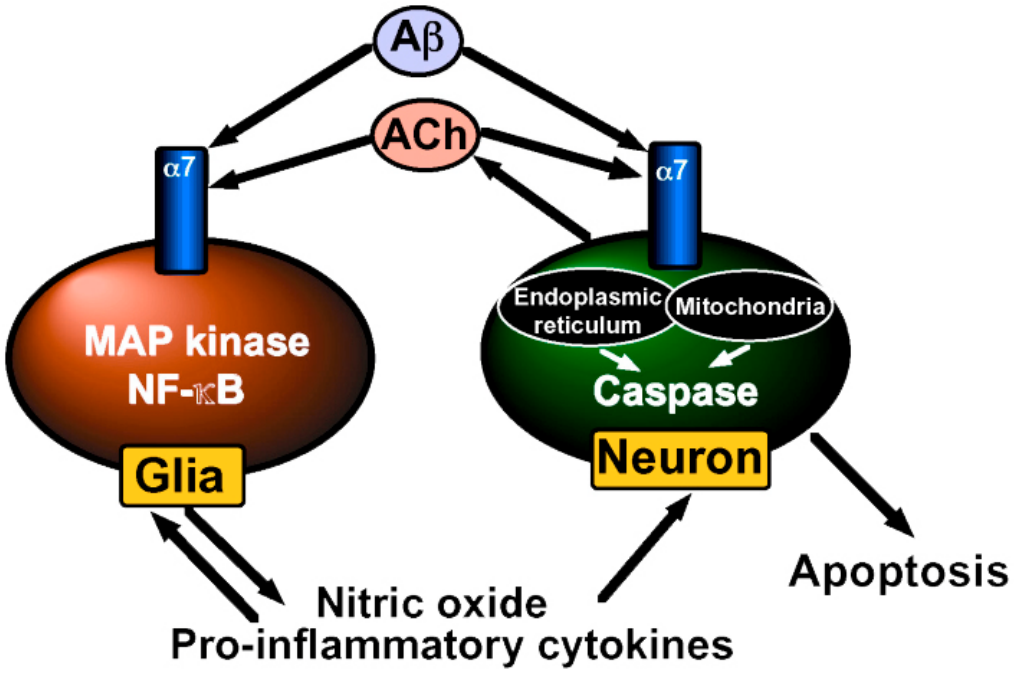

Figure 2. The cross talk between Aβ, cytokine and acetylcholine (ACh) in the neuron-glia interaction.

The proposed mechanisms of the brain's response to the peripheral immune system may include: 1) the direct entry of cytokine into the brain across the blood-brain barrier by a saturable transport mechanism (43); 2) the interaction of cytokine with circumventricular organs which lack the blood-brain barrier (44); and 3) activation of afferent neurons of the vagus nerve (45). On the other hand, central proinflammatory cytokines induce activation of both the sympathetic nervous system and HPA axis (46, 47). Recently, a novel pathway of the brain-mediated regulation of the peripheral immune response has been suggested. Borovikova *et al.* suggested that a "cholinergic anti-inflammatory pathway" may directly modulate the systemic immune response to pathogenic invasion (1). They reported that electrical stimulation of the efferent vagus nerve inhibits LPS-induced TNF-α synthesis in the liver, whose effects seem to be due to ACh since ACh significantly attenuates the LPS-stimulated release of cytokines such as IL-1β, IL-6, TNF-α and IL-18 in cultured macrophages. Moreover, the ACh-mediated receptors that respond to the efferent vagus nerve signal have been identified as nicotinic ACh receptor α7 subunits (48). They showed that: 1) α7 nicotinic receptor subunits are expressed on macrophages and that nicotine inhibits LPS-induced TNF-α release, and 2) electrical stimulation of the efferent vagus nerve inhibits TNF-α synthesis in wild-type mice, but fails to inhibit TNF synthesis in α7 nicotinic receptor-deficient mice. Thus, they demonstrated a new role of ACh which acts on the macrophages to inhibit inflammation. It should be noted that the paper proposed a new pathway for the brain mediated anti-inflammatory parasympathetic pathway. In addition, the central application of CNI-1493, a tetravalent guanylhydrazone molecule, inhibits an LPS-induced increase in the serum TNF-α level via vagally mediated mechanisms (49). These findings suggest possible pharmacological therapy for cytokine-mediated diseases.

6. ACETYLCHOLINE AND GLIA IN ALZHEIMER'S DISEASE

It has been suggested that dysfunction of ACh containing neurons in the brain underlies Alzheimer's disease. The severity on cognitive dysfunction in Alzheimer's disease patients is significantly correlated with decline in choline acetyltransferase activity and loss of cholinergic neurons (50-52). Furthermore, amyloid β peptide has been shown to suppress ACh synthesis (53). Several epidemiological evidences suggest that the incidence of Alzheimer's disease is lower in smokers compared with nonsmokers (54, 55). Cigarette smoke contains various compounds with pharmacological activity. Of these compounds, nicotine is most important. Interestingly, it has been reported that β-amyloid binds to α7 nicotinic acetylcholine receptor subtype (56) and β-amyloid activates α7 nicotinic ACh receptors expressed in *Xenopus oocytes* (57). Moreover, β-amyloid has been shown to activate MAP kinase cascade via α7 nicotinic ACh receptor (58). On the other hand, Aβ_antagonizes the activation of α7 nicotinic ACh receptor-like currents in hippocampal interneurons (59). Glial cells express nicotinic and muscarinic ACh receptors as well as neuronal cells (60, 61). However, functional roles of ACh receptors on the glial cells have been poorly defined. As previously indicated, nicotine has an anti-inflammatory role in the LPS-stimulated macrophages. Thus, it would be interesting to clarify whether acetylcholine affects LPS- or Aβ-induced expression of cytokine production in glial cells in future studies. Brain ACh may act on the glial cells to

inhibit Aβ-induced inflammation and thus inhibit the progression of Alzheimer's disease. Nicotinic agonists may be useful drugs to prevent/treat Alzheimer's disease. It will be an interesting subject to investigate the immunological as well as neurological roles of ACh and glial cells in the brain with regard to the pathogenesis of Alzheimer's disease (Figures 1 and 2).

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