Can Peripheral Inflammation Cause Alzheimer’s Disease?

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Abstract

Inflammation is known to be important in Alzheimer’s disease (AD). Inflammatory cells invade into the brain to establish this inflammation. Several adipokines, derived from visceral fat, appear to be involved in damaging the blood brain barrier and promoting neuroinflammation that may lead to AD.

Core tips: Inflammatory adipokines are more abundant in AD, damage the blood brain barrier, attract inflammatory cells and lead to neuroinflammation that causes AD. Adams. Can peripheral inflammation cause Alzheimer’s disease?

Introduction

The cause of AD has been called into question by recent clinical trials showing drugs that decrease brain β-amyloid do not improve disease symptoms [1], including vaccines against β-amyloid, tarenflurbil, scyllo-inositol, gamma-secretase inhibitors and others. B-Amyloid and tau have been assumed to be related and perhaps mutually stimulatory in the causation of AD. These clinical results seem to indicate that AD is not caused by β-amyloid or tau, but is the result of another mechanism.

Recent publications have shown the importance of inflammatory adipokines in AD [2]. With aging, fat accumulates in visceral, periarterial and other ectopic sites. This fat secretes many different adipokines that have a number of different inflammatory activities [3]. The inflammation damages arteries in the brain, the blood brain barrier and creates a proinflammatory condition in the brain.

Dipeptidyl peptidase-4 (DPP4), a novel adipokine, was found to correlate with impaired cognition in elderly people [4]. DPP4 degrades incretins such as glucagon like peptide-1 and increases blood glucose levels. DPP4 diffuses across the blood brain barrier and is involved in satiety [5]. High blood levels of glucose may be toxic to endothelial progenitor cells such that inhibition of DPP4 activity increases these progenitor cells and promotes the repair of damaged arterioles in the blood brain barrier [6]. Sitagliptin, an inhibitor of DPP4, has been shown to improve cognition in elderly patients suffering from type 2 diabetes [7]. However, sitagliptin has neuroprotective effects, perhaps by multiple mechanisms [8].

IL-1β is an adipokine found at higher levels in the blood of patients with AD compared to healthy controls [9]. This adipokine induces vascular cell adhesion molecule-1 (VCAM1) which stimulates the adhesion of lymphocytes to arterial walls [10]. This establishes a proinflammatory situation in the vasculature. IL-1β also induces cyclooxygenase-2 in the brain [11]. Prostaglandins derived from this enzyme may contribute to neuroinflammation.

IL-2 is an adipokine that is made more abundantly by AD patients than controls [9]. IL-2 stimulates and regulates T cells [12]. This can establish a T cell inflammatory process.

IL-6 is produced by adipocytes in higher amounts in AD than in controls [9]. IL-6 is also a myokine that can be anti-inflammatory. However, with the loss of muscle tissue in AD, the inflammatory effects of IL-6 become important. IL-6 promotes the differentiation of B cells, T cells and induces C reactive protein [13]. IL-6 crosses the blood brain barrier [14] to promote neuroinflammation.

IL-18 is an adipokine found in higher blood levels in AD patients than controls [9]. It...
induces the secretion of interferon-γ by T cells [15] and may be important in some neuroinflammatory conditions [16]. IL-18 can also induce the expression of interferon-γ by smooth muscle cells following injury to arterioles [17].

Interferon-γ is an adipokine detected at higher levels in the blood of AD patients compared to normal controls [9]. This may be partly because of the stimulation of its synthesis by IL-18. Interferon-γ activates macrophages [18]. It also is present in the brain during some disease conditions and may damage neurons [19].

Homocysteine is an amino-acid synthesized from methionine and found in higher levels in AD patients than normal controls [9]. It is a peripheral inflammatory marker associated with age and sedentary lifestyles [20]. Homocysteine damages endothelial cells in small vessels of the brain [21]. It also disrupts nitric oxide synthesis and release [22] perhaps because of oxidative inactivation of nitric oxide synthase. This inhibits vasodilation in arterioles of the blood brain barrier.

C-Reactive protein is an adipokine produced more abundantly in AD than normal control patients [9]. It binds to lysophosphatidylcholine found on the surfaces of dead and dying cells and is involved in inflammation. IL-6 stimulates C-reactive protein synthesis [13]. C-reactive protein binds to Fcγ receptors on macrophages which activates NADPH oxidase on these endothelial cells and induces oxygen radical formation [23]. These oxygen radicals contribute to disruption of the blood brain barrier.

VCAM1 is an adipokine found at higher circulating levels in AD than normal control patients [9]. This chemokine binds to specific chemokine receptors (CXCR3), attracts activated T cells and inhibits angiogenesis [24]. This may contribute to inflammation of the blood brain barrier.

Epidermal growth factor (EGF) is produced by visceral fat more abundantly in AD than normal patients [9]. EGF stimulates angiogenesis and the growth of other cells including brain cells [25]. EGF also induces chemokine synthesis which might increase inflammation [26].

CXC Chemokine-10 is secreted by visceral adipocytes in AD patients more than in normal controls [9]. This chemokine binds to specific chemokine receptors (CXCXR3), attracts activated T cells and inhibits angiogenesis [24]. This may contribute to inflammation of the blood brain barrier.

TNFa converting enzyme is an adipokine made more abundantly in AD than normal control patients [9]. It is involved in the activation of TNFa and several membrane-bound cytokines. Blood levels of TNFa are normal in AD patients. However, the converting enzyme may produce high local levels of TNFa in some vascular sites. TNFa is an inflammatory protein that stimulates neutrophil and macrophage functions [29]. It also stimulates VCAM1 binding to endothelial cells.

Leptin is made more by visceral fat in AD than normal control patients [9]. Leptin may be involved in causing atherosclerosis [30] and stimulates oxygen radical formation in endothelial cells that may damage the blood brain barrier [31]. Leptin crosses the blood brain barrier to interact with specific receptors in the hypothalamus [32]. Leptin resistance occurs to the satiety effects of leptin in obese patients [32]. However, other effects of leptin in the brain may not decrease due to resistance, such as the oxygen radical generating effects.

Conclusion

Adipokines increase in AD more than in normal people. Some of these adipokines damage the blood brain barrier, such as leptin and visfatin [33,34]. Although visfatin is not found at higher levels in the blood of AD patients than normal controls, the oxidative conditions established by other adipokines may make the blood brain barriers of AD patients much more susceptible to the effects of visfatin. Homocysteine and C-reactive protein also damage the blood brain barrier, perhaps leading to leakiness and inflammation. DPP4 decreases endothelial progenitor cell viability, making repair of the blood brain barrier more difficult.

After initial damage to the blood brain barrier, an inflammatory condition begins. This involves IL-1β, IL-2, IL-6, interferon-γ, CXC chemokine-10 and VCAM-1 stimulated adherence of inflammatory cells and activation of inflammatory cells. The blood brain barrier becomes inflamed by activated macrophages, neutrophils, T cells, monocytes, basophils and eosinophils. These inflammatory cells may also penetrate into the brain to establish neuroinflammation.

A recent publication found that damage to the blood brain barrier leading to a leaky blood brain barrier correlates with cognitive dysfunction in patients [35]. The leaky blood brain barrier was a more important determinant of cognitive dysfunction than amyloid or tau in these patients. The leaky blood brain barrier may become inflamed as discussed above.

Damage and inflammation of the blood brain barrier may alter the penetration of nutrients, vitamins and neurotransmitter precursors into the brain. The brain becomes less efficient and nutritionally stressed. Neuroinflammation from inflammatory cell penetration into the brain may damage the brain and cause dementia and short-term memory loss leading to AD. The best treatment for AD is prevention, by decreasing visceral and ectopic fat deposits[2].

Conflict of Interest Statement

The author has no conflicts of interest with this work.

References


