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Inflammation, defective insulin signaling, and neuronal dysfunction in Alzheimer's disease

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Abstract A link between Alzheimer's disease (AD) and metabolic disorders has been established, with patients with type 2 diabetes at increased risk of developing AD and vice versa. The incidence of metabolic disorders, including insulin resistance and type 2 diabetes is increasing at alarming rates worldwide, primarily as a result of poor lifestyle habits. In parallel, as the world population ages, the prevalence of AD, the most common form of dementia in the elderly, also increases. In addition to their epidemiologic and clinical association, mounting recent evidence indicates shared mechanisms of pathogenesis between metabolic disorders and AD. We discuss the concept that peripheral and central nervous system inflammation link the pathogenesis of AD and metabolic diseases. We also explore the contribution of brain inflammation to defective insulin signaling and neuronal dysfunction. Last, we review recent evidence indicating that targeting neuroinflammation may provide novel therapeutic avenues for AD.

Keywords: Inflammation; Alzheimer's disease; Diabetes; Obesity; Insulin signaling; Aging

1. Introduction

Inflammation is part of the body's defense mechanisms against multiple threats, including infections and injury. Inflammation is complex and involves both soluble factors and specialized cells that are mobilized to neutralize and fight threats to restore normal body physiology [1]. Similar inflammatory processes are thought to occur in the brain and in peripheral tissues. In the brain, glial cells, especially astrocytes and microglia, undergo activation under pro-inflammatory conditions. In a process similar to that described for peripheral immune cells, activated microglia in the central nervous system (CNS) increase production of inflammatory cytokines. Both in the brain and in peripheral tissues, unchecked or chronic inflammation becomes deleterious, leading to progressive tissue damage in degenerative diseases.

Inflammation plays critical roles in the pathogenesis of Alzheimer's disease (AD) and metabolic diseases, including type 2 diabetes. These disorders are chronic, debilitating, and extremely costly for health programs in developed and developing countries. Since the Rotterdam study was published, suggesting that diabetes almost doubles the risk of AD [2], a number of clinical and epidemiologic studies have strengthened the link between these diseases [3–6].

Several studies have established further the presence of inflammatory markers in the AD brain, including elevated levels of cytokines/chemokines and gliosis (notably microgliosis) in damaged regions [7–10]. A recent meta-analysis showed that blood concentrations of several inflammatory mediators, including tumor necrosis factor-alpha (TNF-α), interleukin (IL) 6, and IL-1β are increased in AD patients [11].

Overproduction of pro-inflammatory cytokines, including TNF-α, is a key feature of the pathophysiology of metabolic disorders. TNF-α is overexpressed in adipose tissue of obese individuals [12], and landmark studies by Hotamisligil and colleagues [12,13] demonstrated that elevated TNF-α levels cause peripheral insulin resistance. Interestingly, brain inflammation has recently been proposed to underlie defective neuronal insulin signaling in AD [14]. Several pathological features, including impaired insulin signaling

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and inflammation, appear to be shared by patients with diabetes and patients with AD. Therefore, it is likely that mechanisms analogous to those that account for peripheral insulin resistance in type 2 diabetes underlie impaired brain insulin signaling and neuronal dysfunction in AD. In the following sections, we discuss molecular/cellular mechanisms underlying defective brain insulin signaling and neuronal dysfunction in AD, with emphasis on evidence that AD and diabetes share common inflammatory signaling pathways.

2. Elevated TNF-α and activation of stress kinases underlie defective neuronal insulin signaling in AD

The molecular events and pathways leading to disrupted brain insulin signaling in AD have only recently begun to be unraveled. Insulin and insulin-like growth factor receptors belong to the tyrosine kinase receptor family and signal via insulin receptor substrate (IRS) proteins. These are closely related, high-molecular weight proteins named IRS-1 through IRS-4, of which IRS-1 and IRS-2 are the most important and best studied [15,16]. Physiologically, activation of insulin receptors (IRs) in peripheral tissues stimulates tyrosine phosphorylation of IRS to initiate intracellular signaling pathways. In type 2 diabetes, elevated TNF-α levels trigger serine phosphorylation of IRS-1 by stress kinases [13,17,18], which interferes with its ability to engage in IR signaling and blocks the intracellular actions of insulin [19–22]. Underlining its role in disrupted insulin signaling, blockade of TNF-α in obese mouse models results in improved insulin sensitivity and glucose homeostasis [23,24].

In the brain, TNF-α is secreted mainly by microglial cells in response to trauma, infection, or abnormal accumulation of protein aggregates [25]. TNF-α levels are elevated in AD cerebrospinal fluid and AD brain microvessels [26,27], as well as in the brain of transgenic mouse models of AD [28,29]. Initial evidence that impaired neuronal insulin signaling in AD is linked to pro-inflammatory signaling came from the finding that soluble oligomers of the amyloid-β (Aβ) peptide—synaptotoxins that accumulate in AD [30,31]—cause IRS-1 inhibition through TNF-α activation [14]. In fact, IRS-1 phosphoserine triggered by Aβ oligomers in hippocampal neurons is blocked by infliximab, a TNF-α neutralizing antibody [14].

Aβ oligomers have been shown to instigate removal of IRs from the membranes of neuronal processes [32,33] and to cause defective insulin signaling (revealed by increased serine phosphorylation and reduced tyrosine phosphorylation of IRS-1) in postmortem AD brains and in several experimental models of AD [14,34,35]. Insulin signaling in the CNS promotes neuronal survival and regulates key processes underlying learning and memory, including synapse density, dendritic plasticity, and circuit function [36–38]. Thus, the induction of pro-inflammatory pathways and ensuing defective insulin signaling instigated by Aβ oligomers are thought to be linked to neuronal dysfunction in AD.

c-Jun N-terminal kinase (JNK) is the major intracellular stress kinase linking TNF-α to inhibitory serine phosphorylation of IRS-1 in type 2 diabetes [13,20], and activated JNK (pJNK) is also a feature of human obesity [39–41]. Aβ oligomer-induced activation of JNK was recently proposed to participate in AD pathology. AD brains exhibit elevated levels of pJNK [14,35], and increased pJNK has been demonstrated in hippocampi of a transgenic mouse model of AD and in cynomolgus monkeys that received intracerebral infusions of Aβ oligomers [14].

IκBα kinase (IKK), another stress kinase activated by TNF-α in peripheral insulin resistance [42], also mediates Aβ oligomer-induced neuronal IRS-1 inhibition [14]. It has now been established that overnutrition induces an inflammatory response in peripheral metabolic tissues. This form of metabolic inflammation, or "metaflammation," as proposed by Calay and Hotamisligil [43], causes metabolic defects that underlie type 2 diabetes and obesity [44,45]. In this context, IKK has been identified as a target for anti-inflammatory therapy in obesity-associated type 2 diabetes [46]. Positive results were obtained in obese mice treated with pharmacological inhibitors of IKK [47,48], providing preclinical support to clinical trials aiming to assess the potential benefit of salsalate, an inhibitor of IKK, to type 2 diabetes patients [49]. The recently established involvement of IKK in IRS-1 inhibition in AD provides additional evidence for a close parallelism between inflammation-associated defective brain insulin signaling in AD and chronic inflammation-induced insulin resistance in peripheral tissues. Additional studies aiming to explore the role of IKK in neuronal dysfunction are warranted and may bring novel clues on mechanisms underlying AD pathology.

The double-stranded RNA-dependent protein kinase (PKR), originally identified as a pathogen sensor and a regulator of the innate immune response against viral infections in higher eukaryotes [50], can regulate or act in conjunction with major inflammatory kinases/signaling pathways implicated in metabolic homeostasis, including JNK and IKK [51–53]. Interestingly, PKR is involved in Aβ oligomer-induced neuronal IRS-1 inhibition [14], reinforcing the hypothesis that common mechanisms underlie peripheral insulin resistance in type 2 diabetes and impaired brain insulin signaling in AD.

Current evidence thus indicates that pro-inflammatory TNF-α signaling and activation of stress-sensitive kinases play a key role in inducing IRS-1 inhibition and neuronal dysfunction in AD (Fig. 1).

3. Possible links between peripheral and CNS inflammation

Inflammation in AD has been associated primarily with activation of CNS-resident microglia induced by Aβ

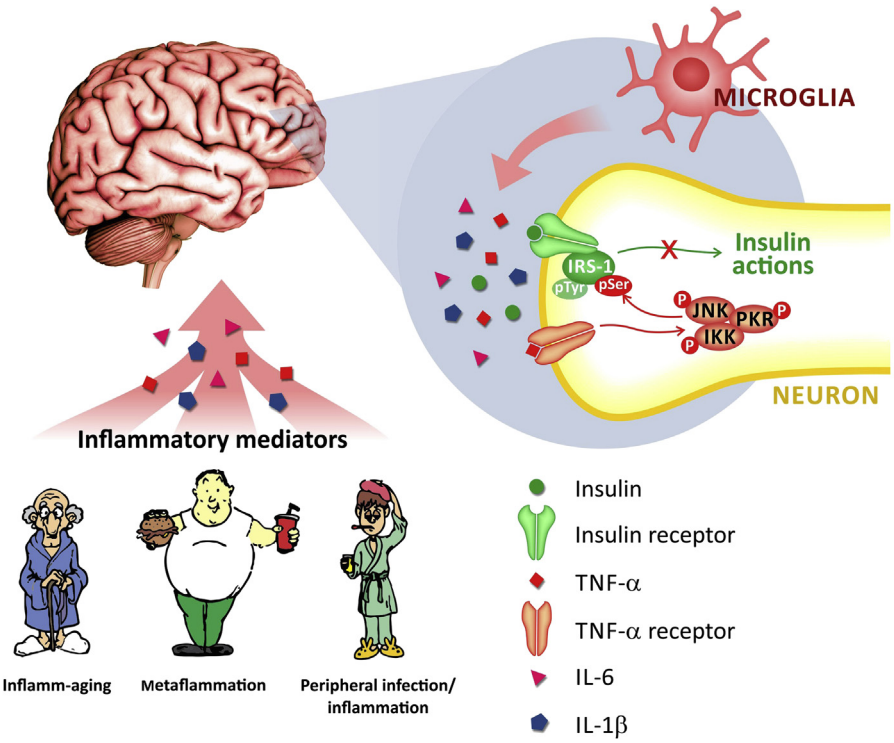

Fig. 1. Peripheral inflammatory mediators contribute to brain inflammation, neuronal insulin resistance, and neuronal dysfunction in Alzheimer's disease. Inflamm-aging [54], metaflammation [43] (as seen in obesity-related metabolic disorders, including type 2 diabetes and insulin resistance), and peripheral infection/inflammation (caused by pathogens or systemic inflammatory disorders) give rise to states of chronic, low-grade systemic inflammation, leading to overproduction of pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin (IL) 1β, and IL-6. Elevated levels of adipokines may also link peripheral and central nervous system (CNS) inflammation in obesity. Peripheral inflammatory mediators cross the blood–brain barrier and, in conjunction with mediators produced by activated microglia, may lead to CNS inflammation. Activation of neuronal cytokine receptors (e.g., TNF-α receptor) induces aberrant activation of stress kinases (c-Jun N-terminal kinase [JNK], IκBα kinase [IKK], and double-stranded RNA-dependent protein kinase [PKR]), which phosphorylate insulin receptor substrate 1 (IRS-1) at serine residues and inhibit insulin-induced physiological tyrosine phosphorylation of IRS-1. This interferes with the ability of IRS-1 to engage in insulin signaling and blocks the intracellular actions of insulin.

aggregates [55]. Increased brain levels of pro-inflammatory cytokines can lead to several pathological features of AD. Cytokines have been associated with increased tau phosphorylation and decreased synaptophysin levels, establishing their roles in cytoskeletal and synaptic alteration in AD [56,57]. Targeting the increased circulating levels of IL-1β with a neutralizing antibody has been shown to reduce the activity of several tau kinases and levels of phosphorylated tau (p-tau), and also to reduce the load of oligomeric and fibrillar Aβ in brains of triple-transgenic AD mice (3xTg) [58]. Interestingly, treatment with a drug targeting the p38 mitogen-activated protein kinase pathway [59] was shown recently to normalize levels of pro-inflammatory cytokines and to attenuate synaptic protein loss and impaired synaptic plasticity in AD mouse models [60].

In addition, the clinical association between type 2 diabetes and AD has led to the hypothesis that periphery-derived pro-inflammatory molecules could also influence pathogenesis in the Central Nervous System (CNS) (Fig. 1). Adipose tissue inflammation is one of the major traits of diabetes and obesity [61,62], and both adipocytes and adipose-resident macrophages may participate in a crosstalk between periphery and CNS. In obese patients, adipocytes react by producing pro-inflammatory cytokines, adipokines, and chemokines, whereas resident macrophages undergo a phenotypic change to a so-called M1, classically-activated pro-inflammatory state [63]. This leads to increased TNF-α, IL-1β, and IL-6 production, all of which can cross the blood–brain barrier (BBB) [64]. Therefore, adipose-derived inflammatory mediators could be an important addition to cytokines produced by CNS-resident microglia in triggering brain inflammation.

Fat-derived hormones, such as adiponectin and leptin, have been associated with AD and could play a role in connecting peripheral and central pathogenic mechanisms. Adiponectin, derived from visceral fat, helps sensitize the body to insulin by acting on receptors that are distributed ubiquitously, including the brain [65–68]. Plasma adiponectin levels are decreased in animal models of obesity and in obese patients [69–71]. Plasma and cerebrospinal fluid levels of adiponectin show a positive correlation [72] and, intriguingly, recent studies found increased levels of this adipokine in patients with mild cognitive impairment and with AD [72,73]. It will be interesting to determine the precise role, if any, of

adiponectin in impaired neuronal insulin signaling and neuronal dysfunction in AD.

Leptin was found to reduce Aβ generation and tau phosphorylation in vitro [74,75], and leptin replacement therapy induces hippocampal neurogenesis [76] and improves cognitive performance [74] in transgenic models of AD. Initially described for its role in satiety and long-term body weight maintenance, leptin has recently been proposed to regulate cognition, axonal growth, and synaptogenesis in extrahypothalamic regions [77]. Lower plasma levels of leptin have been associated with a fourfold increased risk of development of AD in a 12-year follow-up period compared with patients in whom leptin levels were greater [78].

Dyslipidemia is another important trait of metabolic disorders. Cholesterol- and sphingolipid-enriched cell membrane domains, called lipid rafts, appear to be preferential sites for Aβ generation. In these microdomains, amyloid precursor protein is cleaved preferentially through the amyloidogenic pathway [79–81]. Particular types of sphingolipids, namely ceramide and its metabolites, cause inflammation [82,83], and have been increasingly associated with type 2 diabetes [84]. Peripherally generated ceramides can cross the BBB [85] and thus could contribute to AD pathogenesis in two ways: (*i*) by changing the microenvironment of lipid rafts, thereby favoring Aβ generation, and/or (*ii*) by inducing central inflammation and disruption in neuronal insulin signaling [84].

Preclinical and clinical observations are accumulating that support the notion that peripheral inflammatory mediators link peripheral and central events in metabolic dyshomeostasis and AD. Novel findings in this area could potentially bring about advances for patients with type 2 diabetes and patients with AD, allowing for improved prevention strategies for the former and raising hopes of novel therapeutic approaches for the latter. As pointed out recently, available evidence indicates that a healthy lifestyle and long-term metabolic control are to be encouraged, especially so for diabetic and obese patients, as a preventive measure to reduce the risk of AD [86,87].

4. Aging and other general causes of inflammation

Aging is the single most important risk factor for AD. The concept of "inflamm-aging" was introduced by Claudio Franceschi to define changes in the immune system that accompany physiological aging, leading to chronic systemic inflammation [54,88]. Inflammatory dyshomeostasis in aging can result from loss of control over finely tuned levels of pro- and anti-inflammatory cytokines, or as a consequence of the incapacity to restore equilibrium after it is perturbed by external factors. Whatever the underlying causes, they can lead to a chronic state of low-grade inflammation [89]. Interestingly, it has been proposed that inflamm-aging is a result of lifetime exposure to acute and chronic infections [90], with human longevity associated at least in part with an increased capacity to maintain a inflammatory response at low levels [91]. Nevertheless, a pro-inflammatory profile has also been described in centenarians [90]. Increased levels of pro-inflammatory cytokines and markers, such as IL-1β, IL-6, TNF-α, and C-reactive protein [89], have been reported in "normal" aging, but it is not clear whether this is a cause or a consequence of aging. Inflammation, or rather the defective ability to maintain low inflammation levels as one ages, may contribute to the onset of AD (Fig. 1).

Additional conditions in which low-grade inflammation can be maintained throughout a period of life include recurrent or persistent infections (Fig. 1), and it is tempting to speculate that chronically elevated peripheral inflammatory mediators could be associated with accelerated neuronal dysfunction and cognitive decline, or predispose to earlier onset of AD [86]. Significantly, type 2 diabetes induces changes in BBB permeability [92], and postmortem analysis of diabetic AD brains showed increased levels of IL-6 compared with nondiabetic AD brains [93]. Moreover, the BBB of a transgenic mouse model of AD has been reported to be more permeable to peripheral inflammatory cytokines [94]. These findings raise the possibility that AD brains could be more susceptible to changes in peripheral inflammatory dyshomeostasis.

5. Anti-inflammatory therapies for AD?

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous family of cyclooxygenase (COX) inhibitors. Their therapeutic outcomes vary according to their specificity toward the two known isoforms of the enzyme, COX-1 and COX-2 [95]. Early reports on patients treated chronically with anti-inflammatory drugs for rheumatoid arthritis or leprosy [96,97] found that a 2-year treatment with NSAIDs reduced significantly the risk of AD later in life [98], and that clinical benefit increased with longer periods of treatment [99]. Similar results were reported for patients using aspirin [99] or combined NSAID/steroid therapy [100]. On the other hand, subsequent studies failed to find a correlation between NSAID use and AD risk [101,102]. Intriguingly, considerable variability was found even among studies that showed beneficial actions of NSAIDs, possibly reflecting differences in dosage, period of treatment, and patient age. Benefits were observed when anti-inflammatory drugs were used well before the onset of dementia [103] and might be limited to apolipoprotein E4-carrying patients [104].

Results from the observational studies described here encouraged the search for molecular mechanisms that could explain the positive effects of NSAIDs in delaying/preventing AD. Interestingly, certain NSAIDs, such as ibuprofen, indomethacin, and sulindac sulfide, were shown to decrease $A\beta_{42}$ production by up to 80% in cultured cells, apparently via a COX-independent mechanism [105]. Mice overexpressing amyloid precursor protein and treated with ibuprofen also showed a significant reduction in cortical

amyloid plaque load along with reduced microglial activation [106]. Neurons treated with COX-1 preferential inhibitors, such as ibuprofen and aspirin, were more resistant to Aβ toxicity than neurons treated with COX-2-specific inhibitors [107]. In line with this finding, Kotilinek and colleagues [108] reported improved synaptic plasticity and memory formation in AD transgenic mice treated with COX-2- but not COX-1-selective inhibitors.

Despite the initial optimism generated by these observations, randomized clinical trials provided disappointing results that did not support disease-modifying or beneficial actions of NSAIDs in AD [109–114]. As suggested previously [103], such trials might have failed in finding positive effects of NSAIDs for one or more of the following reasons: (*i*) most trials tested NSAIDs for treatment of clinically established AD, whereas epidemiologic data supported a positive effect of anti-inflammatory agents before clinical onset of symptoms; and (*ii*) beneficial effects may be specific to anti-inflammatory drugs capable of reducing Aβ levels (the so-called selective Aβ-lowering agents). Thus, general testing of several members of the large NSAID family may have generated conflicting results.

Renewed hopes for an effective AD treatment based on anti-inflammatory therapy came from a report that perispinal administration of etanercept, an anti-TNF-α fusion protein, improved cognitive performance of patients with AD in a 6-month pilot study [115], followed by another report on rapid cognitive improvement (within minutes) on etanercept administration to one patient with late-onset AD [116]. Despite their possible significance, additional clinical studies using larger cohorts and patients at different stages of the disease are needed to validate these initial findings. In this regard, two clinical trials are currently under way [49] to investigate the possible benefit of etanercept to treat mild/moderate AD.

Anti-TNF-α strategies for AD have received further support from experimental findings using the neutralizing antibody infliximab. Intracerebroventricular infusion of infliximab in AD transgenic mice reduced the number of amyloid plaques and the levels of p-tau [117]. The same group subsequently reported cognitive improvement in one patient with AD after intrathecal administration of infliximab [118]. Clinical trials are currently investigating the efficacy of infliximab in a wide range of pathologies, including major depression, obesity-associated insulin resistance, and diabetic complications, among many others [49]. There are no trials, however, investigating specifically the safety and efficacy of infliximab to treat patients with AD. Given the evidence indicating a role of TNF-α in the pathogenesis of AD [119], clinical trials using infliximab appear warranted.

Neither etanercept nor infliximab cross the BBB, thus requiring invasive forms of central administration. Thalidomide, on the other hand, is a BBB-permeable drug that has attracted increasing attention because of its anti-inflammatory actions related to the inhibition of TNF-α production [120]. When given intraperitoneally, both thalidomide and a synthetic analog (3,6′-dithiothalidomide [3,6′-DTT] [121]) inhibited lipopolysaccharide-induced increases in TNF-α messenger RNA and protein levels in the cortex [122] and hippocampus [123] of rodents. 3,6′-DTT, but not thalidomide, reversed cognitive impairment in 3xTg mice in the eight-arm radial maze [122] and in the Morris Water Maze [123]. Whether 3,6′-DTT also rescues brain levels of synaptic proteins, p-tau, and $A\beta_{42}$ remains controversial [122,123]. Thalidomide also protected rats from neuronal loss induced by intrahippocampal $A\beta_{42}$ injection [124]. Thalidomide is now in a phase 2 clinical trial to treat mild to moderate AD, and results will establish its potential value in preventing or halting the progression of AD.

6. Conclusion

CNS inflammation, impaired neuronal insulin signaling, and neuronal dysfunction in AD may be a consequence of systemic inflammatory processes that occur throughout life [86,87]. Inflammatory mediators—notably pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β—may play a role in the crosstalk between peripheral tissues and the brain. Inflamm-aging [54], metaflammation [43], and peripheral infection/inflammation caused by pathogens or systemic inflammatory disorders may give rise to chronic, low-grade inflammation. Ultimately, this could contribute to or accelerate the onset of clinical manifestations of AD.

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