Developmental origins of aging in brain and blood vessels: an overview

Caleb E. Finch*

Department of Biological Sciences, Andrus Gerontology Center, University of Southern California, Los Angeles, CA 90089-0191, USA

Received 1 December 2003; received in revised form 17 March 2004; accepted 30 March 2004

Abstract

Emerging evidence suggests a remarkable convergence of inflammatory mechanisms in the etiology of cardiovascular disease and Alzheimer disease. A broad set of NSAIDs and statins used to reduce the risk of vascular occlusion and to slow atherogenesis may also be protective for Alzheimer disease. Elevated blood levels of C-reactive protein are risk factors for cardiovascular disease and possibly for Alzheimer disease. Monocyte-lineage cells are also fundamental to both conditions: in blood vessels, macrophages are important to atherogenesis for the accumulation of lipids (foam cells), whereas brain microglia show activation during aging and direct involvement in amyloid metabolism in the senile plaque. Genetic influences are recognized through the apoE4 allele, which is associated with hypercholesterolemia and is a risk factor in vascular events and Alzheimer disease, and is recognized for its proinflammatory profile. ApoE4 also accelerates Alzheimer disease pathogenesis in Down's syndrome and many other chronic neurodegenerative conditions, as is well-supported by animal models. Inflammatory changes are present at the earliest stages of vascular disease and Down's syndrome in human fetuses, and are also prominent early in Alzheimer disease. These findings give a basis for considering inflammatory processes early in life which can lead to fully fired pathogenesis of cardiovascular disease and possibly for Alzheimer disease.

© 2004 Elsevier Inc. All rights reserved.

Keywords: Brain; Blood vessel; Alzheimer disease

1. Introduction

This essay considers certain shared features in the pathogenesis of vascular disease and Alzheimer disease. I hope to provide a framework for developing specific hypotheses about slow inflammatory processes in these apparently disparate conditions. This discussion extends the concept of the "gero-inflammatory manifold" which considers interactions between inflammatory processes during aging throughout the body, as developed by Valter Longo [34a], and related concepts of "inflammaging" developed by Franceschi and co-workers [79a].

Both vascular disease and Alzheimer disease evolve over decades, with the progressive accumulation of cellular and extracellular materials and many evidently similar inflammatory processes (Table 1). As discussed in the following, there is evidence that inflammatory processes are present very early in human arteries and in the earliest stages of Alzheimer disease. Both diseases share certain inflammatory activities of monocyte lineage cells and are also influenced by the proinflammatory apoE4 allele. Drugs with anti-inflammatory features appear to be protective for both, and the characteristic 'plaques' are very dynamic and can regress. The developmental origins of vascular disease may extend to fatty streaks found in fetal vessels (Table 2). The earliest stages of Alzheimer’s are not known, but may be inferred from fetal and neonatal Down's brains (Table 3). Other articles in this symposium volume are cited for further details.

Before launching into this narrative, I will briefly review aspects of the increasingly complex and ambiguous concept of 'inflammation'. About 2000 years ago, Cornelius Celsus described four cardinal signs of inflammation: rubor (redness), calor (heat), tumor (swelling, edema), and dolor (pain). In modern terms, these classical signs are now recognized as local (secondary) responses to specific inflammatory
Table 1
Inflammatory components of atheromas and senile plaques

<table>
<thead>
<tr>
<th></th>
<th>Atheroma</th>
<th>Senile plaque</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cells</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocytes</td>
<td>0</td>
<td>++</td>
</tr>
<tr>
<td>Mononuclear cells</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Macrophage</td>
<td>+++ (foam cell, macrophage, CD68)</td>
<td>++ (microglia, CD68)</td>
</tr>
<tr>
<td>T-cell</td>
<td>++ (CD11/CD14)</td>
<td>0</td>
</tr>
<tr>
<td>Mast cells</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Platelets</td>
<td>++</td>
<td>0</td>
</tr>
<tr>
<td>Neurovascularization</td>
<td>++</td>
<td>(?)</td>
</tr>
<tr>
<td><strong>Extracellular</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amyloids</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aβ</td>
<td>? (macrophages with ingested platelets)</td>
<td>++ and in neurons</td>
</tr>
<tr>
<td>CRP</td>
<td>++</td>
<td>+ (neurotic)</td>
</tr>
<tr>
<td>SAP</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Clotting factors</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>Complement C3b-9</td>
<td>+ (fibrinogen)</td>
<td>+</td>
</tr>
<tr>
<td>Cytokines: IL-1, -6</td>
<td>+</td>
<td>+ (associated with CRP)</td>
</tr>
<tr>
<td>Lipoproteins apoE, LRP</td>
<td>++</td>
<td>+</td>
</tr>
</tbody>
</table>

Abbreviations: 0, absent; +, definitive; ++, moderate; ++++, extensive; complement C5b-9, the terminal complex (membrane attack complex); CRP, C-reactive protein; SAP, serum amyloid A; astrocytes: senile plaque [2,30,119]; cholesterol: senile plaque [19,83]; lipoproteins: senile plaque [7]; macrophages: atheroma [28,112]; senile plaque [2,4]; T-cells: [9,25,45,79]; B-cells are also present in some preclinical atheromas [79]; mast cells: atheroma [57,79]; senile plaque [21]; neovascularization: senile plaques [144]; platelets: atheroma [28,52,91,141]; amyloids, Aβ: atheroma [28], senile plaque [38,47,58]; amyloids, CRP: atheroma [111,134], senile plaque [2,139]; amyloids, SAP: atheroma [66,78], senile plaque [24,139]; complement: atheroma [134], senile plaque [2,32,72]; cytokines: atheromas [115], senile plaque [2,73,120].

Table 2
Ontogeny of Alzheimer disease (AlzD) and vascular disease (VascD)

<table>
<thead>
<tr>
<th></th>
<th>Fetal 0–10 years</th>
<th>21–40 years</th>
<th>41–60 years</th>
<th>60–80 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxidation (8-OHG)</td>
<td>0</td>
<td>0</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Brain metab (apoE4)</td>
<td>0.5–5 av apoE4, stage 1</td>
<td>0.5–1 av</td>
<td>1–3</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Neurovascular activation</td>
<td></td>
<td>+ to ++</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
<tr>
<td><strong>VascD fatty streaks</strong></td>
<td>+ Linear growth</td>
<td>+ to ++</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Macrophage</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Advanced plaques</td>
<td>Rare</td>
<td>Rare</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
</tbody>
</table>

Table 3
Accelerated AD in Down syndrome

<table>
<thead>
<tr>
<th></th>
<th>Fetus 0–9 years</th>
<th>10–19 years</th>
<th>20–39 years</th>
<th>&gt;40 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aβ</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intraneuronal</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/−−</td>
</tr>
<tr>
<td>Extracellular</td>
<td>0</td>
<td>0</td>
<td>0/compact Aβ</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Neurofibrillary tangles</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
</tr>
<tr>
<td>Neuroendosome</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Glia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Astrocyte</td>
<td>+</td>
<td>+/−−</td>
<td>+/− to ++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Microgliosis</td>
<td>+</td>
<td>+/− to ++</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Complement C1q</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C3b-9</td>
<td>+/− to +</td>
<td>+/− to +</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
<tr>
<td>Neuronal oxidative stress</td>
<td>+/− to +</td>
<td>+ to +++</td>
<td>+ to +++</td>
<td>+ to +++</td>
</tr>
</tbody>
</table>

Abbreviations: 0, absent; +, weak; +/−, moderate; ++, extensive. References: Aβ, intraneuronal Aβ precedes plaque formation [40,82]; extracellular Aβ [44,48,82,114,129]; neurons near diffuse plaque had no intraneuronal Aβ; older brains had less intraneuronal Aβ [82]; neurofibrillary tangles [49] glosis, mostly with mature plaques: astrocyte: GFAP [42,129]; microglia, ferritin [129]; microglia, IL-1 [42]; complement: C1q [46,129]; C3b-9 [129] neuronal oxidative stress [93] is greater in earlier stages. neuronal endosome [92].
2. The etiology and ontogeny of vascular disease

2.1. Overview of vascular plaque composition and morphology

The processes leading to vascular occlusion through plaque growth and thrombosis is complex and variable between plaques and between individuals [113,146], see articles by Napoli and Palinski [90], and Tuzcu [135], this symposium. Atherosclerotic plaques in humans occur mainly in medium-to-large arteries and, by providing surfaces for accumulating blood clots (thrombi) cause ischaemia that can lead to infarcts, manifested as heart attacks and strokes. Macrophages are attracted to growing plaques by the chemotactant protein (MCP-1) and by binding to adhesion molecules, e.g. P-selectins and ICAM-1. CD14, another monocyte adhesion protein, may bind hsp-60.

Macrophages and lymphocytes also proliferate within the plaque, whereas smooth muscle cells proliferate in the vascular endothelium. Systemic C-reactive protein (CRP) and fibrinogen also enhance macrophage accumulation. Many inflammatory factors are released within the plaque, e.g. interleukin 1 (IL-1); TNFα; transforming growth factor (TGF-β1), and macrophage colony stimulating factor (MCSF). Low-density lipoproteins (LDL) are taken up by macrophages through scavenger receptors, leading to foam cells; the lipid deposits become oxidized forming proinflammatory lipid peroxides. The amyloid β-peptide (Aβl) of Alzheimer’s senile plaques (see the following) is detected in infiltrating macrophages [28].

Auto-immune aspects of atherosclerosis are a major new topic, because T-cells are generally found in atheromas [9,20,79], see article by Napoli and Palinski [90], this symposium. B-cells are often present and may be protective [20,46,79]. Statins may be protective by impairing lymphocyte proliferation [98].

Smooth muscle cell proliferation may be stimulated by hypertension-induced elevations of angiotensin II, which also induces lipoxygenase and can increase the oxidation of LDL. Modified LDL induces further inflammatory processes which may initially protect endothelial and smooth muscle cells. Arteries undergo a characteristic "remodeling" in response to these growth processes with compensatory dilatation, see article by Tuzcu [135], this symposium.

Various advanced lesions are being classified by the degree of stability see articles by Napoli and Palinski [90], and Tuzcu [135], this symposium [113,140,146]. Plaques with fibrous caps and smooth muscle cell proliferation may be more stable and less prone to thrombus formation. Other plaques are more unstable and considered very dangerous. Unstable (vulnerable) plaques are thought to have a thinner fibrous cap ("thin-cap fibroatheromas"), a necrotic core with more inflammatory macrophages and lipid deposits; their instability may be due to mechanical weakening from metalloproteinases secreted by macrophages. Plaque rupture may attract platelets and lead to a thrombotic mass. Another factor is the degree of blood coagulability, which can alter platelet binding. Thrombus formation may not immediately cause critical ischaemia and can induce further changes in an atheroma [50]. The prolonged subcritical persistence of thrombi could interact with systemic chronic inflammatory processes that are common in the elderly (Section 5).

2.2. Ontogeny of atheromas

Predromal stages of atherosclerotic lesions are now well-recognized to arise early in human life [26,51,65,87,97,127] see also, Napoli and Palinski [90], this symposium. Compelling data on early lesions come from autopsy studies: fate of early lesions in children (FELIC) showed unequivocally that minute fatty streaks are common in fetal aortas and have the characteristic repertoire of macrophages, monocytes, and oxidized LDL found in adult plaques [89,97]. After birth, plaque size increased linearly with age in the aortic arch and abdominal aorta from 1 to 14 years. Moreover, and of great importance, the rate of increase in plaque size was much greater in children born of mothers hypercholesterolemic during pregnancy, although none of these children had hypercholesterolemia. The variability of lesion size increased during later childhood in the FELIC study, which suggests input from traditional cardiovascular risk factors such as diet, exercise, and socio-economic status [89]. Although fatty streaks are considered to be the main precursor of advanced lesions, there is no consensus that their level early in life predicts the later level of advanced lesions [68,127].

Fatty streaks, while ‘clinically silent’ may regress or develop further into advanced plaques that are associated with occlusive vascular disease. Thus, the fate of the early predromal fatty streaks in the adult years may vary widely. However, more advanced vascular plaques are common in early adult life. An early glimpse of this came from autopsies of American soldiers killed during the Korean and Vietnam conflicts:
Despite their generally robust health prior to fatal wounding, the majority had raised cardiovascular lesions [77]. These early findings are amply confirmed by the Pathological Determinants of Atherosclerosis in Youth (PDAY) multicenter cooperative study which define raised vascular plaques in the majority of young adults [75,79]. Asymptomatic coronary vascular disease is found in about 15% of teenagers and exceeds 50% by 50 years [136], see also Tuzcu [135], this symposium. Early indicators of cardiovascular disease are also found in the Bogalusa Heart Study, a community-based study of Caucasian and African Americans, see also Berenson [10], this symposium.

Ultrasonic techniques now are approaching the resolution of postmortem histopathology, with three-dimensional assessment of coronary arteries and plaques [59] (see also Tuzcu [135], this symposium) and demonstrate that statin therapy can cause rapid regression of plaques [116]. It may be soon possible to resolve changes of lipids in the plaque core and alternate pathways to advanced plaques that are suspected to be independent of fatty streaks.

Animal models are being developed for these complex phenomena. Rabbits with diet-induced hypercholesterolemia during pregnancy showed lesions in the offspring that proportionate in size to maternal cholesterol levels during pregnancy; treatment with cholestyramine diminished neonatal arterial lesions in proportion to the reduction of maternal cholesterolemia, whereas Vitamin E was not effective [97]. Similarly, maternal hypercholesterolemia in LDL-receptor deficient mice (−/−) increased lesions in adult offspring, but only in males [88]. However, an apoe-null mouse model (apoE−/−) with five-fold increases of total cholesterol during pregnancy did not show effects of maternal cholesterolemia on aortic plaques in adults [68]. Note that these studies did not evaluate fatty streaks at earlier ages. The apoE−/− mouse is a promising model for angiotensin-2 induced aneurysms and for the protective effect of estrogens on diet-induced atherosclerosis (see Wang [143], this symposium).

3. Alzheimer disease

3.1. Overview

In the general population, clinical dementia of the Alzheimer type is rare before 65 and accelerates rapidly with a doubling of risk every 5 years thereafter [56]. The earliest indications of Alzheimer disease in common genotypes arise at least 30 years after the fatty streaks of the fetus or neonate.

The neuropathologic diagnosis of AD is based on quantitation of two abnormalities: neurofibrillary degeneration (intraneuronal neurofibrillary ‘tangles’) and extracellular senile plaques (neuritic plaques), which include fibrillar agglomerates of the amyloid-peptide (Aβ) with abnormal neuritides and inflammatory cells (Tables 1 and 2). Aβ deposits are very heterogeneous in their morphology and composition. With aging, human brains accumulate ‘diffuse’ deposits of Aβ that are not fibrillar and are not associated with local neuronal abnormalities or with cognitive deficits [13,105]. The boundaries between “usual aging” and Alzheimer disease become less clear at later ages. Non-demented elderly show modest cortical atrophy with aging [5,62] and increasing numbers of neurofibrillary tangles to levels in the cortex that overlap with early clinical stages of Alzheimer [13,105]. In cognitively normal elderly, plaques and tangles can arise independently, and some accumulate little amyloid even at advanced ages. In contrast to the ubiquitous neurofibrillary tangles, senile plaques are not found in all non-demented elderly [13,105]. Cardiac insufficiency (critical coronary artery disease [cCAD]) and hypertension may be associated with the presence of senile plaques and/or neurofibrillary tangles independent of stroke or occlusive vascular disease in non-demented elderly [126].

A long-standing confound is that the classical Aβ deposits show poor correlations with the degree of neurodegeneration and cognitive status [58,132] (see Colton [23], Griffin [41], Lott [67], and Nixon [92], this symposium). Soluble forms of Aβ are also recognized for potential roles in neurodegeneration, particularly oligomeric Aβ (ADDLs, amyloid-derived diffusible ligands), which may correlate better with neurodegeneration. (Readers should be aware of my commercial interests in ADDLs as a founder of Acumen Pharmaceuticals Inc.) ADDLs were first recognized for enhanced in vitro neurotoxicity relative to fibrillar Aβ [58,94] and were recently shown greatly elevated in AD brain regions [39].

Brain amyloid deposits show many indications of inflammatory processes that are shared with atheromas of blood vessels (Table 1). The classic senile plaques of advanced Alzheimer disease have numerous microglial cells that express CD 68 and other monocyte-lineage epitopes found in the atheromas [2,35] see articles by Colton [23], Griffin [41], Lott [67], and Nixon [92] (this symposium). Soluble forms of Aβ are also recognized for potential roles in neurodegeneration, particular oligomeric Aβ (ADDLs, amyloid-derived diffusible ligands), which may correlate better with neurodegeneration. (Readers should be aware of my commercial interests in ADDLs as a founder of Acumen Pharmaceuticals Inc.) ADDLs were first recognized for enhanced in vitro neurotoxicity relative to fibrillar Aβ [58,94] and were recently shown greatly elevated in AD brain regions [39].

Brain amyloid deposits show many indications of inflammatory processes that are shared with atheromas of blood vessels (Table 1). The classic senile plaques of advanced Alzheimer disease have numerous microglial cells that express CD 68 and other monocyte-lineage epitopes found in the atheromas [2,35] see articles by Colton [23], Griffin [41], Lott [67], and Nixon [92] (this symposium). Soluble forms of Aβ are also recognized for potential roles in neurodegeneration, particularly oligomeric Aβ (ADDLs, amyloid-derived diffusible ligands), which may correlate better with neurodegeneration. (Readers should be aware of my commercial interests in ADDLs as a founder of Acumen Pharmaceuticals Inc.) ADDLs were first recognized for enhanced in vitro neurotoxicity relative to fibrillar Aβ [58,94] and were recently shown greatly elevated in AD brain regions [39].

Brain amyloid deposits show many indications of inflammatory processes that are shared with atheromas of blood vessels (Table 1). The classic senile plaques of advanced Alzheimer disease have numerous microglial cells that express CD 68 and other monocyte-lineage epitopes found in the atheromas [2,35] see articles by Colton [23], Griffin [41], Lott [67], and Nixon [92] (this symposium). Soluble forms of Aβ are also recognized for potential roles in neurodegeneration, particularly oligomeric Aβ (ADDLs, amyloid-derived diffusible ligands), which may correlate better with neurodegeneration. (Readers should be aware of my commercial interests in ADDLs as a founder of Acumen Pharmaceuticals Inc.) ADDLs were first recognized for enhanced in vitro neurotoxicity relative to fibrillar Aβ [58,94] and were recently shown greatly elevated in AD brain regions [39].

Brain amyloid deposits show many indications of inflammatory processes that are shared with atheromas of blood vessels (Table 1). The classic senile plaques of advanced Alzheimer disease have numerous microglial cells that express CD 68 and other monocyte-lineage epitopes found in the atheromas [2,35] see articles by Colton [23], Griffin [41], Lott [67], and Nixon [92] (this symposium). Soluble forms of Aβ are also recognized for potential roles in neurodegeneration, particularly oligomeric Aβ (ADDLs, amyloid-derived diffusible ligands), which may correlate better with neurodegeneration. (Readers should be aware of my commercial interests in ADDLs as a founder of Acumen Pharmaceuticals Inc.) ADDLs were first recognized for enhanced in vitro neurotoxicity relative to fibrillar Aβ [58,94] and were recently shown greatly elevated in AD brain regions [39].
capillaries [144]. Isolated microvessels from Alzheimer brains show an increased capillary network with thicker basement membranes [101]. Moreover, during normal aging in the absence of Alzheimer disease, cortical vessels show increased tortuosity [1,124]. Similar changes are found in the aging rat retinal vessels [22]. The vascular–neural interface could be a major target of aging and the seat of yet unrecognized connections between peripheral vascular disease and Alzheimer pathogenesis.

3.2. Ontogeny of Alzheimer disease

The onset of Alzheimer neurodegeneration is poorly defined [Table 2]. The sequence of lesions is not as well-understood as in vascular disease because longitudinal in vivo assessment techniques are so far available only for rodent models (see the following). The most detailed analysis of plaque ontogeny comes from the Braak’s huge autopsy series (N = 887) from 20 to 104 years [13,14,96]. The older samples represent deaths in nursing homes in north-eastern Germany. Six neuropathological stages in the disease are described based on neurofibrillary degeneration (stages I–VI), but without detailed clinical assessment of most cases. In other study populations, longitudinal clinical assessments on the Clinical Disease Rating scale recognize CDR 0.5 (subtle cognitive changes) and clinical stages CDR 1–5 [84.85]. At autopsy, CDR 0.5 brains show extensive neuron death, senile plaques, and neurofibrillary degeneration [104,105] and generally correspond to Braak stages III–V [86].

In the Braak system, plaques and tangles spread from small regions of the transentorhinal cortex to nearby cortex and hippocampus. Stage I is rare before 40 years, later stages becoming common after 65 [96], which is consistent with clinical cognitive assessments [56]. The estimated transition time between stages: stages I and II, 16+ years; II and III, 14 years; III and IV, 13 years; IV and V, 5 years. The shorter duration of later stages suggests acceleration and possible interactions with age, which is consistent with the accelerating incidence of later decades [13,105].

The total duration of changes appears to span 50 years from the first neurofibrillary changes until definitive Alzheimer disease and “... may even extend to adolescence” [96]. Reiman [106] describes impairments in glucose utilization in young adult apoE4 carriers in the same brain regions afflicted in clinical Alzheimer (see the following). Another early indicator was found in the Nun Study: a low intellectual content in an essay written as young adults was associated with risk of dementia at later ages (see Riley [110], this symposium).

Neurofibrillary Aβ is being evaluated as an early marker. Non-fibrillar intraneuronal Aβ occurs early in clinical Alzheimer (CDR 0.5) and may be a local source of extracellular Aβ [40]. Nixon [92] has convincing evidence for early changes in neuronal endosomes that increase Aβ production in Alzheimer brains and in transgenic models.

Down syndrome (trisomy 21) gives additional insights because nearly all Down's develop the classic Alzheimer neuropathology decades earlier, with nearly 100% prevalence by 40 years (Table 3; see articles by Griffin [41], Nixon [92], and Lott [67], this symposium). Intraneuronal Aβ is found in Down’s brains as early as 3 years, which is about 5 years before diffuse amyloid or neurofibrillary degeneration is detected [44,82]. The activation of the neuronal endosome, however, occurs in fetal Down’s [92] as does the activation of astrocytes [41].

At later stages, there may be a dissociation of local inflammatory processes and amyloidogenesis. No local inflammatory cells were seen near neurons with intraneuronal Aβ in a 16-year-old Down's brain [82]. In a triple transgenic mouse carrying mutant human APP P5-1, and tau, intraneuronal Aβ also preceded amyloid deposits and neurofibrillary changes (tau pathology) [95]. In support of possible mechanisms shared with Alzheimer and vascular disease, about 50% of genetically normal individuals with heart disease had intraneuronal Aβ, whereas age-matched non-heart disease controls did not [125]. Intraneuronal Aβ is also induced in juvenile pigs by coronary artery ligation, which reduces cardiac output [125]. In another model of vascular disease cholesterol fed adult rabbits also had intraneuronal Aβ [125]. Thus, it is possible that coronary insufficiency (cCAD), high cholesterol diets, and familial Alzheimer genes can independently contribute to this new marker of AD pathogenesis.

3.3. ApoE4, a genetic risk factor of Alzheimer disease shared with vascular disease

The apolipoprotein-4 allele (apoE4), which was first recognized in association with elevated blood cholesterol [12] and is considered the most common genetic risk factor for Alzheimer disease [17,69,102,117], see articles in this symposium by Borenstein [11] and Poirier [103]. ApoE4 appears to accelerate Alzheimer disease, see articles by Borenstein [11], Colton [23], Poirier [103] and Reiman [106]. In the Braak’s series, the apoE4 allele was two-fold more common in Stage 1 brains aged 22–46 years than in non-carriers [37]. The earlier onset in E4 carriers is consistent with the lower cerebral glucose metabolism of clinically asymptomatic E4 carriers [107,123]. Interactions of middle hypertension with apoE4 and greater cognitive decline at later ages are shown in the Honolulu-Asia Aging Study (HAAAS) [100]; see articles by Launer [61] and Borenstein [11]. ApoE4 also predicted faster cognitive decline in the MacArthur Studies in Successful Aging [16]. ApoE4 alleles accelerate other Alzheimer in familial dominant Alzheimer disease and Down syndrome [29,53]; see chapters by Lott [67], Nixon [92], and Griffin [41]. An interaction of apoE4 and smaller head size appears to increase Alzheimer risk [11].
ApoE4 is also a mild risk factor for cardiovascular disease [69,118]. In the Baltimore Longitudinal Study, apoE4 was associated with a three-fold higher incidence of cardiovascular events in men, but not in women, and the association was independent of blood total cholesterol [118]. ApoE4 is also being studied for associations of hypertension and the risk of hemorrhagic and ischemic stroke [70,149]. See article by Wang [143] on apoE-deficient mice.

Much evidence shows that apoE4 is proinflammatory in peripheral macropahges and in microglia [23]. Moreover, in transgenic models with human apoE allele knock-ins, apoE4 supports less neurite outgrowth than apoE3. The question of apoE alleles on brain development and brain size is being studied and could be a factor in the apoE4-head size-Alzheimer interactions noted above.

4. Ontogeny of inflammatory changes during normal aging

Some inflammatory markers of senile plaques are also found during normal aging in the absence of Alzheimer disease, as reviewed in detail [35]. Microglia and other inflammatory markers are prominent in Alzheimer brains, but also increase to a lesser degree during normal aging. Overall, the increases of activated microglia during normal aging are 25–75% smaller than those in Alzheimer brains. Microglial-monocyte activation during aging may be confounded by the presence of amyloids, which can activate monocytes in the brain and other tissues. For example, Aβ deposits can increase the influx of blood-born monocytes [34], whereas glycoxidated β2-microglobulin amyloid in hemodialysis patients is associated with activated macrophages [80]. Because aging wild-type rodent brains lack amyloid, yet show comparable microglial activation to that in humans, it is clear that microglial activation during aging may not generally be initiated by amyloid deposits.

In healthy aging, microglia present activated phenotypes without neurological disease. The most detailed age series (3, 12, 24, 27 months) of rat cerebral cortex showed progressive age-related increases of microglia [138]. By 24 months, rats show increases in OX42 (five-fold) and OX6 (two-fold) immunoreactive microglia around the myelinated corticostriatal tracts [81] and in the doral spinal cord [131]. Humans shows similar increases in activated microglia, in the absence of neuropathology, e.g. 5-130% increases in activated microglia in hippocampal-entorhinal cortex in normal elderly [31].

Increased microglial activation in rodents is associated with increased production of IL-6, TNF, which are proinflammatory cytokines [151]. However, the activated microglia were not more neurotoxic. Moreover, in some circumstances activated microglia can be neuroprotective [130]. RNA profiling shows increased expression of complement system genes, e.g. C1q and other inflammatory mediators [64,99]. Complement activation products are also found in diffuse Aβ deposits of non-demented elderly [152]. Corpora amylacea are another locus of age-related increase in brain complement proteins: these microscopic bodies contain classical complement proteins surrounding a polyglucosan core and are further increased in Alzheimer [122].

Blood inflammatory markers (acute phase proteins) also show increases during aging [147], see article by Lauter [61]. IL-6 becomes elevated in an increasing subpopulation of community-living elderly and is a recognized risk factor for disability, heart attacks, and mortality [54,71]. CRP may be even better as risk indicators for heart attacks [108,109]. Moreover, in the Honolulu-Asia Aging Study, higher levels of CRP in 1975 were associated with dementia 25 years later [61,118a].

These findings suggest that chronic inflammatory processes become increasingly manifest during aging even in the absence of clinical disease. The proinflammatory activities of apoE4 (see article by Colton [23]) are consistent with the fundamental role of inflammation in vascular and Alzheimer disease.

5. Protective effects of NSAIDS and statins

This evidence for the pervasiveness of inflammatory processes in “normal” aging and in Alzheimer and vascular disease gives plausibility to an emergent trend that otherwise is unexpected: certain drugs that protect against heart disease may also reduce the risk of Alzheimer disease. It is daunting to review this complex literature because clinical end-points differ between studies, as do drug doses and durations, as well as heterogeneity in age, health status, ethnicity, socioeconomic and education variables, etc. Nonetheless, recent meta-analyses generally agree in the shared broad efficacy of quite different drugs in reducing the risk of both vascular events and Alzheimer disease, with effects in the range of 10–60%.

5.1. NSAIDS

NSAIDS consistently reduce the risk of heart attack and stroke in clinical trials. Some of these studies were observational, but most were planned trials. Aspirin is the most widely used. The Anti-thrombotic Trialists’ Collaboration, a massive meta-analysis of 287 studies with 135,000 patients, showed that aspirin and anti-platelet drugs collectively reduced vascular events: 25% risk reduction for myocardial infarction (primary or recurrent) and 11% reduction of stroke; aspirin (low dose, 75–150 mg/day) reduced risk by 32% [6]. Another meta-analysis of low dose aspirin found an overall 16% reduction in stroke, which represents a greater reduction in thrombotic strokes than the increase of haemorrhagic stroke [142]. The COX-2 inhibitors celecoxib, naproxen, and low dose rofecoxib reduce vascular accidents by about 15% [60,142,145].
The incidence of Alzheimer disease also appears to be reduced in some of these same post hoc studies, by about 13% for aspirin and 28% for NSAIDs (reviews [2, 15, 33, 74]). However, NSAID administration to Alzheimer patients has shown modest to no benefit, which may be due to insufficient time of treatment. There is a recognized need for much longer drug trials which would include younger age groups of apoe4 carriers and other risk factors.

5.2. Statins

Statins were first used clinically to lower blood cholesterol by inhibiting HMG-CoA reductase, the initial enzyme of cholesterol synthesis. A meta-analysis found that statins reduced the risk of CAD events by about 60% and stroke by 17%, in association with lower LDL cholesterol [63]. Among secondary prevention medications for CAD, statins can reduce CAD mortality by 24–42%, which is at least as effective as aspirin, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors [36, 43]. Statins also lowered CAD mortality in patients with normal cholesterol in the Scandinavian Simvastatin Survival Study (4S) and the Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) trial [36].

Statins appear to influence vascular plaque size by mechanisms which could be separate from blood cholesterol [146]. The FATS trial showed 75% decrease of CAD events, whereas the improvement in stenosis was much smaller (<1%) [18]. It was hypothesized that statin therapy selectively depleted a “...dangerous subgroup of fatty lesions containing large lipid cores and clusters of macrophages...”, which stabilized the lesions and hence, reduced thrombosis [18]. Plaque shrinkage was tracked during pravastatin treatment [116]. Statins show anti-inflammatory activities that are not directly dependent on lowering blood cholesterol, which include lowering blood CRP [3] and inflammatory cell infiltration and cell death [146]. Statin users also appear to have a lower risk of AD in post hoc studies [25, 55, 137, 148] and may also benefit multiple sclerosis and stroke [128]. Animal models show that statins have anti-inflammatory activities [128]. Double-blind randomized cross-over studies are needed to establish these indications.

5.3. Other mechanisms

Vagnucci and Li [137] suggest that the apparent protective effects of NSAIDs and statins involves additional angiogenic activities, because H2 blockers, which are not known for effects on inflammation or cholesterol may be equally effective. As noted above, there is evidence that small arterioles grow during normal aging. Last but by no means the least, NSAIDs modulate β-amyloid metabolism, with evidence for both direct and indirect effects on the secretases that cleave APP [115a, 143a, 153]. Recall here that the secreted form of APP, protease nexin 2 (PN-2), is powerful anti-coagulant also found in platelets [137a]. Thus, the drugs that appear to modulate risk of Alzheimer’s as well as vascular disease impact multiple domains beyond the classic inflammatory pathways, at least into coagulation and lipid metabolism.

6. Conclusions

These findings give a firm basis for considering specific relationships between inflammatory cell functions early in life and the subsequent stages leading to fully fired pathogenesis of Alzheimer and vascular disease. The following questions lie ahead:

- How to resolve cause and effect in inflammatory processes during vascular and Alzheimer disease?
- What are the earliest inflammatory changes during aging in brain?
- What are shared molecular targets of NSAIDs and statins in different cell types and tissues?
- Are there effects of maternal infection on later inflammatory processes in surviving offspring? This is relevant to maternal HIV and TB which are rampant in some populations.
- What new animal models are needed?

References


