

Review

Convergence of atherosclerosis and Alzheimer's disease: inflammation, cholesterol, and misfolded proteins

Ivan Casserly, Eric Topol

Late-onset sporadic Alzheimer's disease is a heterogeneous disorder. In elderly patients, increasing evidence suggests a link between this neurodegenerative disease, and vascular risk factors and atherosclerosis. The nature of this link remains speculative. Some investigators have suggested that the disease arises as a secondary event related to atherosclerosis of extracranial or intracranial vessels. A toxic effect of vascular factors on the microvasculature of susceptible brain regions has also been argued. An alternative explanation is that atherosclerosis and Alzheimer's disease are independent but convergent disease processes. This hypothesis is lent support by observations of shared epidemiology, pathophysiological elements, and response to treatment in both disorders. It provides a potential framework for an improved understanding of the pathogenesis of Alzheimer's disease, especially in elderly patients with vascular risk factors, and offers some promise toward the search for preventive and therapeutic treatments.

Introduction

Alzheimer's disease is a progressive neurodegenerative disease that in western society accounts for most cases of dementia.¹ Over the past five decades, there has been a sharp rise in the death rate from Alzheimer's disease in the USA (figure 1).^{2,3} By 2050, the number of Americans with Alzheimer's disease is expected to triple (from 4.6 to 16 million).⁴ This epidemic has enormous implications for society, in terms of both human suffering and monetary cost.

The prevailing paradigm of Alzheimer's disease pathogenesis contends that the primary pathogenic event is the extraneuronal or intraneuronal, or both, accumulation of the misfolded protein, amyloid β -peptide ($A\beta$), which initiates a pathogenic cascade resulting in neurotoxicity and ultimately the clinical syndrome of Alzheimer's disease (figure 2).⁵ This paradigm has its origins in the autosomal dominant forms of the disease, which account for 1–2% of all cases. These inherited forms are associated with mis-sense mutations of genes that encode the amyloid precursor protein (APP), or proteolytic enzymes that cleave APP (eg, presenilin 1 and 2). Such mutations are associated with an increased production of $A\beta$ (figure 3), and result in early-onset Alzheimer's disease that typically presents in the third or fourth decade of life.

Clinical and basic investigation has revealed that Alzheimer's disease should not be regarded as a single nosological entity.⁶ Late-onset disease, which accounts for 90–95% of all cases, differs from early-onset disease. Within the category of late-onset disease, considerable heterogeneity also exists, in terms of risk factor profiles, pathogenesis, and neuropathological findings. In elderly patients, increasing evidence suggests a link between Alzheimer's disease, and both vascular risk factors and atherosclerosis. The nature of this link remains

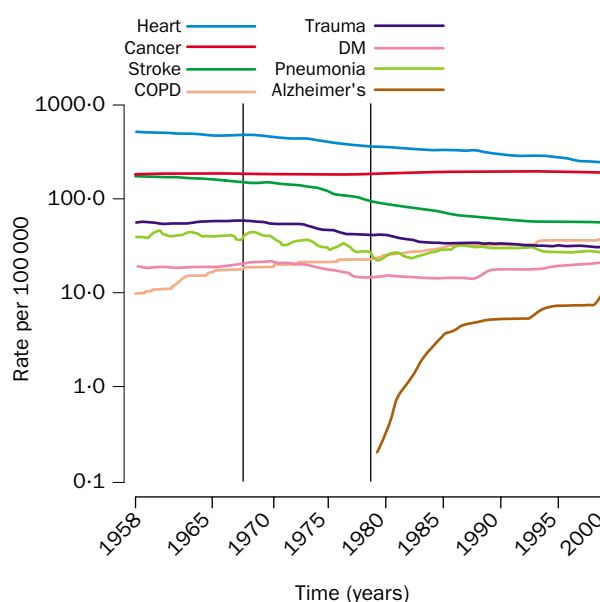


Figure 1: Mortality rates per 100 000 of the population from leading causes of death over the past five decades

Reproduced from *National Vital Statistics* 2002; 50.

COPD=chronic obstructive pulmonary disease. DM=diabetes mellitus.

speculative. Some investigators have suggested that Alzheimer's disease occurs as a secondary event related to atherosclerosis of extracranial⁷ or intracranial⁸ vessels on

Search strategy

We searched MEDLINE using Ovid Technologies, Version 9.0.0 for 1996–2003 with the keywords atherosclerosis and Alzheimer's disease. This search was supplemented by our knowledge of the primary published work in both the clinical and basic science literature, and from the bibliography of retrieved articles. 468 scientific reports were chosen for in-depth review based on their relevance to this review topic. In addition, we searched the internet using Google, and specifically searched <http://www.cdc.gov/nchs/nvss.htm> and <http://www.alzforum.org/home.asp>.

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Department of Cardiovascular Medicine, Cleveland Clinic Foundation, Cleveland, OH, USA (I P Casserly MB BCh, E J Topol MD)

Correspondence to: Eric J Topol, Department of Cardiovascular Medicine, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA.
(e-mail: topole@ccf.org)

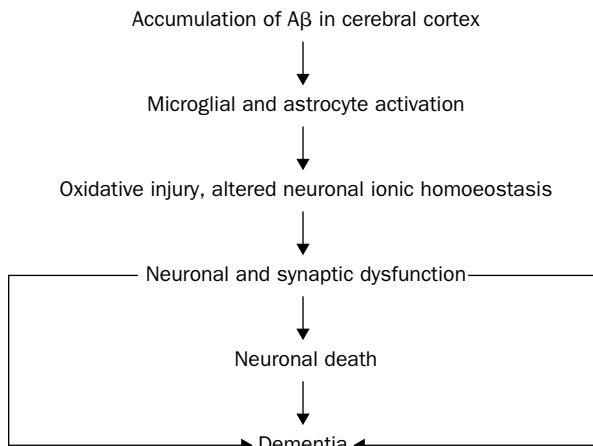


Figure 2: **Hypothetical sequence of events in the pathogenic cascade initiated by Aβ deposition resulting in Alzheimer's disease**

the basis of brain hypoperfusion⁹ or discrete brain infarction.¹⁰ A toxic effect of these vascular factors on the microvasculature of susceptible brain regions (ie, medial temporal lobe) has also been argued.¹¹ An alternative explanation is that atherosclerosis and Alzheimer's disease are independent but convergent disease processes. Based on observations of common epidemiology, pathophysiological elements, and response to therapies in both disorders, we believe this to be a tenable hypothesis.

Epidemiology

Increasing age represents the dominant risk factor for both atherosclerosis and Alzheimer's disease. The disorders are uniquely characterised by lengthy "latency periods" in which subclinical evidence of disease is evident for decades before clinical presentation. Pathological and intravascular ultrasound studies of teenagers and young adults show non-obstructive coronary atheroma.¹² In Alzheimer's disease, histological evidence of senile plaque and neurofibrillary tangle formation can be seen in the temporal lobe up to 40–50 years before the onset of dementia, and might even extend into adolescence¹³ (figure 4).

The overlap between additional "vascular" risk factors for both Alzheimer's disease and atherosclerosis is also striking (panel). The association of each of these factors with atherosclerosis is indisputable. Although the importance of some of these factors in Alzheimer's disease pathogenesis is debatable, those studies that were prospectively designed, used a population-based approach, measured the exposures in middle age, and followed patients for long periods (up to 25 years) have suggested the largest effect. Such investigations have the greatest power to suggest a causal association between the exposure and disease. The influence of vascular risk factors in Alzheimer's disease is consistent with the finding that atherosclerosis and Alzheimer's disease seems to be predominant in developed countries,⁶ suggesting a strong environmental link; the influence is also consistent with the association between Alzheimer's disease and both cerebrovascular^{7,8} and coronary atherosclerosis^{8,14} seen from clinical and post-mortem studies.

Common pathophysiological elements

Hypercholesterolaemia and inflammation have emerged as the dominant mechanisms implicated in the development of atherosclerosis, and have important interactions.¹⁵ Superimposed on these basic elements are several factors that seem to affect the disease process largely through effects on cholesterol homeostasis or the inflammatory response to injury. Inflammation has been implicated in Alzheimer's disease pathogenesis for over a decade, and increasing evidence suggests that abnormalities in cholesterol homeostasis could have an important role. Similarly, many of the contributory factors in atherogenesis have emerged as potential contributors in Alzheimer's disease.

Cholesterol

The causal link between elevated serum cholesterol and atherosclerosis is well established.¹⁶ Prompted largely by results of epidemiological studies,¹⁷ the concept of altered cholesterol homeostasis as an important factor in the pathogenesis of Alzheimer's disease has emerged. In cell cultures, increased and decreased cholesterol levels promote and inhibit the formation of Aβ from APP, respectively^{18,19} (figure 3). Animals fed a high cholesterol

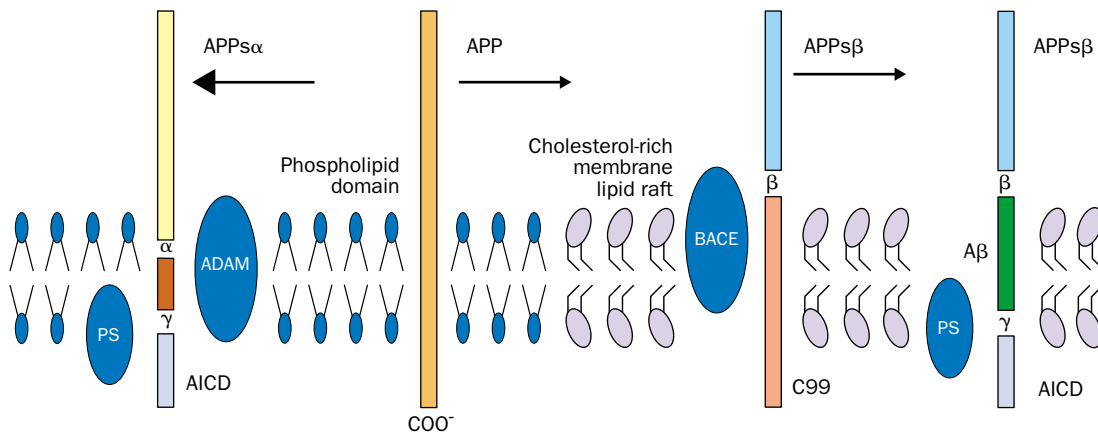


Figure 3: **Alternative cleavage of APP by α or β secretase**

APPsα, the product of cleavage with α secretase has neurotrophic properties. Cleavage with β secretase yields APPsβ molecule and C99. C99 is cleaved by γ secretase (eg, PS1) producing the neurotoxic Aβ peptide (dark green). β and γ secretases can co-localise at sites of increased membrane cholesterol favouring the production of Aβ peptide. ADAM=a disintegrin and metalloproteinase domain. PS=presenilin. AICD=APP intracellular domain. BACE=β site APP-cleaving enzyme. Reproduced with modifications from Wolozin B. *Proc Natl Acad Sci* 2001; **98**: 5371–73.

diet have shown increased intraneuronal A β immunoreactivity and occasionally extracellular plaques.²⁰ Finally, a polymorphism of the *CYP46* gene (*CYP46A1*), which encodes cholesterol 24S-hydroxylase, and is thought to reduce activity of the enzyme and raise concentrations of cholesterol in the brain, has been linked with histological evidence of increased A β deposition in the medial temporal lobe, and an increased risk of late-onset Alzheimer's disease.²¹

Increased concentrations of free cholesterol in the neuronal membrane stimulate increased A β production through intracellular and membrane effects. In cell cultures, high membrane cholesterol levels induce cellular acyl-coenzyme A: cholesterol acyltransferase (ACAT) to produce cholesterol esters within intracellular granules.²² Through an unspecified mechanism, this raised ACAT activity seems to modulate A β production causing increased synthesis. ACAT has become a target for the treatment of atherosclerosis. Inhibition of ACAT reduces atherosclerosis in apolipoprotein E-deficient mice,²³ and restricts foam cell formation by enhancing cholesterol efflux from human monocyte macrophage foam cells.²⁴ Acting at the membrane surface, increased free cholesterol may cause the formation of "lipid rafts", cholesterol-rich areas of membrane, where APP, and β and γ secretases tend to co-localise (figure 3).²⁵ By favouring the formation of such regions, increased membrane cholesterol levels could result in the preferential processing of APP toward the formation of A β .

Inflammation

Over the past 15 years, investigation has shown the importance of inflammation in the pathogenesis of atherosclerosis and Alzheimer's disease.^{26,27} As in many human inflammatory diseases, the inciting stimulus in each case remains uncertain, although experimental evidence supports a role for modified low density lipoprotein²⁸ and A β peptide²⁷ in atherosclerosis and Alzheimer's disease, respectively. Although the initial inflammatory response can be protective (ie, clearance of modified low density lipoprotein or A β peptide²⁹), failure to adequately clear the inciting stimulus results in a chronic inflammatory response that greatly contributes to the clinical manifestation of the disorder.

The presence of inflammation in brain tissue protected by a blood brain barrier might initially appear incongruous. However, the brain is populated by microglia, which are resident brain macrophages, similar to those found in the intima of atherosclerotic lesions.³⁰ Remarkably, brain microglia are capable of producing almost all of the same cytokines, chemokines, growth factors, enzymes, complement and coagulation factors, and reactive oxygen species, as their peripheral counterparts, and express many of the same surface receptors that mediate peripheral immune interactions.³¹

The supporting cellular cast in Alzheimer's disease is provided by another glial cell, the astrocyte, that secretes a

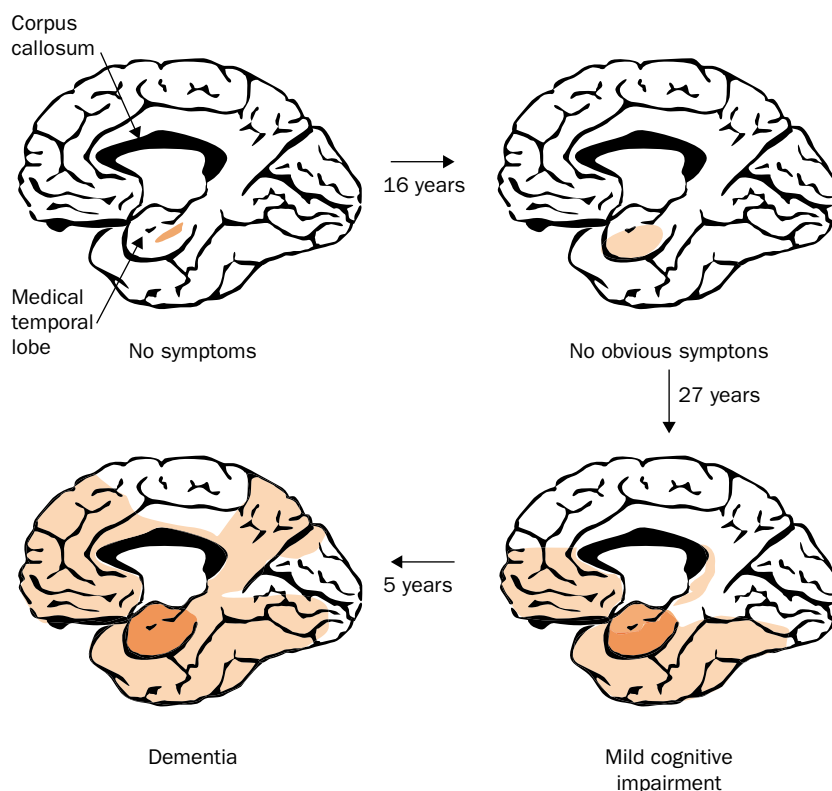


Figure 4: **Sagittal view of medial aspect of cerebral cortex showing postulated spatial sequence of spread of pathology in Alzheimer's disease from medial temporal lobe to sensory association cortices.**

The postulated temporal sequence is also shown indicating the prolonged incubation period of this disease. The depth of colour is in proportion to the density of pathology. Reproduced with permission from Smith DA, *Proc Natl Acad Sci* 2002; **99**: 4135–37.

more restricted array of pro-inflammatory products and matrix proteins, and by neurons themselves, which produce inflammatory mediators, including C-reactive protein, amyloid P, and complement factors.³² These cellular elements co-localise at sites of Alzheimer's disease pathology (ie, senile plaque) and occupy a consistent spatial relation at these sites. Their pro-inflammatory and immune mediator products are upregulated and seen in increased concentrations in these regions. Although the precise sequence of events is uncertain, this inflammatory response is believed to contribute significantly to neuronal dysfunction, and ultimately to neuronal death. Results of an in vivo study provided evidence of microglial activation at typical sites of Alzheimer's disease pathology in patients with early disease.³³ Additionally, investigators from the Honolulu-Asia study³⁴ reported that elevated C-reactive protein in middle age was associated with an increased

Common genetic and environmental risk factors for Alzheimer's disease and atherosclerosis

Epidemiological Factor

ApoE ϵ 4 polymorphism³⁶
 Hypercholesterolaemia^{17,98}
 Hypertension⁹⁸
 Hyperhomocysteinaemia⁹⁹
 Diabetes mellitus¹⁰⁰
 Metabolic syndrome¹⁰¹
 Smoking¹⁰²
 Systemic inflammation³⁴
 Increased fat intake and obesity¹⁰³

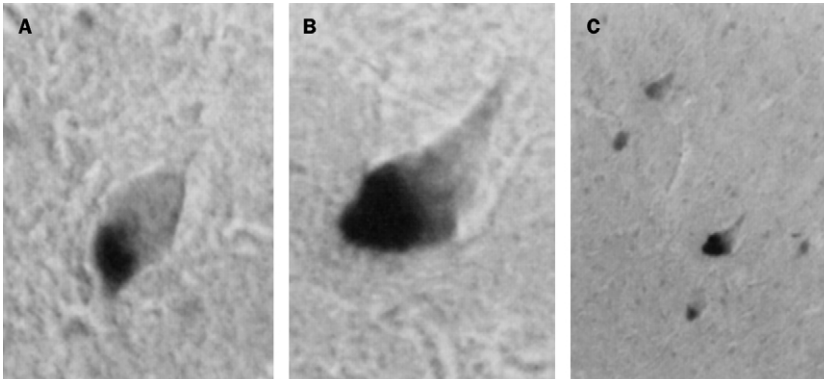


Figure 5: **Immunohistochemical analysis**

(A) Control patient showing normal angiotensin-converting enzyme (ACE) immunoreactivity in a pyramidal neuron. (B) Patient with Alzheimer's disease showing increased ACE immunoreactivity in a pyramidal neuron. (C) Only a subset of pyramidal neurons show immunoreactivity for ACE activity in Alzheimer's disease brain. Reproduced with permission from Savaskan E, Hock C, Olivieri G, et al. *Neurobiol Aging*, 2001; **22**: 541–46.

incidence of Alzheimer's disease in the subsequent 25 years, independent of cardiovascular risk factors.³⁴ These studies suggest that, as in atherosclerosis, inflammation might play an important part during the earliest phase of Alzheimer's disease pathogenesis.

Other common pathophysiological elements Apolipoprotein E e4 polymorphism

The e4 allele of the apolipoprotein E gene (*APOE*) represents a modest genetic risk factor for atherosclerosis,³⁵ and is the most important genetic risk factor for sporadic Alzheimer's disease in the general population.³⁶ Although this allelic variant seems to function as a disease susceptibility gene (ie, it is neither necessary nor sufficient), its importance is underscored by the prevalence of the carrier status for e4 allele in the general population, estimated at about 25%.³⁷

Peripheral apolipoprotein E is synthesised in the liver, and brain apolipoprotein E is synthesised in situ largely by astrocytes.³⁸ The mechanism by which these compartmentalised pools of apolipoprotein E e4 (product of *APOEe4* allele) contribute to these two diseases is uncertain, however, there are common mechanisms by which apolipoprotein E e4 might affect both processes. In cell cultures, apolipoprotein E e4 is associated with reduced efflux of cholesterol from macrophages,³⁹ and also neurons and astrocytes.⁴⁰ Within macrophages, this association is likely to promote foam cell formation, whereas in neurons, an increase in APP processing toward A β production is possible. Evidence also suggests that apolipoprotein E e4 shows less antioxidant effects compared with apolipoprotein E e3.⁴¹ Both atherosclerosis and Alzheimer's disease are associated with the production of reactive oxygen and nitrogen species that oxidise aminoacids and lipids, which contribute to disease pathogenesis. Loss of a protective antioxidant factor may exacerbate any damage due to oxidant stress.

Renin-angiotensin system

Several experimental models and clinical trials support a modulatory role for the renin-angiotensin system in atherosclerosis, independent of its haemodynamic homeostatic function. In atherosclerotic plaque, angiotensin II can be derived from systemic sources or produced locally in the vascular wall.⁴² Angiotensin receptor (AT) 1 activation by angiotensin II produces a series of responses that augment vascular inflammation, which contributes to endothelial

dysfunction and enhances the atherogenic process.⁴² Many of the components of the renin-angiotensin system have been described in mammalian brain including angiotensinogen, angiotensin-converting enzyme, angiotensin II, and AT1 and AT2 receptors.^{43,44} This has led to the concept of a "self contained" renin-angiotensin system in brain tissue. There is also evidence that over-activation of this system might contribute to the pathogenesis of Alzheimer's disease. In rats, long-term administration of angiotensin-converting-enzyme inhibitors and AT-1 receptor antagonists is associated with improvement in memory function.⁴⁵ Compared with controls, immunohistochemical analyses of the brains of patients with Alzheimer's disease show increased staining for membrane-bound angiotensin-converting enzyme, angiotensin II, and AT1, suggesting an increase in activity of the renin-angiotensin system (figure 5).⁴³ Of interest, the increased staining for these antigens was localised to the pyramidal neurons of the cortex, which are typically the most prominently affected neuronal type in Alzheimer's disease. Activation of the renin-angiotensin system might contribute to Alzheimer's disease pathology by inhibiting the release of acetylcholine from cortical neurons⁴⁶ or by promoting the inflammatory response in the brain parenchyma. A contradictory note regarding this hypothesis is the finding that in vitro angiotensin-converting enzyme prevents A β aggregation, and that angiotensin-converting enzyme inhibition blocked this effect.⁴⁷

Platelets

The presence of APP in the brain has been most focused on, but it also exists in substantial quantities in non-neural tissues.⁴⁸ Platelets contain APP in their α granules and represent the primary source (>90%) of circulating APP and A β .⁴⁹ Evidence suggests that platelet-derived A β might play a part in atherosclerosis. Immunohistochemical analysis of advanced carotid atherosclerotic plaques showed the presence of APP, A β , platelets, and activated macrophages surrounding intimal microvessels.⁵⁰ In-vitro studies demonstrated that macrophages are capable of platelet phagocytosis, which resulted in macrophage activation and foam cell formation. Macrophage activation seemed to be mediated by the processing of platelet-derived APP to A β by secretase enzymes within the macrophage. Other investigators have shown that activation of platelets that enter atherosclerotic plaque through neovessels by collagen, thrombin, or arachidonic acid, results in APP and A β release.^{51,52} Subsequent uptake of APP by scavenger (class P) receptors on the macrophage surface could lead to similar activation of macrophages as that mediated by platelet phagocytosis.⁵² These studies highlight the possible role of misfolded proteins in atherogenesis.⁵³

Liver X receptors

Liver X receptors (LXRs) are a subfamily of the nuclear receptor superfamily of transcription factors. These receptors are of interest in both atherosclerosis and Alzheimer's disease, since they regulate the expression of several genes involved in both lipid metabolism and transport, and immune responses.⁵⁴ Consistent with this

idea is that LXRs have been identified in macrophages and are broadly expressed in animal brain.⁵⁵ Activation of these receptors results in reciprocal upregulation of genes that accelerate cholesterol efflux from cells (eg, Apo E, ABCA1) and inhibition of the expression of inflammatory mediators such as inducible nitric oxide synthase, cyclooxygenase-1, and interleukins 1 and 6.⁵⁶ Investigations into LXR-deficient mice have shown an increase in foam cell formation in the arterial wall,⁵⁷ and increased aortic atherosclerosis.⁵⁸ In atherosclerotic mice, LXR agonists reduced the expression of proinflammatory genes in response to cytokine administration.⁵⁶ These findings point to the relevance of this receptor system in atherogenesis. A recent knockout mouse model also provides evidence of an age-dependent neuroprotective effect of this receptor, and an important role in lipid homeostasis in the brain.⁵⁵ The relevance of these findings to Alzheimer's disease merits further study.

RAGE

RAGE (receptor for advanced glycation end-products) is a multi-ligand receptor of the immunoglobulin superfamily.⁵⁹ The first recognised ligand for this receptor was a heterogeneous group of structures, termed advanced glycation end-products, which are produced as a result of non-enzymatic glycation and oxidation of the free amino groups of proteins. Hyperglycaemia promotes the production of advanced glycation end-products, but they are also produced in the setting of increasing age and renal failure, and at sites of oxidant stress and inflammation in tissues.⁶⁰ In diabetic animals, advanced glycation end-products are enriched in the vasculature and activate RAGE receptors on endothelial and smooth muscle cells, and macrophages.⁵⁹ In in-vitro and animal studies, interaction between advanced glycation end-products and RAGE is associated with increased vascular permeability and vascular inflammation. These effects are mediated by increased nuclear translocation of NF- κ B transcription factor, which leads to the expression of a range of pro-inflammatory molecules.⁶¹ Because interaction between advanced glycation end-products and RAGE leads to increased expression of the receptor rather than down-regulation, a positive feedback loop is initiated which might contribute to chronic inflammation and tissue injury. RAGE can also bind cytokines of the S100/calgranulin family,⁶¹ providing a further link between RAGE activation and inflammation. In-vivo evidence of the role of RAGE in atherosclerosis is provided by animal models, in which blockade of RAGE has been associated with inhibition of both atherosclerotic lesion formation and lesion progression.^{59,62}

Within the brain, RAGEs have been seen on the surface of neurons and microglia.⁶³ Immunoreactivity for advanced glycation end-products is increased three-fold in Alzheimer's disease patients compared to controls, and co-localises with the typical Alzheimer's disease histopathology.⁶⁴ It seems likely that increasing age, oxidant stress, and the inflammatory response associated with Alzheimer's disease pathology contributes to the presence of these structures. However, advanced glycation end-products might not be the primary ligand for RAGE in the nervous system. RAGE can act as a signal transduction receptor for A β . In cell cultures, RAGE activation by A β was associated with oxidant stress in neurons, and cellular activation of microglia.⁶⁵ If these in-vitro actions are replicated in vivo, they may contribute directly to neurotoxicity, or indirectly by promoting the inflammatory response.

Angiogenesis

In human atherosclerotic lesions, neovascularisation of the intima is thought to promote plaque progression through the supply of nutrients and oxygen and the accumulation of blood monocytes in the intima.⁶⁵ These new vessels arise from the vasa vasorum, which under normal circumstances supply only the adventitia.⁶⁶ The stimuli for atherosclerotic neovascularisation include hypoxia and cytokines that function as angiogenic growth factors (eg, VEGF).^{67,68} Evidence for these concepts comes from animal models of atherosclerosis, in which VEGF enhanced plaque progression, whereas angiogenesis inhibitors reduced intimal neovascularisation and plaque growth.^{69,70}

Vagnucci and colleagues⁷¹ have also hypothesised that angiogenesis may have a role in pathogenesis of Alzheimer's disease. The robust inflammatory response in Alzheimer's disease could serve as the source of angiogenic growth factors, many of which are present in the brain parenchyma of these patients (eg, VEGF, MCP1, TNF α and interleukin 6). Several investigators have noted ultrastructural and functional abnormalities in the microcirculation of brains of people with Alzheimer's disease, and have argued that they promote ischaemia and hypoxia of brain parenchyma, which are further stimuli for angiogenesis.^{72,73} Cerebrovascular microvessels in Alzheimer's disease have the potential to contribute to tissue damage. Grammas and colleagues⁷⁴ identified a peptide neurotoxic factor secreted by microvessels from patients.⁷⁴ Cerebral microvessels in Alzheimer's disease might also produce inflammatory mediators and contribute to the extracellular pool of A β through increased expression of APP.⁷⁵ Thus, although unlikely to be a sufficient cause of Alzheimer's disease, pathological angiogenesis in the Alzheimer's disease brain might have a contributory role. Further definitive experimental and clinicopathological data are needed.

Response to therapies

Statins

Randomised placebo-controlled trials of statin treatment have shown the beneficial effects of the drugs in primary and secondary prevention of cardiovascular and cerebrovascular disease events.⁷⁶ Through direct effects on LDL cholesterol and triglyceride levels, and cholesterol-independent effects on endothelial function, smooth muscle cell proliferation and migration, platelet reactivity, macrophage activation, and vascular inflammation,⁷⁷ statins slow the progression of atherosclerosis and promote plaque stabilisation.

Epidemiological studies with different study designs and patient populations have shown a 40–70% reduction in the risk of Alzheimer's disease associated with statin use.^{78–81} Despite the inherent limitations of these data to ascribe a causal link between statin use and a decreased risk of Alzheimer's disease, the magnitude and consistency of the effect observed is remarkable. Two recent randomised placebo-controlled trials have failed to show a benefit of statin therapy on age-associated cognitive decline,^{82,83} but some scepticism about the implication of these findings for the role of statins in the prevention of Alzheimer's disease is warranted. The short follow-up of 3·2 years and 5 years in both trials,^{82,83} and the elderly population studied in the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) trial⁸² might have undermined the ability of these studies to show an effect. Also, age-associated cognitive decline is at best a poor surrogate for Alzheimer's disease.

As in atherosclerosis, both cholesterol and cholesterol-independent effects could explain the benefit of statins in Alzheimer's disease. In neuronal and peripheral cell lines, statins seem to promote a favourable shift in APP processing toward secretion of the neurotrophic APPs α peptide and away from A β production.^{25,84} Depletion of membrane cholesterol by statins produces an increase in the activity of enzymes with α secretase activity, and a reciprocal decrease in β -secretase-mediated APP proteolysis. In vivo studies provide additional support for these effects. In guinea pigs given a statin for 3 weeks, reduced levels of A β in the CSF, and reduced brain tissue A β levels were recorded.⁸⁴ In view of the long half-life (about 6 months) of brain cholesterol, any benefit of statins in preventing Alzheimer's disease in humans that is mediated by cholesterol reduction is likely to be very slow and could have particular relevance in clinical studies.

Several previously described pleiotropic effects of statins might also be implicated in any potential benefit in Alzheimer's disease. In animal models of cerebral ischaemia, and in preliminary investigations in human beings, statins favourably alter the expression of adhesion molecules preventing leucocyte-endothelial and leucocyte glial interactions, suppress cytokine production, inhibit astrocyte, microglial, and macrophage inducible nitric oxide synthase production, and have anti-oxidant effects.⁸⁵⁻⁸⁷ Whereas inflammation in Alzheimer's disease is not thought to be driven by systemic mediators, and the inflammatory response is distinct from that induced by ischaemic injury, the potential benefit of an in-situ anti-inflammatory effect of statins in the brain in the disease seems likely, and is supported by in-vitro studies.⁸⁸

Aspirin and NSAIDs

The argument for the convergence of atherosclerosis and Alzheimer's disease based on a common response to aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) is speculative. Despite the negative results from a randomised study of the effects of a non-selective NSAID and selective COX-2 inhibitor on disease progression,⁸⁹ findings from multiple cross-sectional and prospective epidemiological studies support a treatment benefit of low-dose aspirin and NSAIDs in Alzheimer's disease.⁹⁰ The magnitude of this benefit seems to be greatest in individuals with long-term use (ie, >2 years), and to be stronger with NSAID compared with aspirin.⁹⁰ Although initial attempts to explain the mechanism of this beneficial effect have centered on the anti-inflammatory effect of these agents due to inhibition of COX1 and COX2 (present in microglia⁹¹ and neurons⁹²), inflammation-independent effects may be operative in the case of NSAIDs. In cell cultures, a subset of NSAIDs (not including aspirin) greatly reduced the production of A β independent of an effect on cyclo-oxygenase activity.⁹³ In-vivo results seem to confirm this finding (Breteler MM, unpublished data, <http://www.alzforum.org>).

In patients with coronary or cerebral atherosclerosis, aspirin has proven highly effective in the secondary prevention of ischaemic events in patients with established coronary or cerebrovascular disease.⁹⁴ Although the benefit of aspirin in this setting has traditionally been attributed to its anti-platelet effect, clinical⁹⁵ and basic⁹⁶ findings support an anti-inflammatory effect of aspirin, even at low (ie, anti-platelet) doses, which might improve the progression and evolution of atherosclerotic plaque. Despite the absence of clinical data, experimental evidence also suggests an attenuating effect of NSAIDs in atherogenesis. In LDL-receptor knockout mice, indomethacin suppresses systemic markers of inflam-

mation, and reduces the extent of aortic atherosclerosis by more than 50%.⁹⁷ Whether this anti-atherogenic effect results from inhibition of the COX1 or COX2 isoform of the cyclo-oxygenase enzyme is unclear.

Implications

The recognition that atherosclerosis and Alzheimer's disease are independent but convergent disease processes represents a paradigm shift in our thinking about their pathogenesis. We argue that this hypothesis provides a framework for an improved understanding of the pathogenesis of Alzheimer's disease, especially in elderly patients with vascular risk factors, and offers some promise toward the search for preventive and therapeutic treatments for Alzheimer's disease.

Support for this hypothesis could begin with a rigorous quantitative assessment of atherosclerotic burden in various vascular territories and Alzheimer's disease pathology in brain parenchyma in post-mortem cases. The finding of an association between the global burden of atherosclerosis and Alzheimer's disease, which disappears after adjustment for known vascular risk factors, would provide evidence for our hypothesis.

The use of treatments with proven effects on the process of atherosclerosis should be tested systematically in Alzheimer's disease. This should begin with in vitro and animal studies to provide preliminary evidence of efficacy. In view of our hypothesis, agents tested should be capable of achieving therapeutic levels in brain tissue to be effective, since merely treating peripheral atherosclerosis will have little impact on Alzheimer's disease. Cardiovascular medicine has several potential candidate drug groups that might prove useful (table), and more are likely to emerge. Future cardiovascular trials should incorporate pre-specified substudies of cognitive function, and specifically should include mechanisms to allow the diagnosis of incident Alzheimer's disease. Based on our current understanding of the disease and the disappointing results of previous randomised studies, the best chance of proving a benefit of these therapies in the prevention of Alzheimer's disease would seem to need treatment for many years (20-30 years), ideally with life-long follow-up and histological analysis of brain tissue post mortem. The collaboration of cardiologists, neurologists, and histopathologists for these investigations is essential. This proposal represents a major departure from current cardiovascular trial design, and the resources needed are substantial.

Possibly, the pathogenic mechanisms discovered in Alzheimer's disease might advance our understanding of atherosclerosis. Knowledge of the pathogenic role of innate

Drug class	Potential mechanism			
	Cholesterol homeostasis	Anti-inflammatory	Anti-angiogenic	A β effects
ACE inhibitors	-	+	-	?
All blockers	-	+	-	?
PPARG agonists	-	+	-	?
ACAT inhibitors	+	?	-	?
Statins	+	+	+	+
Aspirin	-	+	+	-
NSAIDs	-	+	+	+
COX2 inhibitors	-	+	+	?
Thienopyridines	-	?	?	?

+ indicates positive; - indicates negative; and ? indicates uncertainty. ACE=angiotensin-converting enzyme. All=angiotensin II. PPAR=peroxisomal proliferator activating receptor. ACAT=acyl Co-A cholesterol acyl transferase, COX=cyclo-oxygenase.

Cardiovascular drug groups with potential therapeutic benefit in Alzheimer's disease and possible mechanism

immunity in atherosclerosis and the potential pathogenic role of APP and A β in carotid atherogenesis represent the first examples of what will hopefully be a fertile symbiosis between investigation into both disease processes. It is reasonable to suggest that our search for the elusive factor initiating atherosclerosis should begin to focus more closely on further species of misfolded proteins.

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