Critically attained threshold of cerebral hypoperfusion: the CATCH hypothesis of Alzheimer’s pathogenesis

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Abstract

This review discusses the experimental and clinical data which indicate that chronic cerebral hypoperfusion can affect metabolic, anatomic, and cognitive function adversely. In aged but not young animals, chronic brain hypoperfusion results in regional pre- and post-synaptic changes, protein synthesis abnormalities, energy metabolic dysregulation, reduced glucose utilization, cholinergic receptor loss, and visuo-spatial memory deficits. Additionally, aging animals that are kept for prolonged periods of time after chronic brain hypoperfusion, also develop brain capillary degeneration in CA1 hippocampus and neuronal damage extending from the hippocampal region to the tempo-parietal cortex where neurodegenerative tissue atrophy eventually forms. All these pathologic events occur in rodents in the absence of senile plaques and neurofibrillary tangles. Alzheimer brains reveal similar biochemical and structural changes as those experimentally induced in aging animals. Moreover, regional cerebral hypoperfusion is one of the earlier (if not the earliest) clinical manifestations in both the sporadic and familial forms of Alzheimer’s disease. In addition, therapy that improves or increases cerebral perfusion is generally of some benefit to Alzheimer patients. Conversely, a variety of disorders with different etiologies that impair or diminish cerebral perfusion are reported to be risk factors for this dementia. These findings have prompted us to propose the concept that advanced aging in the presence of a vascular risk factor can converge to create a critically attained threshold of cerebral hypoperfusion (CATCH) that triggers regional brain microcirculatory disturbances and impairs optimal delivery of energy substrates needed for normal brain cell function. The outcome of this defect generates a chain of events leading to the progressive evolution of brain metabolic, cognitive and tissue pathology that characterize Alzheimer’s disease. The possible role of CATCH in familial and early onset Alzheimer’s disease is briefly discussed from a theoretical vantagepoint. The growing and most recent evidence in support of the CATCH concept is the focus of this review.

Keywords: Cerebral hypoperfusion; Alzheimer’s disease; Familial Alzheimer’s disease; Metabolism; Protein synthesis; Golgi complex; Endoplasmic reticulum; Blood pressure; Capillaries; Aging; Vascular risk factors; Vascular dementia; Menopause; Presenilins; Amyloid precursor protein; Aβ; SPECT; Cerebral blood flow; Hemodynamics; Hemorheology; Cognition; Genetic mutations; Brain

1. Introduction

Normal brain function requires a steady supply of energy substrate to carry out all of its cellular and molecular needs. Glucose is the primary source of fuel for any energy-demanding activity in mammalian brain that together with oxygen, is delivered by the circulation for the metabolic chores that keep brain cells healthy [41]. When glucose delivery to the brain stops, as in sudden cardiac arrest lasting several minutes, catastrophic neurological consequences or even death can develop.

But, what happens to brain cells when glucose delivery becomes suboptimal for long periods of time? Inexplicably, this question has received little historical attention in so far as animal experimentation is concerned. Because of the obvious clinical implications involving chronic cerebrovascular insufficiency and a variety of central nervous system (CNS) disease processes, some of which are linked to neurodegeneration, we became interested in studying this phenomenon experimentally. A series of experiments beginning in 1989 and continuing to the present time, were designed around a rat model of chronic brain hypoperfusion (CBH) developed in our laboratory [1,22,23,26–30,32,33,37,38,83,84].

Why CBH? We reasoned that glucose-oxygen levels could be more easily manipulated physiologically by alter-
ing the hemodynamic status of cerebral blood flow (CBF) using a rat model that would assume some clinical relevance. CBF could be influenced by manipulating one or more of three parameters: 1) age of rat, 2) duration of CBH, 3) severity of CBH.

CBH was achieved by permanent or reversible occlusion of two or three major vessels (severity) supplying the brain, for example, both common carotid arteries (2-vessel occlusion, or 2-VO) with the option of additionally occluding the left subclavian artery (3-vessel occlusion, or 3-VO) [38]. Occlusion of the left subclavian artery essentially stopped blood flow to the brain from the left vertebral artery. Thus, either one or both vertebral arteries remained patent at all times. Moreover, CBH could be maintained for 1 to 52 weeks (duration) in young or aged rats (age). Neither 2-VO nor 3-VO was sufficient to elicit any sensory-motor deficits or cardio-pulmonary problems in these animals during the period of observation [30,32].

However, it quickly became clear from our initial experiments that 3-VO in aged (19–22 months) Sprague–Dawley rats was much too severe an insult and rats would not survive the surgery unless they were middle aged, 9 to 12 months old. Lowering the age of the animal allowed a series of experiments to be carried out where manipulation of the two parameters above was still an option.

These animal experiments were instrumental in changing our perception of how Alzheimer’s disease pathophysiology may actually begin. The reason, which is discussed further on in this review, is the revealing pathologic picture obtained in the CBH model that is also characteristic of Alzheimer’s disease, keeping in mind that the rat findings such as they are, are still only a model or crude reflection of this dementia [1,2,23,26–30,32,33,37,38,83,84]. More surprising was the fact that mimicry of metabolic, anatomic, and cognitive pathology reported in Alzheimer patients could be obtained using this rat model in the absence of senile plaques and neurofibrillary tangles.

Because much of the fun in science is based on the hypothetical predictions that can be constructed from data aimed at problem solving, the opportunity to review and possibly call forth new phenomena seems a reasonable goal, if only for the purpose of questioning the rigid paradigm that has characterized the basic research of this field in the last quarter century. In this sense, we agree with Kuhn [16] that one of the most important goals of science is to test established knowledge to potentially crack open new territories.

2. Animal data

Our experimental studies revealed a number of curious findings beginning with the observation that young rats with 3-VO could in time recover spontaneously from visuo-spatial memory impairment induced by 9 weeks of CBH [33]. Middle age rats however, not only did not recover from CBH, but went on to develop progressive degeneration of the CA1 hippocampal sector and eventually atrophic necrosis of the parietal and temporal cortex [84]. This progressive degeneration was associated always with increased impairment of visuo-spatial ability as measured on the Morris water maze (Fig. 1).

Other experiments in our series showed that aged rats subjected to 2-VO for 1 to 2 weeks, could recover from their anticipated behavioral, physiologic and anatomic changes that would consistently accompany this vascular insult, if CBF was restored to pre-2-VO levels [32]. The functional changes usually observed after 2-VO consisted of visuo-spatial memory impairment, hippocampal gliosis, mean hippocampal CBF reduction of 32%, microtubule associated protein-2 loss in the CA1 apical dendrites (a marker of protein synthesis and pre-synaptic activity), cytochrome oxidase decline in CA1 and posterior parietal cortex (a marker of neuronal energy activity), increased hemeoxygenase-1 expression (a marker of oxidative stress), and extracellular deposits of amyloid precursor protein, normally localized to neuronal cell membranes [27,28,32,84] (Fig. 1). Recently, we have reported that 2-VO for 8 weeks and restoration of CBF by carotid artery reanastomosis, can reverse visuo-spatial impairment in aging rats [48]. Generally, for the first 12 weeks, the above changes were almost always observed with little or no neuronal loss or structural damage to CA1 or other neurons in the brain.

Others have found similar histocytochemical and behavioral changes after CBH [77,118] as well as reduced glucose utilization created by 2-VO [120]. Similarly, reduction of post-synaptic cholinergic activity for short time periods after 2-VO has been reported without alterations of neuronal structure [81,118].

An important recent finding by Luiten and his group [21] (see also Farkas et al., this issue) showed that rats subjected to 2-VO for 12 months, developed significant capillary abnormalities selectively in CA1 as determined ultrastructurally. Findings from that study suggested that the microvessels supplying CA1 may be as vulnerable to persistent cerebral hypoperfusion as the ischemic-sensitive CA1 neurons in that region. In fact, the question can now be posed whether CA1 capillary degeneration precedes CA1 neuronal damage and possibly even causes it. If this premise is correct, it could provide an important clue in piecing together a reasonable explanation relative to the pathogenesis of Alzheimer’s disease.

3. Basic findings and clinical assumptions

Rats whose blood flow to the brain is chronically reduced, develop a progressive pathology consisting of metabolic, behavioral, and structural changes involving neuronal-glial and microvascular brain tissue. The trigger that elicits these reactions in rats is reduced blood flow to the brain.
The progressive pathology that develops in Alzheimer’s disease consists of metabolic, behavioral and structural changes involving neurono-glial and microvascular brain tissue. The trigger that elicits these reactions in Alzheimer’s disease is presently unknown.

We will assume here for the sake of argument, that the trigger for Alzheimer’s disease is related to a reduction of blood flow to the brain and this assumption is based on correlative experimental and clinical findings (Fig. 1).

Our working hypothesis as previously reported, is that advanced aging in the presence of a vascular risk factor for Alzheimer’s disease will converge to create a critically attained threshold of cerebral hypoperfusion (CATCH) that will subsequently affect the microcirculation and delivery of energy substrates required for optimal brain cell function [39]. The cerebral metabolic, tissue pathologic and cognitive disturbances known to exist in Alzheimer’s disease have their root radiating from CATCH [31,36,39]. If this concept is true, what is the evidence to support it?

4. Evidence that Alzheimer’s disease develops from chronic brain hypoperfusion

There is a strong association between the risk factors found in vascular dementia and in Alzheimer’s disease (see Table 1). Much of this data has been obtained from The Rotterdam Study of elderly and demented patients (see below). Because vascular dementia is acknowledged by most workers in the field to be caused by vascular factors, the issue becomes whether such an association between vascular and Alzheimer’s dementia, is significant or coincidental. The risk factors listed in Table 1, it should be pointed out, share a similar morbid outcome despite their widely different pathologic etiologies and clinical course. The morbid outcome is that all these risk factors also impair or reduce cerebral perfusion in some way. The statistical probability of two dozen different risk factors for Alzheimer’s disease (or any other disease) sharing a common pathologic action on a specific system (cerebral perfusion)
were examined (among other things) for the frequency and lifetime risk of dementia and its subtypes, including Alzheimer’s disease [8–10,17,58,79,80,121]. One of the first reports of this epidemiological opus described the increased prevalence of atherosclerosis found in both vascular dementia and Alzheimer’s disease [50]. Atherosclerosis of the internal carotid arteries that leads to occlusion of one or both vessels is reported to impair cerebral perfusion and cause hemodynamic changes at the level of the anterior and/or posterior communicating arteries in the brain [61]. As in our chronic brain hypoperfusion rat model, when the severity of the carotid lesion in humans increases, cerebral hemodynamic status deteriorates [61].

Other risk factors, such as diabetes [79], cardiovascular disease [73,110,111], mitral valve prolapse [112], cigarette smoking [73,80], changes in brain microvessels [12,31,56,71,74,95,100], stroke [89], and vascular disorders [104–106] were also found associated with Alzheimer’s disease and vascular dementia (Table 1).

Two general statements can be made about the Rotterdam study:

1. All of the risk factors found for Alzheimer’s disease thus far are capable of causing or contributing to cerebral hypoperfusion;
2. The majority of the vascular risk factors that are associated with Alzheimer’s disease also seem to be linked with vascular dementia.

Other risk factors for Alzheimer’s disease worthy of mention are menopause, hypertension/hypotension, cholesterolemia, and transient ischemic attacks in the absence of a lesion.

6. Menopause

A substantial number of articles have appeared within the last 5 years relating to the beneficial effects of estrogen on cerebral ischemia [78,99,103,116]. These studies are important for two reasons. First, during menopause, estrogen levels fall and with it, the risk for Alzheimer’s disease increases in women to the same extent as age-matched males. Second, estrogen replacement therapy during menopause seems to reduce the risk for Alzheimer’s disease [53,124] possibly as a result of increasing blood flow to the brain [43,78,98].

How estrogen increases CBF and cognitive function in elderly females is not presently known but a recent study has implicated the actions of this hormone on cyclic guanosine monophosphate (cGMP) in the hippocampus and in cerebral microvessels [82]. Another possibility is that estrogen reduces cerebrovascular resistance [5] that is known to increase with aging [35], consequently improving perfusion to the brain.

Estrogen can also increase cerebral glucose uptake ostensibly by enhancing glucose transporter 1 (Glut1) activity

### Table 1

Common risk factors for the development of vascular dementia and sporadic Alzheimer’s disease as reported in the literature (see text for details and references)

<table>
<thead>
<tr>
<th>Vascular risk factor</th>
<th>Dementia affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced aging</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Cardiac arrhythmias</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Thrombogenic factors</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Brain vessel wall pathology</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Hypertension/hypotension</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Amyloid angiopathy</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Blood-brain barrier</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Dysfunction</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>High serum fibrinogen levels</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Elevated serum viscosity</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>High homocysteine levels</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Hyperlipidemia (HDL-cholesterol)</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Smoking/alcoholism</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>Apolipoprotein E (ApoE)</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
<tr>
<td>White matter changes</td>
<td>Alzheimer’s disease/vascular dementia</td>
</tr>
</tbody>
</table>

Three issues are of interest: 1) Note the common morbid links between these two dementias, one known to be caused by vascular factors (vascular dementia) and the other presumed to have a neurodegenerative etiology (Alzheimer’s disease). 2) Both dementias also share the most important risk factor for the development of either disorder, advanced aging. 3) All the vascular risk factors listed in the table are reported to reduce or impair cerebral perfusion.

are highly unlikely to be coincidental. The reverse seems to be also true. For example, if one examines all the compounds that have thus far been reported useful to some extent in Alzheimer patients (cholinomimetics, NSAID’s, estrogen replacement therapy, cholinesterase inhibitors, vitamin E, ginkgo biloba, etc.), despite their widely different pharmacologic and pharmacokinetic activities, they all share one common effect, that is, they improve or increase cerebral perfusion in some way [34].

One rare condition that CATCH does not predict is early onset Alzheimer’s disease (EOAD) that affects subjects generally below the age of 60. How do a small percentage of younger subjects develop Alzheimer’s disease? No one knows and the topic has not been as well examined clinically as late onset Alzheimer’s disease. Could two or several vascular risk factors be present in these subjects thus substituting advanced age for several co-morbid cerebrovascular risk factors creating a less chronic but more severe variant of CATCH? This is a question that could be clarified by prospective epidemiological studies of this rather unusual dementia group.

5. Alzheimer vascular risk factors

The Rotterdam Study is a population-based prospective study involving nearly 8000 subjects over the age of 55 who
in the endothelial cells of brain capillaries [102]. This latter effect by estrogen could help explain the protective actions of this hormone in neurodegenerative disorders such as Alzheimer’s disease where cerebral capillary degeneration with endothelial cell compression (where Glut1 is localized) leads to reduced glucose transport into the brain. [12,31,56,71,74,95,100].

7. Hypertension/hypotension

A considerable number of Alzheimer patients are found to have hypertension or hypotension [90,105,106]. Of these two, hypotension seems to be more prevalent among these patients [90,91]. Because arterial hypertension is the most important risk factor for stroke [89] it is not surprising that a number of hypertensive Alzheimer patients would show white matter changes consisting of lipohyalinosis and thickening of the vessel walls [11]. Neurofibrillary tangles and senile plaque formation are reported to be more common among hypertensive than normotensive subjects [111]. This link between the pathologic hallmarks of Alzheimer’s disease and hypertension is all the more intriguing because of studies indicating that elevation of blood pressure or atrial fibrillation can lead to cognitive decline [59,60].

Likewise, cardiac arrhythmias and hypotension are associated with cognitive impairment in the elderly probably because of persistent chronic cerebral hypoperfusion [45,75,91]. If, as evidence suggests, hypotension is shown to be an important risk factor for dementia, one should question the wisdom of prescribing antihypertensive therapy to aging subjects with mild or moderate hypertension. An interesting note to the problem of prescribing antihypertensives to the elderly, is the suggestion that overtreating the elderly to manage their blood pressure, can lead to hypotension and increased risk of dementia [64]. However, several studies (see review [105]) have not seen an association between dementia and antihypertensive therapy although this issue is far from resolved.

Both blood pressure changes can reduce blood flow to the brain by either increasing cerebrovascular resistance through vessel non-compliance (hypertension) or by contributing less blood volume and a hypoperfusion state to ischemic-sensitive neurons, for example, in the hippocampus (hypotension). This “yin-yang” contrast is paradoxical because it indicates that both extremes of the blood pressure scale can achieve a similar, negative response on cerebral perfusion. Consequently, what may be important in the above findings is that both hypertension and hypotension can increase the risk of Alzheimer’s disease by different mechanisms [25,90,105].

8. Regional CBF in Alzheimer’s disease

A considerable number of PET, functional MRI and single photon emission tomography (SPECT) studies have demonstrated a significant reduction of regional CBF in Alzheimer patients [13,62,67,92,122]. These studies show that very early detection of this dementia is possible using various neuroimaging techniques that measure cerebral perfusion decline in specific brain regions, such as the temporo-parietal cortex.

In one study, a group of elderly patients complaining of memory disturbances (classified as “questionable” Alzheimer’s) received quantitative SPECT measures and were followed up for two years. Subjects were divided into two groups: those that showed significant hypoperfusion of the hippocampal-amygdaloid-cingulate region (areas linked to memory function) and who later developed ADRDA criteria for Alzheimer’s disease, and those that showed no hypoperfusion in any brain region and did not develop Alzheimer’s criteria [54]. This study concluded that SPECT measures of regional cerebral perfusion can pre-clinically predict the development of Alzheimer’s disease years before its clinical manifestations [54]. If confirmed, this technique could become an effective tool for detecting potential patients that may later develop Alzheimer’s disease and serve as a screen for designing preventive therapy that can delay or arrest the impending pathology associated with this disorder.

9. Protein synthesis

The relationship between regional protein synthesis in the brain and regional cerebral blood flow has been shown to be closely linked. An example can be seen when gerbils are subjected to hemispheric brain ischemia, even a mild decline in optimal blood flow is capable of reducing brain protein synthesis [126]. In this model, when blood flow was reduced to 60% of the total flow, protein synthesis was practically suppressed [126]. After adequate reperfusion, protein synthesis returned to pre-ichemic levels [126]. This phenomenon suggests that protein synthesis is very sensitive to cellular ischemic disturbance even when perfusion pressure does not reach autoregulatory failure. Protein synthesis is an extremely important and complex cell function carried out in the ribosomes of the endoplasmic reticulum (ER) with energy provided by the hydrolysis of ATP [107].

Because glucose and oxygen are needed for the constant manufacturing of brain energy, it follows that disturbances in the glucose-oxygen delivery to neurons can have an important effect on protein synthesis, which subsequently, may result in the elaboration of amino acid sequence errors. This concept is supported by evidence showing that brief periods of ischemia can markedly affect neuronal protein synthesis that can recover only after reperfusion except, in vulnerable neurons such as those found in the CA1 hippocampus [6]. When abnormal proteins or polypeptides are synthesized in the ribosomes of the ER, they can pass directly to the Golgi complex where transport to axons, dendrites or soma is accomplished. Because transcription
(the process by which DNA makes RNA) and translation (the process by which RNA makes proteins) involve many energy-dependent steps, specific abnormalities in the pathway leading to protein expression, synthesis, packaging, and delivery to target tissue can occur in neurons whose energy capacity is compromised. For example, abnormal protein synthesis or processing of amyloid precursor protein (APP) and abnormal post-translational changes of the protein tau, may occur in neurons exposed to continued energy-compromise. The outcome of such energy-deficiencies could involve Aβ formation and disrupted tau phosphorylation, leading to the production of senile plaques and neurofibrillary tangles, respectively.

The anatomic loci where protein aberrations can occur are the endoplasmic reticulum (ER) and Golgi complex. Brain ischemia is reported to disturb the function of the ER more in the hippocampus than cortex [87,88]. This piece of information is intriguing when it is realized that, 1) aminocyclation (the adding of an amino acid to a tRNA molecule) requires ATP to drive the enzymatic reaction and; 2) the hippocampus is known to be an extremely vulnerable region to ischemia. Consequently, if tRNA is altered in some way by suboptimal availability of energy, mutations of specific proteins (see below) can result that can damage or block the cell’s ability to carry out normal cytoplasmic functions.

Correct amino acid sequence during protein synthesis requires high-energy consumption and disturbances of such protein synthesis can injure the neuron from within [2].

Other studies have revealed that brain ischemia can increase cytoplasmic calcium activity through mitochondrial and ER release of calcium into the cytosol as well as from abnormal calcium ion influx generated from outside the cell [87,88]. This loss of cytosolic calcium homeostasis has been shown to involve a coupling abnormality between calcium molecules and ATP hydrolysis in the ER resulting from the ischemic process [85].

One of the functions of the Golgi complex is to modify and sort secretory particles from the ER and then transport them for release in terminals [101]. This process may be relevant to AD because recent data shows that Aβ_{1-40} is generated and packaged into secretory vesicles exclusively in the Golgi whereas AB_{1-42} is made and retained within the ER in an insoluble form [18,44,47]. Both Aβ_{40} and Aβ_{42} peptides are known to accumulate excessively in selected brain regions of Alzheimer brains but of the two, Aβ_{42} seems more toxic and is believed to form the core of senile plaques [96].

The mechanism involving fast-transported proteins require that they cross the Golgi complex where some proteins are modified post-translationally by proteolytic cleavage, glycosylation, and phosphorylation, then packaged into vesicles and transported to the axon or dendrites where they are propelled by motor proteins attached to microtubules [15,46,114,115]. This orderly cytoskeletal traffic goes in both directions and requires energy without which fast axonal transport and synaptic activity would become dysfunctional and contribute to cell death [76]. Retrograde axonal transport from the terminal back to the cytoplasm also requires energy, and dysregulation of this mechanism might ostensibly affect neurotrophic factors needed for cell survival and protection from such insults as ischemia.

10. Genetic mutations

Mutations of presenilins and amyloid precursor protein genes can lead to early onset (< 60 years of age) autosomal Alzheimer’s disease. The outcome from such genetic mutation leads to familial Alzheimer’s disease (FAD) that has nearly 100% penetrance in affected individuals. The exact cellular function of presenilins and APP are unknown as are the underlying mechanisms whereby mutation of these genes leads to FAD. Because of their strategic localization in the transmembrane proteins of the ER and Golgi complex, one suggested function of presenilins is their possible transport or sorting of proteins produced in these organelles. Because we have proposed that the CATCH concept is based on two conditions involving advanced age and a vascular risk factor that converge to diminish cerebral blood flow to a critical threshold and trigger subsequent development of Alzheimer’s disease, how does CATCH explain genetic mutation leading to FAD in younger individuals? The answer to this question remains a mystery but we offer the following thoughts on the matter.

Amyloid precursor protein (APP) is almost exclusively cleaved by α-secretase at the cell surface of neurons within the Aβ domain and consequently does not contribute to the amyloidogenic product forming senile plaques [86].

By contrast, β- and γ-secretase act on APP in the neuronal secretory pathway within the ER and Golgi where they produce amyloidogenic Aβ. It is the Aβ polypeptide that is eventually secreted from the cell to form senile plaques extracellularly and within the cerebrovasculature [14,18,16].

These findings are of interest because it has been shown that presenilin 1 (PS1) mutation, which is responsible for nearly 50% of all familial Alzheimer’s disease cases, also resides in the ER-Golgi complex where it is associated with an increased production of the senile plaque constituent Aβ_{1-42} [7,40,47]. Assuming such an association between PS1 mutation and Aβ production exists in FAD subjects, the interesting possibility arises that PS1 mutation modulates Aβ production by epigenetic factors, that is, environmental conditions that remain relatively independent of gene expression. One factor that may induce accelerated clinical expression of FAD is the presence of chronic cerebral hypoperfusion. In this scheme, excessive and rapid amyloidogenic Aβ production from presenilin mutation would induce FAD via an ischemic, energy-deficient process affecting PS1 (possibly through a Notch defective gene highly homologous to the presenilin FAD gene [68]) and implicated in stroke and vas-
cular dementia [54]) eventually resulting in intracellular pathology and neurodegeneration.

Because proteolytic and cell-regulatory activities require and consume energy as part of a system charged with keeping brain cells healthy, any deviation from this process will result in inefficient brain cell function.

An example of how an epigenetic factor may induce FAD symptoms should be mentioned. Presenilin mutation and regional cerebral ischemia was investigated in a group of subjects from a large FAD kindred found in Antioquio, Colombia, who display a point mutation in codon 280 that results in glutamic acid-to-alanine substitution. Subjects tested included symptomatic FAD patients who were shown to express PS1 mutation and a group of asymptomatic subjects who similarly carried the PS1 mutated gene [53]. A third kindred group from this large pedigree were asymptomatic, non-Alzheimer’s, non-PS1 carriers [53]. This study revealed a consistent regional cerebral hypoperfusion in the temporo-parietal region of the affected PS1 carriers regardless of whether they were symptomatic or asymptomatic for Alzheimer’s disease. Cerebral hypoperfusion was not evident in the kindred non-PS1 carriers who were asymptomatic for Alzheimer’s disease [53].

This study demonstrated that regional cerebral perfusion abnormalities are detectable before the onset of clinical symptoms in PS1 mutation carriers and may in fact precede the pathologic changes associated with early onset familial Alzheimer’s disease. This finding may be interpreted as supportive of a role by cerebral perfusion impairment in triggering FAD symptoms in PS1 carriers. The exact mechanism how this may occur remains elusive but may involve abnormal Ca\textsuperscript{2+} influx intracellularly [87,88] spurred by an energy-deficient process in the ER that stimulates the effect of mutated PS1 on A\textbeta production.

Moreover, animal studies have shown that the presenilin1 and 2 genes can be expressed in the hippocampus and cortex after global [119] or focal [94] cerebral ischemia. These findings become all the more intriguing in light of the presumed role of presenilins in protecting brain cells [20, 117] and acting as chaperones for extracellular-bound proteins [65].

The little studied effect of cerebral hypoperfusion and energy compromise on presenilin mutation raises several intriguing questions. Could reduced energy substrate availability during chronic cerebral hypoperfusion modulate presenilin mutation in the ER : Golgi complex that results in abnormal extracellular protein activity? Does mutated presenilin induction of FAD worsen faster by an intracellular hypoperfused state that weakens brain cell protection and accelerates the onset of Alzheimer’s symptoms?

Likewise, because amyloid precursor protein has also been shown to be neuroprotective during ischemic brain injury [108], mutations of this protein that are known to initiate a rarer form of familial Alzheimer’s disease, could similarly result from energy-induced abnormal enzymatic breakdown of this long-chained polypeptide leading to the production of A\textbeta.

Other questions must also be addressed. For example what degree or threshold of cerebral blood flow is required to reach an energy-deficient system that can adversely affect the quality and the biomechanics of intracellular reactions? Conversely, what abnormal end products of such a deviant energy process might result that would be harmful to brain cells? Answers to these questions could provide valuable clues in deciphering the neurodegenerative process involved not only in the sporadic but also familial forms of this dementia.

11. Hemorheological disturbances

In this special issue, Rifkind [97] and Solerte [109] discuss the hemorheologic disturbances found in 1) normal aging and, 2) Alzheimer’s disease. It is noteworthy to observe that a series of hemorheological problems associated with aging also seem to be present but grossly exaggerated in Alzheimer’s disease [3,42,97]. For example, factors that affect blood viscosity, fibrinogen concentration, homocysteine levels, red cell deformability, shear stress, and vascular resistance appear as key elements in the development of cerebral hypoperfusion. Such blood flow disturbances may reach a sufficient magnitude to initiate and sustain metabolic, structural, and cognitive decline within Alzheimer brains [3,31,42,73,97,109].

An example of tissue changes influenced by hemorheologic disturbance is the suppression of endothelial nitric oxide synthase (eNOS) mRNA transcription by hypoxia and its induction by shear stress, which is the tractive force on endothelial cells induced by vascular flow [69,70]. Nitric oxide is produced by NOS and functions partly to regulate blood flow in various organs through activation of guanylyl cyclase in smooth muscle cells. Important evidence suggests that NOS gene expression may be an important mechanism in the degenerative process characteristic in Alzheimer brain tissue (see de la Monte, this issue). Endothelin-1, a powerful vasoconstrictor released from vessel walls and implicated in the pathogenesis of cerebral vasospasm [19] and myocardial infarction [125], has also been reported to be released by experimental shear stress [49] and may be related to hemorheologic problems associated with aging [4].

We have proposed that when advanced aging and the presence of a vascular risk factor for Alzheimer’s disease converge, a critically attained threshold of cerebral hypoperfusion (CATCH) results that modifies the structural integrity of capillaries and results in abnormal hemorheologic and hemodynamic flow patterns in the brain. This condition may require many years before the onset of clinical symptoms [25,36,39,109] and is less likely to appear abruptly even under the proper adverse conditions (Fig. 2).

Our proposal is supported by experimental data showing
capillary degeneration in CA1 of rats subjected to brain hypoperfusion for 12 months [21] and by similar capillary degenerative changes in Alzheimer brains [12,34,71,74,95,100]. Because both advanced aging [72] or a vascular risk factor (Table 1) can each reduce cerebral blood flow to levels that will cause regional structural and hemodynamic disturbances of brain capillaries. Initially affected regions of capillary degeneration include CA1 and entorhinal cortex, where neuronal loss and pathologic markers are most prominent. Mitochondrial dysfunction caused by chronic cerebral hypoperfusion results in neuronal metabolic energy compromise (as reflected by reduced cytochrome oxidase, ATP levels and glucose oxidation) leading to altered protein synthesis, abnormal amyloid precursor protein (APP) processing and post-translational changes affecting tau phosphorylation intracellularly. Energy-dependent APP and tau abnormalities create extracellular Ab deposits and intracellular neurofibrillary tangles. Increased calcium (Ca) influx into brain cells results from ionic pump energy deficits at the cell membrane, a phenomenon also affecting the Na⁺, K⁺-ATPase pump that requires about 60% of all ATP available to the brain tissue. Cytotoxic free radical formation follows mitochondrial oxidative stress leading to inhibition of glial uptake of glutamate. Increased free radical formation and excessive glutamate accumulation accelerates and contributes to neuronal death pathways (apoptosis and necrosis) generating in its wake more widespread neurodegeneration. Severity of cognitive decline seems directly proportional to reduced glucose metabolism and progressive cerebral hypoperfusion (for more on this subject, see reviews [31,36,39]).
12. Summary of basic and clinical findings

We have attempted to be brief in this report because much of the evidence leading to the CATCH hypothesis has been reported by us elsewhere [22–39]. The collective evidence presented here can be crystallized for the purpose of a synopsis as follows.

Energy is required for virtually all intracellular chemical reactions. Brain energy is obtained solely from plasma glucose that together with oxygen, serves as the substrate for the production of cell fuel, generally in the form of ATP. Acute cerebral ischemia is known to reduce glucose-oxygen availability to neurons and glia where impaired metabolic function can result and lead to brain cell damage or death. We have demonstrated that experimental chronic brain hypoperfusion in the presence of aging can affect metabolic, anatomic and cognitive systems that resemble the effects of acute ischemia but requires considerably more time.

Because increased aging involves an inverse reduction of cerebral blood flow [10,17,35,72,97] and it is generally conceded that vascular risk factors for Alzheimer’s disease are also capable of reducing cerebral perfusion, we have proposed that these two conditions can converge to create regional microcirculatory impairment of blood flow that reaches a critical threshold to directly compromise neuronal-glial function.

Thus, CATCH assembles the many pieces of the puzzle associated with the spectrum of neuronal metabolic abnormalities that eventually trigger the cognitive decline and progressive neurodegeneration observed in this disorder.

Finally, CATCH explains the heterogeneic profile that is characteristic of Alzheimer’s disease because it identifies a wide assortment of pre-clinical conditions (vascular risk factors) with varying etiologies but one common pathologic outcome, that is, cerebral hypoperfusion, which can potentially develop into this dementia.

The field of vascular factors and their effect on the development and evolution of Alzheimer’s disease has emerged in the past several years as one of the most exciting new lines of investigation in the long search for a solution to this devastating disorder. Interest in this field is evidenced by the quality and depth of recent publications, including those contained in this special issue, that have focused on this topic [24,55].

References


