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Review

Deciphering Alzheimer's Disease Pathogenic Pathway: Role of Chronic Brain Hypoperfusion on p-Tau and mTOR

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Abstract. This review examines new biomolecular findings that lend support to the hemodynamic role played by chronic brain hypoperfusion (CBH) in driving a pathway to Alzheimer's disease (AD). CBH is a common clinical feature of AD and the current topic of intense investigation in AD models. CBH is also the basis for the vascular hypothesis of AD which we originally proposed in 1993. New biomolecular findings reveal the interplay of CBH in increasing tau phosphorylation (p-Tau) in the hippocampus and cortex of AD mice, damaging fast axonal transport, increasing signaling of mammalian target of rapamycin (mTOR), impairing learning-memory function, and promoting the formation of neurofibrillary tangles, a neuropathologic hallmark of AD. These pathologic elements have been singularly linked with neurodegeneration and AD but their abnormal, collective participation during brain aging have not been fully examined. The format for this review will provide a consolidated analysis of each pathologic phase contributing to cognitive decline and AD onset, summarized in nine chronological steps. These steps galvanize each factor's active participation and contribution in constructing a biomolecular pathway to AD onset generated by CBH.

Keywords: Axonal transport, brain hypoperfusion, cognition, mammalian target of rapamycin, neurofibrillary tangles, tau, vascular hypothesis of Alzheimer's

OVERVIEW

There is currently considerable evidence indicating brain hemodynamic dysfunction is a critical process in the pathogenesis of cognitive decline and Alzheimer's disease (AD) [1–6].

Hemodynamic abnormalities serve not only as an early, preclinical marker of AD, but also provide a pathophysiological target for disease modifying interventions that aim to lower the incidence of cognitive decline during aging [1, 2, 7–9].

The hemodynamic role played by chronic brain hypoperfusion (CBH) in driving a distinct pathway to AD is the central subject of this review. CBH is a clinical feature of AD and the current subject of intense investigation in AD animal models and aging humans [1, 10–15.]. CBH is also the basis for the vascular hypothesis of AD which we originally proposed in 1993 [16].

CBH is defined as long-term cerebral perfusion that is not commensurate with the neurometabolic demands of brain tissue. CBH is not brain ischemia, which is defined as stenosis or blockage of an intracranial artery which can lead to rapid loss of sensory-motor function and focal neuronal death.

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New findings have come to light that add *de facto* evidence to previous findings in the interplay of CBH in disrupting axonal transport, inducing tau hyperphosphorylation (p-Tau) in the hippocampus of AD mice models, increasing signaling of mammalian target of rapamycin (mTOR), and initiating the formation of neurofibrillary tangles (NFTs), a neuropathologic hallmark of AD [8, 17–20]. These events are consistently associated with neurodegeneration and cognitive failure but their pathogenic occurrences during brain aging have not been fully clarified or factored in [21–24].

Besides aging, major environmental risks to AD form a spectrum of co-conspirators called vascular risk factors, including cardiovascular disease, severe arterial pressure changes, diabetes 2, atherosclerosis, hyperlipidemia, obesity, and many others [25–28].

Virtually all AD vascular risk factors acquired environmentally during aging appear to have a common consequence: that is to lower cerebral blood flow (CBF) [29–31]. This action can accelerate the development of AD when several of these risk factors converge on age-dependent CBF decline [1, 32–34]. Such convergence adds a significant burden on normal CBF decline by promoting additional CBH from vascular risk factors [35–37]. Specifically, clinical studies have revealed that acquired CBH results in synaptic dysfunction and neuronal degeneration/loss, leading to gray and white matter atrophy, cognitive dysfunction, and AD [2, 4, 8, 10].

CBH differs from age-dependent CBF decline because the latter involves a physiologically normal and gradual fall in cerebral perfusion resulting from the wear and tear of aging. CBH on the other hand, results from acquiring vasoactive disorders during aging that can influence hemodynamic changes in the caliber and tone of the cerebral microcirculation [27].

CBH is currently considered at the cutting-edge of neurological research [2, 8, 10, 38–40] although in our judgment, its clinical potential for inducing devastating body harm has not been fully appreciated as an important focus of treatment opportunity.

The main objective of this review is to examine recent findings involving how increased neuronal p-Tau hyperphosphorylation (a precursor of NFTs) is driven by CBH in the rat hippocampus and cortex [18, 19] and how mTOR, a molecule associated with memory and learning, generates CBH activity [20].

These new findings fill an important gap in knowledge relevant to our 1993 proposal that AD pathogenesis is generated by cerebral microhemodynamic dysfunction and should be considered

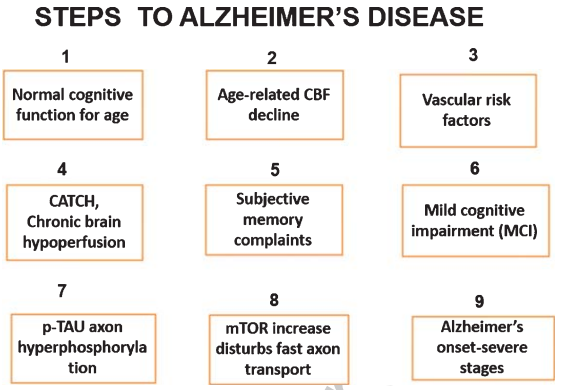

Fig. 1. Flowchart depicting nine sequential steps (phases) following a data-driven construct composing a pathological pathway to Alzheimer's disease onset. See text for descriptive details. CBF, cerebral blood flow; CATCH, critically-attained threshold of cerebral hypoperfusion; mTOR, mammalian target of rapamycin.

a vascular disease with neurodegenerative consequences [16]. Adding light to this knowledge gap should unravel the biomolecular sequence that can lead directly to AD onset, and in so doing, crack open the door slightly to treatment prospects aimed at AD prevention.

Figure 1 provides a flowchart of nine major steps documenting a conceptual pathway leading to the development of AD. These steps are not meant to systematically construct the biomolecular framework inherent of AD but rather throw a sliver of light below the neuropathological 'rabbit hole' where some clues may wallow in obscuring how progressive cognitive decline develops in its trajectory toward AD.

NFTs AND AMYLOID-β PLAQUES

It is now well-accepted CBH is a hemodynamic abnormality chiefly generated by vascular risk factors acquired mainly during aging [29, 41, 42].

CBH has been shown to precede and promote neurodegenerative changes several decades before clinical AD symptoms appear [6, 7, 18, 26, 43]. There is compelling evidence that CBH is present prior to the deposition and aggregation of amyloid-β (Aβ)-containing plaques and hyperphosphorylation-forming tau tangles [2, 44].

It is worthy of note that NFTs appear earlier than amyloid plaques during brain aging and they accumulate in cognitive brain regions prior to AD onset where no Aβ deposition occurs [45]. By contrast, Aβ plaques are never found without NFTs and are commonly seen in cognitively intact persons, but NFTs

are always found in AD brains despite the absence of Aβ plaques [45–47]. The reason may lie in the fact that NFTs, unlike Aβ plaque formation, have been shown in multiple clinicopathological studies to correlate with the neurodegenerative progression of AD characterized by neural, synaptic, neurometabolic, and cognitive deterioration [48–50].

These findings essentially reveal that the formation of Aβ peptide accumulation in the brain is a late event, unlikely to be the primary cause of AD [2, 47, 51], or that its accumulation triggers or precedes NFTs, as previously argued in the amyloid cascade hypothesis [45, 47, 52, 53].

From a purely clinical viewpoint, it is a palpable truism that the amyloid cascade hypothesis is an example of magical thinking whose narrow-minded focus has become its own executioner, a victim of ugly facts. It is therefore bewildering why this hypothesis continues to occupy the front seat of AD research when decades of solid evidence has repeatedly shown its festering clinical failures.

DECONSTRUCTING AND DECIPHERING AD

A method for deciphering the suspected pathogenic pathway to AD should rely on data-driven evidence and on prior objective research observations to help document proof of concept. The dynamic analysis of data-points draws partly from Bayesian inference in combining prior knowledge with current data and applies it to what is evidentially suspected about AD pathology.

This system of inquiry is far from flawless and will not explain most issues, but it may bring a slice of congruity to unresolved pathomechanisms shrouding the AD enigma.

An empirical strategy in research uses empirical evidence obtained from direct observations and possibly from elective mechanistic reasoning [54]. The purpose of the latter stratagem, as used here, is to increase reliability of the evidence. It is not an infallible approach. It does offer some usefulness for gathered evidence which can be improved if the systematic piecing together of complementary observations fit together much like the pieces of a giant jigsaw puzzle that can provide a meaningful picture. The theoretical pathway leading to AD onset is summarized in Fig. 1. The pathology pertinent to this pathway is discussed in the text, step by step. Deciphering an AD pathway in this manner may also provide offshoot clues, for example, to determine if mild cognitive impairment (MCI) stabilization or delayed progression to AD is predictable.

There is a conviction by many researchers that common sense is a key ingredient that can broaden intuition when evaluating empirical evidence. An example is an old aphorism, "when you hear hoofbeats in the American plains, don't look for zebras."

Common sense applied to empirical evidence is reasonable when key data points can interpret each step that takes part in a pathological cascade, for example, progression to AD.

Deconstructing (disassembling the parts) and deciphering (interpreting the parts), relating to the theoretical steps involved in a multifactorial disease, especially one as complex as AD, is no easy task.

Deconstructing relies on observing repeated clues gathered from experimentation and from generous use of deductive reasoning. Most often, these clues are insufficient in disentangling verifiable observations. To minimize meta-analytic blind alleys, objective clues need to be gathered from laboratory experimentation and assessed clinically in patients *a priori* to clinical symptoms, during symptoms, and at the termination of symptoms when a cure, remission, or death occur.

Deciphering observable findings relies on experience of the subject, such as fair knowledge of the disease being analyzed, and an ability to exclude narrow, immaterial, or mismatched clues. In the case of AD, the observer must be fully aware of the chance that confounding data may favor more than one biologically meaningful explanation of AD development. This advice has not always been followed in AD research.

The fuzzy logic or probabilistic approach to deciphering AD as presented here could provide a framework for data-points relevant to the pathogenic pathway bound for AD (Fig. 1, Step 1). If this strategy is on the right track, it should favor better measures for AD prevention, as practical interventions are discovered.

It is useful to recall Claude Bernard's experimental advice in attempting to decipher the physiomechanics of a disease when he writes, "*In the experimental method, it is a matter of absolute principle to take, as our starting point for disease experimentation or reasoning, an exact fact or a good observation*" [55].

Bernard's precept in following a fact or good observation is helpful here as a brainstorming tool in teasing out the sequence of events involved in AD development. Using a crude example, if the power

of observation serves a pragmatic function, look no further than Sherlock Holmes, who when asked by baffled detectives how he found a 'hidden' bullet hole in the corpse of a victim, he responded, "I looked".

CBH PATHWAY TO AD

What is the true pathway to AD? There is no 'true' pathway to AD; however, the nine steps in Fig. 1 provide a reasonable, data-driven exposition of the chronologic process found in a healthy, mid-age individual at-risk of AD onset. The word 'pathway' to AD is loosely used here to allow other explanations, interpretations, and counter-arguments to filter into this narrative.

A cognitively healthy, normotensive, middle age individual in the United States age 50–60, has a 4-5% chance of getting sporadic AD in his/her lifetime (Fig. 1, Step 1) [56].

The odds of acquiring sporadic AD can vary appreciably depending on a host of biocellular and biomolecular changes that can develop during aging. These include the individual's health status, gene risks, family history, presence of vascular risk factors, history of neurologic disorders, quality of life, and other variables. The odds of acquiring AD increase with advancing age [56].

It is difficult to pin-point the start of age-dependent cognitive slowdown in one's lifetime. Although there is no consensus on the matter, it has been argued by some that it may begin when brain development slows, around age 25. Cognitive processing speed (CPS) may be a good indicator as to when cognitive slowdown generally begins since it reflects age-dependent CBF decline as a normal part of the wear and tear process associated with aging. CPS is related to the speed in which a person responds and reacts to a given mental challenge [57–60]. It is not related to intelligence (Fig. 1, Step 1) [61].

During aging, CPS is known to gradually slow down and the degree from baseline to which it becomes significantly less active is thought to foreshadow incipient MCI and AD [58, 61]. Interestingly, CPS slowdown is also associated with diminished CBF in elderly persons [62–64].

The association between reduced CBF and CPS during aging may explain a crucial neurobiological point of contention where normal or subnormal brain perfusion will determine the pivoting direction of cognitive function to either stabilize or deteriorate during the MCI stage. In this respect, it is interesting to note that CPS declines by more than 50% between the ages of 25 and 65 [65], a drop which parallels the 20% normal fall in CBF during the same age period (Fig. 1, Step 1) [63–65].

CBF in a healthy, normotensive adult, is estimated to range 50–54 ml/100 g brain tissue/minute [66]. This amount of blood flow represents15% of cardiac output (Fig. 1, Step 2).

Normal CBF decline during aging is estimated to fall 16–20% from age 20 to 60 [8, 67–69], but in the face of vascular risk factors, normal CBF decline may further fall to an abnormal threshold where brain cell homeostasis is disrupted (Fig. 1, Step 2) [65, 70–73].

We have described this pivotal CBF decline as critically-attained threshold of cerebral hypoperfusion (CATCH) [70]. CATCH refers to a level of CBF hypoperfusion that reaches a threshold where cerebral hemodynamic deterioration rises to provoke an imbalance involving CBF supply, neuronal energy demand, and cognitive function [70].

The CBF decline from wear and tear during aging is known as 'age-dependent CBF decline' which appears insufficient to bring about moderate or severe cognitive changes in most healthy, elderly individuals, unless it is accompanied by a significant CBF burden, for example, from heart failure, hypertension, atherosclerosis, diabetes 2, smoking, hypercholesterolemia, and others (Fig. 1, Step 2) [71–74].

Age-dependent CBF decline affecting cerebrovascular reactivity in elderly adults, compared to young adults, has been found in different brain regions, including the superior frontal gyrus, precentral and postcentral gyri, superior temporal gyrus, cingulate gyri, and supramarginal gyrus and in various subcortical regions [72, 73]. These findings confirm how reduced vasoactive response of elderly people react to cerebrovascular insufficiency in cognitive domains linked to cognitive dysfunction (Fig. 1, Step 2).

VASCULAR RISK FACTORS DURING AGING

The speed at which AD symptoms can develop during aging depends on a number of factors, most notably, the insidious vascular risk factors to AD (Fig. 1, Step 3).

Vascular risk factors to AD share a common and crucial consequence, virtually all described thus far, further reduce CBF to some degree [37], an

unlikely coincidence in view of the age-dependent CBF decline observed during aging [43, 67–70]. Vascular risk factors to AD and age-dependent CBF decline are thus a likely dynamic duo in creating CBH at a time of great vulnerability to aging neuronal networks.

Major vascular risk factors provoke CBH in the elderly by disrupting microhemodynamic homeostasis and arteriolar tone [1, 24]. Advancing age targets most body systems including structural and functional defects of the heart and its vessels which can significantly reduce cardiac output and induce or worsen CBH, thus promoting speedier cognitive decline [37, 75]. For example, heart failure, a most debilitating vascular risk factor commonly seen during aging, interferes with the aging heart's blood pumping ability while affecting vulnerable brain cells located in cognitive regulatory domains that can initiate or aggravate cognitive function [76]. This is achieved because persistent lowered cardiac output can help generate CBH and hemodynamic instability by promoting vasoactive changes in microvessel tone (Fig. 1, Step 3) [70].

All in all, vascular risk factors must be considered insidious contributors to the pathogenic link between age-dependent CBF decline and cognitive deterioration (Fig. 1, Step 3).

Cognitive function in the adult human brain is totally coupled to neuroenergetic metabolism derived from glucose oxidation within the mitochondria floating in the neuroplasm. The cerebral energy production begins with aerobic respiration, electron transfers, oxidative phosphorylation, and the synthesis of ATP to support all neural activity (Fig. 1, Step 4) [11, 77].

The adaptive machinery for brain energy production is kept constant with adequate CBF delivered by resting cardiac output, which closely responds to cerebral metabolic needs [37]. The structural and functional deficits that can damage the human heart during a lifetime are numerous and significantly increased during aging. Such cardiac deficits play havoc with CBF supply-and-demand due to lowered cardiac output, increased cerebrovascular resistance, and diminished cerebral autoregulation [11, 78]. These heart-to-brain consequences result partly from an abnormal chain of arterial events that progress to disrupt higher-order cognitive function (Fig. 1, Step 3).

The CBH concept as it relates to AD, fundamentally argues that brain cells receiving persistent suboptimal blood flow during advanced aging, will eventually lead to signs of cognitive dysfunction first manifested by subtle, then by more aggressive neurocognitive downfall [24].

Suboptimal blood flow to the brain, described above as CATCH, defines the critical point where neurons can no longer effectively cope with the degree of CBF decline required to maintain neuronal function (Fig. 1, Step 4) [70].

The direct relationship between CBH and increased cognitive decline may depend on several commanding factors: progressive aging, noxious vascular risk factors, autophagy, and vascular-related susceptibility genes, any of which can expedite neuronal loss. The importance of CBH in the AD pathway is critical in that it sets the stage for earlier and more severe brain hemodynamic instability.

The brain's metabolic requirements completely rely on receiving adequate glucose and oxygen delivery to carry out its functions. Cognitive dysfunction runs parallel to a rate proportional to neuronal loss or threshold of neural deficiency. The balancing act between cognitive function and dysfunction in terms of glucose and oxygen delivery to brain is controlled by aging arterioles which regulate the amount of blood flow supplied to brain cells by widening or narrowing their diameters (Fig. 1, Step 4) [24]. There are three main regulators of vessel tone: partial pressure of arterial oxygen (PaO_2), partial pressure of arterial carbon dioxide ($PaCO_2$), and the cerebral metabolic rate of oxygen ($CMRO_2$). Cerebral autoregulation kicks-in to protect against blood pressure changes that might affect neurovascular and neurometabolic uncoupling [79, 80].

Clinical studies show that CBF averages 20% below normal at the onset of AD as compared to cognitively intact age-matched controls [68, 81]. This CBF difference may reflect the 16–20% decline from age 20 to 60 that occurs due to age-dependent wear-and-tear (Fig. 1, Step 4) [43, 68].

SUBJECTIVE MEMORY COMPLAINTS (SMC)

SMC is commonly seen in older persons and may or may not precede objective memory deficits or MCI [82]. SMC consists of self-described or informant-reports of consistent memory lapses in an elderly individual. For the most part, no one really knows for sure when cognitive slowdown begins during aging since prodromal AD signs are difficult to identify with precision (Fig. 1, Step 5).

SMC can be a function of personality traits, anxiety or depression, induced or promoted by vascular risk factors [83]. As a possible initial step in the AD pathway, SMC has been used as a reliable indicator of cognitive decline preceding AD [84]. However, SMC may stabilize and allow the elderly individual to remain relatively clear-minded until death. This is supported by reports that about 62% of individuals who develop cognitive decline do not experience SMC [85]. When SMC does not stabilize, the individual may enter a stage where MCI is clinically observed (Fig. 1, Step 5).

MILD COGNITIVE IMPAIRMENT

MCI involves cognitive difficulties unexpected for one's age although daily living activities can continue with a minimum of mental slowdown. MCI may stabilize symptomatically for years or worsen within a short time on its way to AD onset (Fig. 1, Step 6).

No one knows exactly why MCI stabilizes in some elders and not in others. It is likely assorted factors play a protective or a toxic role. However, at the present time, many researchers realize the importance, if not the pathogenic role played by CBH in progressive cognitive decline [2, 8, 10, 86, 87], and the practicality that AD may be predicted in MCI patients who show CBH [9, 19, 72].

Reduced local CBF detected by SPECT (single-photon emission computed tomography) neuroimaging in the inferior parietal lobule, angular gyrus, and precunei, reveal a significant predictive value for MCI conversion to AD as compared to MCI non-converters with normal CBF in those regions [72].

MCI is unstable and may or not be followed by AD. When it is, accelerated decline of episodic and working memory, said to be predictors of AD, can be detected (Fig. 1, Step 6) [88–90].

To stay healthy, the brain requires 20% of all oxygen and 25% of all glucose produced in the body. This means 4–8 liters of blood need to be pumped out of the heart every minute [37, 42]. In this context, when oxygen and glucose are not supplied to the brain in needed amounts, brain cell function can become chronically vulnerable, dysfunctional or quickly die. Too much serum glucose appears as damaging to brain as too little. For instance, hyperglycemia does not prevent AD but rather increases the risk of AD due to global decrease in rCBF in rats and humans, although the specific mechanism for this consequence remains unexplained [91].

The outlook for neuronal death or dysfunction related to CBF is dependent on a host of factors beyond the scope of this review but generally, global cerebral perfusion is either marginally present to sustain limited neural function as in brain hypoperfusion, or absent, as in cardiac arrest.

It is well accepted that constant ATP (adenosine triphosphate) production from circulating glucose and oxygen is fundamental for nerve cell survival and function [90]. When neurons increase their metabolism in response to cognitive demanding tasks, more glucose is recruited by increasing CBF. Brain energy demand is not uniform and some neuronal networks, especially those that regulate high-order cognitive domains, need substantially more ATP energy than other brain populations to ensure normal cognition (Fig. 1, Step 6) [10].

High-order cognitive functions that initially decline prior to AD onset include regulatory networks such as the dorsolateral prefrontal cortex, the superior and medial frontal gyrus, the lateral parietal cortex, the precuneus, the hippocampus, and the posterior cingulate cortex, among others [3, 78, 92, 93]. These regions reflect dwindling CBF and lower glucose metabolism, a forerunner of episodic and semantic memory decline, two early signs preceding the onset of AD pathology [93]. Data using ^{18}F-FDG-PET shows consistent and significant hypometabolism of glucose in hippocampal, posterior cingulate cortex, and precuneus regions in MCI as compared to healthy controls (Fig. 1, Step 6) [15, 94].

Normal brain cells in these three cognitive regions are generally associated with higher CBF and glucose uptake and a greater production of mitochondrial ATP synthesis because they are among the most energy demanding neurons in the brain and require more fuel than neurons in non-cognitive regions, such as in the auditory, visual, or somatosensory cortex (Fig. 1, Step 6) [3, 95].

If and when such energy demand is unmet, disturbed episodic or working memory may be detected early in older, non-impaired individuals, suggesting MCI may be developing [38, 96]. This is an important preclinical state of incipient AD (Fig. 1, Step 6) [69, 97].

TAU HYPERPHOSPHORYLATION AND NEUROFIBRILLARY TANGLES

Tau is a neuronal microtubule-associated phosphoprotein (MAP) responsible for promoting and

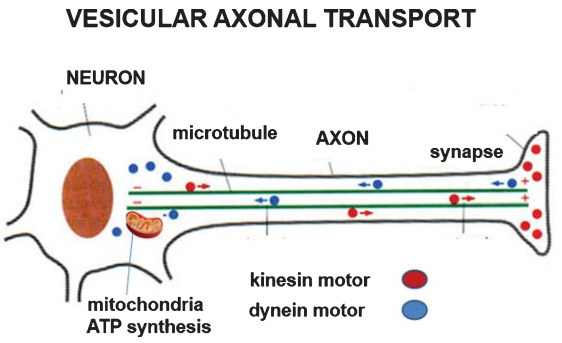

Fig. 2. Characteristic axonal transport of vesicular cargo by motor proteins kinesin (dark red circles) moving toward the synapse and dynein (light blue circles) moving toward the cytoplasm. This cargo moves bidirectionally along axons with power provided by mitochondrial ATP.

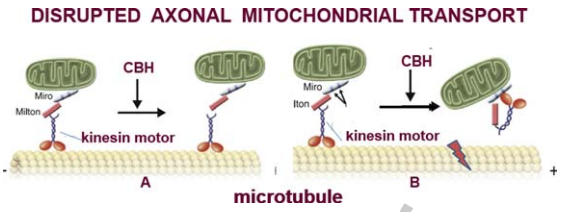

Fig. 3. Axonal mitochondrial transport disrupted by chronic brain hypoperfusion (CBH) which modifies Miro and milton motifs to inhibit mitochondrial motor activity along microtubule. This action is assumed to initiate production of tau pathology (p-Tau) and eventual neurofibrillary tangles formation in axon terminals and neuronal soma. The milton-miro complex are essential mitochondrial proteins responsible for mitochondrial movement that assumedly help trafficked mitochondria bring ATP energy supply where it is needed along the neuronal microtubule track. See text for details. Adapted from Hirokawa et al. [101].

stabilizing microtubule self-assembly in the brain (Fig. 1, Step 7) [98]. p-Tau is first observed in the transentorhinal region where it later forms NFTs [99]. It then spreads to the parahippocampal gyrus, limbic system, and to neocortical and subcortical sites after AD onset [47, 99].

The main function of tau is regulation of the microtubules which act much like railroad tracks to shuttle vital cargo to and from the cell cytoplasm to the axon terminal (Fig. 2) [100]. This cargo includes organelles such as proteins, lipids, synaptic vesicle precursors, neurotransmitters, neurotrophic factors, and mitochondria [101].

Transport of these membrane-bound organelles is achieved along the microtubules by motor proteins, dynein, and kinesin [102]. These motor proteins move cargo in both directions, dynein toward the cell body, and kinesin to the end of the axon, at the presynapse [23].

Energy to move cargo along the microtubules relies on mitochondrial coupling to anterograde kinesin motor and to the retrograde motor dynein (Fig. 2). The transport mechanism of motor proteins is made possible from energy provided by ATP.

Cyclic hydrolysis of ATP derived mainly from mitochondrial oxidation allows the motor protein kinesin to repeatedly bind and unbind to a single protofilament track in microtubules, producing a 'step-like' motion to carry vesicles to their target. This motion allows vesicular cargo to literally "walk" along microtubules at slow or fast speeds (Fig. 3) [23].

When neurons that regulate cognitive domains undergo microtubule disruption, neuronal communication is interrupted, and cognitive deficits generally result [103–105].

The hyperphosphorylation of tau can lead to its abnormal folding and disable its ability to stabilize microtubule assembly. This process can result in tau's fragmentation into toxic, paired-helical filaments that aggregate as NFTs provoking neuronal and synaptic loss (Fig. 3). Substantial evidence indicates that NFTs are highly toxic, hyperphosphorylated tau protein filaments deposited initially in the axon nerve ending with tangle pathology crawling backwards into the neuronal cytoplasm [21]. The reason for this retrograde 'dying back' pattern is unclear but it might represent a loss of synaptic and axonal connectivity that correlate with progressive neurodegeneration and AD symptoms. The formation of NFTs following tau hyperphosphorylation are known as death markers for AD onset since they are seen in selective MCI regions prior to AD (Fig. 1, Step 7) [21, 22].

NFTs can localize intra- and extracellularly and are linked to both the degree of dementia and the duration of this illness [47, 48, 105].

In addition, the concentration of NFTs in AD brain is known to match precisely to the areas exhibiting neuronal loss and cognitive decline [105]. This correlation makes p- Tau a key molecule and neuronal death marker of incipient AD (Fig. 1, Step 7) [21, 22, 104].

It has been amply demonstrated that tau pathology and the subsequent formation of NFTs are crucial steps in the neurodegenerative process leading to AD. What is less clear is, what produces tau hyperphosphorylation?

We subscribe to the convincing evidence that most of the ATP generated in brain neurons originate from oxidative phosphorylation in mitochondria located in the soma. Nonetheless, mitochondria pool any-

where in the neuronal network where ATP energy is highly needed, e.g., at synapses. Nodes of Ranvier and axonal tracks (Fig. 2) [106].

MICROTUBULE TRANSPORT

Microtubule-based axonal transport is fundamental to neuronal survival and function. Disruption of microtubule transport can result in vesicle-trafficking not reaching their synaptic or cytosolic targets. This outcome can cause diverse pathology, including impairment of intrinsic survival signals that determine potential loss of regional brain function resulting in damage or death of neurons [107].

There are countless mechanisms that can disturb axonal transport, including destabilization of motor–cargo binding of ATP, an outcome leading to local energetic meltdown (Fig. 3) [108]. Local neural energy requirements can be met by kinesin axonal transport of mitochondria to the distal synapse [108]), unless this action is prevented by subnormal glucose delivery that slows mitochondrial oxidation to a point where microtubule motor dynamics is destabilized (Fig. 3). This observation is an imperative key to understanding AD development.

MITOCHONDRIAL DYSFUNCTION

One of the most decisive molecular properties of aging is mitochondrial dysfunction [109]. In our view, the most consistent cause of mitochondrial dysfunction in aging is CBH because it occurs in every living mammal and is directly linked to a decline in the electron transport chain and selective reduction in ATP production. Reduced ATP production in brain is a product of mitochondrial impairment and is strongly linked with tau pathology in AD [110] (Fig. 3).

This finding supports the importance of ATP energy source in providing microtubule motor proteins their axonal fuel to transport vital vesicular cargo (Fig. 3). Adding to the many physiological insults facing brain mitochondrial function, are, for example, diminished biogenesis, DNA mutations, toxic byproducts, mitophagy degradation, telomere attrition, and oxidative stress. Another mitochondrial vulnerability to its mass is attenuation by CBH, an outcome reported to significantly reduce ATP levels in neurons [24, 107, 110].

Taken together, these findings indicate that mitochondrial aerobic glycolysis is critical for fast axonal transport (FAT). FAT is a rapid, bidirectional

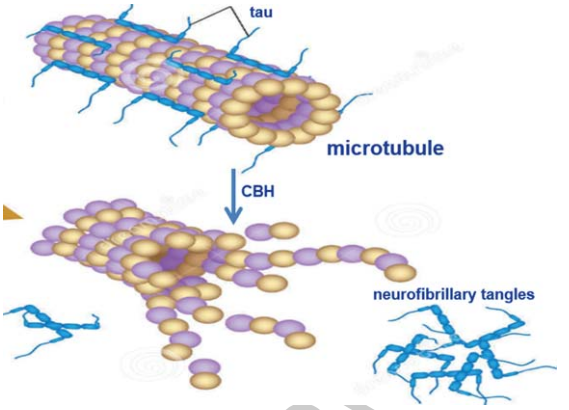

Fig. 4. Disintegration and disassembly of neuronal microtubule by p-Tau, posited to be induced by reduced glucose supply resulting from chronic brain hypoperfusion (CBH). This fragmentation of microtubules leads to the twisting and production of paired helical filaments and the development of neurofibrillary tangles (NFTs) within axons and cells.

(anterograde-retrograde) movement of membrane-bound organelles in microtubules, crucial to neuron survival [111]. It is well to recall that glucose uptake in brain and neurometabolic activity are impaired in AD [112], and this impairment results mainly from consistent brain hypoperfusion reducing glucose and oxygen delivery to brain and ostensibly interfering with mitochondrial aerobic glycolysis and normal FAT [113].

p-Tau plays a vital role in the pathogenesis of AD by disrupting microtubule assembly (Fig. 4), thus disrupting axonal transport of organelles, including mitochondria (Fig. 3) and corrupting inter-neuronal communication by destroying synapses [114, 115].

The concentration of ATP in microtubules strongly affects the velocity at which kinesin and dynein are capable of moving cargo; kinesin and dynein exhibit lower velocities in environments with lower ATP concentrations [116]. This simple rule implies that mechanisms slowing or impeding transport of cargo along the microtubules will negatively affect neuronal signaling (Fig. 1, Step 7).

Since neuronal ATP is generated mostly by mitochondrial oxidative metabolism, neurons absolutely depend on a constant and optimal supply of glucose and oxygen delivered by the circulation for their metabolic function. In summary, the most relevant take-home message of this review is the following conclusion: If glucose and oxygen delivery to brain is reduced to a CATCH level [74], p-Tau, whose synthesis and aggregation is mediated by mTOR, will result in the breakdown of microtubule stability [18,

117] and induce neuronal death from the production of NFTs (Fig. 1, Steps 7 and 8). This pathological picture appears to be the forerunner of AD (Fig. 1, Step 9).

Insufficient glucose delivery to neuronal mitochondria caused by CBH will consequently slow or block microtubular axonal traffic by limiting mitochondrial transport and ATP supply, thus attenuating neuron signaling and function (Fig. 3). This conclusion is supported by recent studies.

For example, evidence indicates that microtubule tau pathology triggered by reduced energy availability will inhibit fast axonal transport mediated by kinesin so that its cargo is dumped without reaching its target [118]. CBH is known to reduce glucose availability which will have a negative impact on mitochondrial ATP energy production (Fig. 3) [9]. This action will likely destroy microtubule assembly at an undetermined rate and could form the basis for axonal hyperphosphorylation of the tau protein in creating NFTs, thus expediting the cytomolecular pathology manifested in AD (Fig. 4).

There is currently an active debate regarding how tau undergoes hyperphosphorylation to unravel microtubules and become a toxic molecule prior to AD (Fig. 4). A host of explanations have been offered including proteolytic cleavage, structural changes, acetylation, glycation, and many other modifications [119–121].

To this list should be added our proposal, which simply states: CBH is the chief initiator of p-Tau pathology and increased signaling of mTOR.

New findings summarized below appear to reinforce the role of CBH on p-Tau and mTOR.

CBH AND P-TAU

First, with respect to tau, it is reported that after CBH was induced using single carotid artery occlusion in wild type mice for 2.5 months, elevated p-Tau was observed in the hippocampus and cortex of the CBH-treated mice [18]. As a consequence, CBH-treated mice showed significant short-term memory deficits and mild, long-term spatial memory impairment not seen in controls [18]. This study strongly suggested that CBH down-regulated tau O-GlcNAcylation because the latter regulates tau phosphorylation inversely [17, 122].

O-GlcNAcylation is a post-translational intracellular protein modification that plays a major role in NFTs formation and is involved in various cellular processes such as transcription, translation, neurometabolism, and cell signaling dynamics in all cells [123]. This outcome is likely due to disrupted mitochondrial ATP energy production and impaired energy transducing complex I activity that can be initiated by CBH (Fig. 1, Step 8) [17, 18, 124].

The above study using single carotid artery occlusion in mice was confirmed and expanded using a transgenic AD model and wild type mice subjected to a similar, single carotid artery occlusion to create CBH [20]. Three months after CBH, AD mice and wild type mice developed increased p-Tau levels and autophagy in the hippocampus and cortex, a finding not seen in AD mice not given CBH [20]. Moreover, no effects in $A\beta_{42}$ levels were observed in AD mice after CBH [20].

These findings support the view that a primary key element in the development of AD may be due to a deficient glucose delivery to the brain by CBH, which we submit, will induce tau disruption in microtubules of the hippocampus and cortex, as indicated in the AD mice studies.

These results, although highly suggestive, need to be considered in view of the fact that the data derive from AD animal models and consequently deserve caution in their interpretation to represent human AD. Nonetheless, a hypothetical explanation may be offered here that could be highly relevant to human AD and which correlates with our previous proposal that AD is a 'vascular disorder with neurodegenerative consequences' [16, 24].

For example, cultured neurons are reported to not only increase the levels of tau phosphorylation in glucose deficient media but also enhance the levels of known active kinases for tau phosphorylation [125]. Increased p-Tau in the hippocampus following CBH in AD mice [20] has a high clinical relevance due to the fact that p-Tau targets the hippocampus and cortex in humans, two of the earliest regions where NFTs markedly aggregate as part of their pathway to AD (Fig. 1, Step 7) [126].

A growing body of evidence indicates cerebrovascular insufficiency producing oxygen/glucose deprivation (OGD) in animal models are capable of significantly increasing the mTOR pathway in brain [126, 127]. The reasons for this outcome remain unclear although acquired CBH during aging is a possible determinant, assuming CBH via OGB induces the damaging effects of mTOR activation.

An alternate way CBH can induce tau pathology is to block cellular unfolded protein response (UPR) activation in response to tau misfolding, thus allowing

tau to continue its unfolded, toxic accumulation by preventing UPR from restoring normal tau folding. We have previously described a scenario where UPR becomes the cellular target of CBH during a neuronal energy crisis [128].

There is a substantial research interest in the role p-Tau plays in the pathogenesis of AD and its apparent association with mTOR. For instance, it is of clinical significance that expression of p-Tau is considered an earlier, more damaging process to cognitive function than the downstream deposition of Aβ-containing plaques in AD brain [38, 45, 47]. NFTs represent a distinct neuropathological hallmark of AD comprised of NFT-positive cells in elderly brain showing a high correlation with cognitive decline, synaptic loss, and AD severity [105, 129]. By contrast, the accumulation of Aβ pathology in aged brain does not correlate with cognitive impairment or AD [128, 130].

This fundamental difference suggests that tau disruption and tangle formation, not Aβ pathology, directly contribute to the pathogenesis of AD. Of note, protein O-GlcNAcylation has been found reduced in AD brain together with lowered glucose uptake and metabolism, much the same as that observed in glucose deficient animals [122].

CBH AND mTOR

With respect to mTOR, studies have shown this kinase mediates the synthesis and aggregation of p-Tau, resulting in impaired microtubule stability (Fig. 3). These results suggest mTOR generates an imbalance in tau homeostasis, thus provoking neuronal functional compromise (Fig. 1, Step 8).

What is yet unclear is whether mTOR can drive CBH to induce p-Tau and NFTs formation. Recent findings indicate that chronic mTOR inhibition with rapamycin can restore reduced CBF in mice displaying brain hypoperfusion [131], suggesting elevated mTOR activity can worsen CBF if left unchecked during brain vascular dysfunction. This is an important consideration during aging since if inhibition of mTOR can slow aging in mice, its hyperactivation may jeopardize memory and learning in normal aging.

mTOR is found throughout the brain where it functions as a serine/threonine protein kinase that regulates multiple biological activities including aging, cell survival, transcription, protein synthesis, and autophagy [95]. mTOR also regulates synaptic plasticity, one of the most fundamental and important functions of the brain and a crucial mediator of learning and memory [132, 133]. mTOR forms two multiprotein complexes, mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 regulates autophagy, protein synthesis, cell growth, and metabolism, while mTORC2 controls cell survival and does not respond to rapamycin.

A growing body of evidence indicates animal models of cerebral ischemia and oxygen/glucose deprivation are capable of significantly increasing the mTOR pathway in brain [134]. The reasons for this outcome remain unclear although acquired CBH during aging is a viable consideration.

mTORC1 pathway activation strongly inhibits autophagy, a crucial process responsible for the cellular degradation of proteins and organelles by lysosomes as well as proteins that are responsible for the initiation of the autophagic process [135].

Excessive activation of mTORC1 pathway has been linked to mouse models of AD [136, 137] and various human neurological disorders, including AD. Moreover, mTOR can drive cerebrovascular, synaptic, and cognitive dysfunction in normative aging [138, 139].

Together, these findings appear to support the thesis that mTORC1 signaling activation is increased in the presence of reduced CBF and glucose deficiency which promote the detrimental effects and maladaptive functions expressed by this kinase. For this reason, it is proposed: The process of CBH during aging may induce mTORC1 hyperactivation, an abnormal event that may worsen or accelerate the hemodynamic damage created by CBH on cognitive decline [24]. It is conceivable that reduced glucose delivery to brain by CBH, increases p-Tau by protein kinases known to activate p-Tau in microtubules [117], a development that may explain p-Tau's association with the markedly enhanced levels of mTOR found in AD brain [13, 140].

Tau hyperphosphorylation elicited by CBH [18, 20] may interfere with kinesin fast axonal transport and prevent neuronal communication by accelerating synaptic damage and loss which can activate mTOR [136]. Activating mTOR signaling cascade is reported to increase tau pathology by forming a direct link between high mTOR signaling and tau accumulation in microtubules [141, 142].

Our proposal is supported by findings that biochemical analyses of postmortem AD brains reveal a correlation between abnormal upregulation of mTOR and the presence of tau neuropathology [133, 140], possibly modified by CBH.

FAT requires consistent energy in the form of ATP over long distances of the axon to fuel motor proteins that transport vesicles. FAT is mediated by the microtubule motors dynein and kinesin that transport vital organelles inside "cargos" to and from the cytosol [102, 143]. When kinesin is disrupted, axonal transport is arrested in its track and synaptic transmission is disrupted or lost (Fig. 3) [144].

FAT moves axonal vesicles at a rate of 50–400 mm/day; anything impeding this transport can result in a host of neurodegenerative disorders [101]. FAT consumes high concentrations of mitochondrial ATP because dynein and kinesin motors require a high energy source to transport cargos along microtubules for long distances [144].

Understanding the disruption of mTOR signaling that can impair synaptic plasticity involved in learning and memory biomechanics can provide considerable insight in the development of strategies to prevent cognitive decline during aging. For example, changes in mTOR activity are often observed in nervous system diseases and neurodegenerative disorders, including AD [140]. Evidence is available that mTOR can promote cerebrovascular dysfunction [145] and its role in CBH is now receiving wider attention. In addition, it has been found that levels of mTOR are not only dramatically increased in AD but are also significantly correlated with phosphorylated tau [13, 140]. Upregulation of mTOR is reported to be associated with tau neuropathology and inhibition of mTOR reduces tau phosphorylation [140, 141].

CONCLUSIONS AND PROSPECTS

This review briefly examines evidence that provides support to our tenet that chronic brain hypoperfusion is the main driving force that propels a dedicated, slowly progressive but direct pathway to AD. This is not a startling conclusion since CBH is a common clinical feature of AD and the current focus of intense investigation in AD models, cognitive function, and human aging [1–10].

The findings presented here may add light to the association between vascular risk factors to AD, CBH, energy supply to brain, mTOR signaling cascade, p-Tau NFTs formation, axonal transport of membrane bound organelles, and mitochondrial dysfunction in aging; a biomolecular cascade contributing to AD onset and a flashpoint to significantly reduce new cases of this dementia.

From all that has been written, here and elsewhere, it is improbable, in our view, that sporadic AD can develop within a human lifetime where CBF remains unchanged from age 20 to senectitude in an otherwise healthy individual (Fig. 1, Step 9). The fact that CBF declines at a steady and predictable pace from early youth, as confirmed in dozens of clinical studies, is compelling evidence that progressive brain hypoperfusion is likely a predominant initiator of cognitive decline during aging.

Given enough time, the wear and tear on blood vessels supplying the brain become ineffectual to carry the volume of CBF needed to satisfy the incessant demand for energy substrates that keep the mind, the brain, and the brain cells normally functioning.

How then, does a nonagenarian individual run the gauntlet of environmental health challenges for 90 + years, including age-dependent CBF decline and resist developing significant neurodegenerative and cognitive disintegration? The answer remains an unsettled conundrum.

Our concept to partly explain this conundrum points to the appearance of vascular risk factors to AD that critically enhance age-dependent cerebral blood flow decline to a level where energy supply no longer matches neuronal demand. This outcome dooms specific neurons to slowly perish as a consequence. Intuitively, hardy resistance to these ubiquitous clinical insults may be consistent with the ability to avoid or combat conditions that significantly diminish brain blood flow in some aged individuals.

We showed this to be the case in previous CBH animal studies, when young and old rats were subjected to CBH for 9 months and only the old rats progressively worsened from the reduced CBF to usher in ATP deficiency, memory impairment, astrocytosis, microtubule associated protein loss, and entorhinal cortical atrophy, characteristics of AD [146, 147].

Importantly, these noxious outcomes in aged rats clinically mimicked AD manifestations that are known to materialize and slowly destroy brain structure and function. Other studies have amply confirmed our findings [148].

Strong evidence favors the view that the vascular path to sporadic AD onset has one crucial mission: to demolish highly active neurons that control cognitive domains. This is generally a slow-paced grind that can take decades to achieve. Knowledge of what sets in motion this cognopathic process should crack open a century of mystery plaguing the aging human mind.

In the last 15 years, good progress has been made in the fields of neuroradiology, biochemistry,

physiology, and behavior, to lend credence to the concept of AD as a vascular disease with neurodegenerate consequences [16].

Nonetheless, '*old paradigms die hard*', as Karl Albrecht once said, even when scientific evidence consistently fails to provide validation of their merit or usefulness.

Because there is currently no effective treatment for AD, its prevention could be applied immediately by monitoring individuals diagnosed with MCI or with pernicious vascular risk factors to AD. This a feasible office procedure, by physicians who come in contact with mid-age and older patients with memory complaints. The practice could determine if treatment or management of detected vascular abnormalities that can be treated or managed can be applied to prevent CBH acceleration of AD onset.

It goes without saying that our long held algorhithmic-based proposal favoring AD as a vascular disorder and primary driver of CBH during aging, likely has its share of shortcomings, much like any other conceptual framework. Thus far, however, no shortcoming appears sufficiently deadly to collapse the construct of this concept. Perhaps this review will stimulate such challenges.

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