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Disordered APP metabolism and neurovasculature in trauma and aging: Combined risks for chronic neurodegenerative disorders

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Abstract

Traumatic brain injury (TBI), advanced age, and cerebral vascular disease are factors conferring increased risk for late onset Alzheimer's disease (AD). These conditions are also related pathologically through multiple interacting mechanisms. The hallmark pathology of AD consists of pathological aggregates of amyloid- β ($A\beta$) peptides and tau proteins. These molecules are also involved in neuropathology of several other chronic neurodegenerative diseases, and are under intense investigation in the aftermath of TBI as potential contributors to the risk for developing AD and chronic traumatic encephalopathy (CTE). The pathology of TBI is complex and dependent on injury severity, age-at-injury, and length of time between injury and neuropathological evaluation. In addition, the mechanisms influencing pathology and recovery after TBI likely involve genetic/epigenetic factors as well as additional disorders or comorbid states related to age and central and peripheral vascular health. In this regard, dysfunction of the aging neurovascular system could be an important link between TBI and chronic neurodegenerative diseases, either as a precipitating event or related to accumulation of AD-like pathology which is amplified in the context of aging. Thus with advanced age and vascular dysfunction, TBI can trigger self-propagating cycles of neuronal injury, pathological protein aggregation, and synaptic loss resulting in chronic neurodegenerative disease. In this review we discuss evidence supporting TBI and aging as dual, interacting risk factors for AD, and the role of $A\beta$ and cerebral vascular dysfunction in this relationship. Evidence is discussed that $A\beta$ is involved in cyto- and synapto-toxicity after severe TBI, and that its chronic effects are potentiated by aging and impaired cerebral vascular function. From a therapeutic perspective, we emphasize that in the fields of TBI- and aging-related neurodegeneration protective strategies should include preservation of neurovascular function.

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Keywords

Aging; Alzheimer's disease; Amyloid-beta; Brain trauma; Neurodegeneration; Neurovascular unit

1. Goal of review

To discuss concepts and published research relating to disordered APP metabolism in the framework of traumatic brain injury (TBI) and aging as dual risk factors for development of late-onset Alzheimer's disease (AD). The pathology of TBI is complex and dependent on multiple factors including injury severity, age-at-injury, and time between TBI and neuropathological evaluation. In this regard, the main pathological culprit underlying the link between TBI, aging, and chronic neurodegenerative disease is not well defined. Accumulations of amyloid- β (A β) peptide and hyper-phosphorylated tau (p-tau) protein occur in AD, and their presence is required for neuropathological diagnosis of the disease. However, similar aggregates are also detected in many aged cognitively normal people (Mufson et al., 2016; Price and Morris, 1999) and after TBI. Extracellular plaques of A β are documented acutely and chronically after severe TBI (Ikonomic et al., 2004; Johnson et al., 2012; Roberts et al., 1991, 1994; Smith et al., 2003) as well as repetitive mild TBI (rmTBI) (Roberts et al., 1990; Stein et al., 2015). In the aging injured brain, A β may participate in a vicious cycle involving neuronal, synaptic, and cerebral vascular dysfunction and neuroinflammatory reaction (Cotman et al., 1996; Ramlackhansingh et al., 2011). Intracellular aggregates of p-tau are also detected after TBI and are currently designated as the defining pathology of chronic traumatic encephalopathy (CTE) (DeKosky et al., 2013; Gandy et al., 2014; Geddes et al., 1999; McKee et al., 2009; Omalu et al., 2005; Schmidt et al., 2001). Because brain accumulation of A β is the earliest biomarker change seen in the preclinical phase of AD (Jack et al., 2012), and is central to the amyloid cascade hypothesis of AD (Hardy and Selkoe, 2002), in this review we focus mainly on A β as a neuropathological link between TBI, aging, and AD.

2. Evidence linking TBI and AD

2.1. TBI as a risk factor for AD

TBI is considered a risk factor for AD, either as a precipitating event or by accelerating development of the disease (reviewed in (Lye and Shores, 2000; Van Den Heuvel et al., 2007; Vincent et al., 2014)). A link has been established between history of moderate or severe TBI with loss of consciousness (LOC) and AD (Mortimer et al., 1991) but the effect of outcomes varied among reports and some studies did not confirm this finding. This could be due to differences in TBI severity, age at the time of injury, and length of the injury-to-assessment interval, factors that are difficult to confirm in self-reported TBI (undocumented in medical records). For example, a study of 6645 subjects 55 yo and older with self-reported head trauma found no significant association between TBI with LOC and risk of dementia (Mehta et al., 1999). Similarly, TBI with LOC was not associated with dementia or AD neuropathology in three cohorts of patients segregated by duration of LOC, although an association was observed between history of TBI and Lewy body pathology (Crane et al., 2016). The use of self-reported, undocumented TBI, inclusion of a unique case cohort not

representative of general population, and missing neuropathology data in some cohorts (e.g., diffuse plaques which are of principal interest in the pathology of severe TBI) complicates the interpretation of these reports. In contrast, self-reported TBI was associated with greater frequency of A β plaques in injured compared to age-matched uninjured subjects (Abner et al., 2014). A study of 79 healthy controls and 69 mild-moderate TBI patients with a short (1–2 years) follow up reported no association between TBI and amnesic mild cognitive impairment (MCI) or dementia (Rapoport et al., 2008). However, in a longer (5–7 years) follow up study of 164,661 trauma (TBI and non-TBI) patients older than 55 years and without baseline dementia during hospitalization, dementia was more prevalent after TBI (8.4%) compared to non-TBI trauma (5.9%) (Gardner et al., 2014). Moreover, risk of dementia was significantly associated with both age-at-injury and severity of injury, underscoring the importance of inclusion and accuracy of this information in these types of studies. After moderate-severe TBI, risk of dementia was increased in patients with age-at-TBI > 55, while mild TBI was a greater predictor of dementia in subjects with age-at-TBI > 65 (Gardner et al., 2014). Future studies should assess more precisely the influence of age at injury, time interval between TBI and assessment, and severity of injury on risk of dementia. Of importance, many studies fail to factor comorbid states such as peripheral or central vascular disease in the analyses. Does a history of hypertension or hyperlipidemia, stroke and ischemia influence risk for dementia after TBI? Insight into this question could prove invaluable for long term treatment of TBI patients if such a connection is made.

2.2. The spectrum of A β and tau pathology after TBI

2.2.1. Human studies—A β is the main component of amyloid plaques which are morphologically complex lesions (Dickson, 1997; Thal et al., 2015). In the earliest (preclinical) stages of AD, A β plaques are diffuse (Mufson et al., 2016) and composed predominantly of the longer A β 42 form, comparable to A β plaques detected acutely in about 30% of people with severe TBI (Horsburgh et al., 2000; Ikonomic et al., 2004; Roberts et al., 1994) (Fig. 1). In contrast, many chronic survivors of severe TBI, especially at advanced age, show widespread distribution of diffuse and neuritic A β plaques that are similar to those in pathologically confirmed AD (Johnson et al., 2012). The A β precursor protein (APP) also accumulates after TBI (Gentleman et al., 1993a; Graham et al., 1995; Ikonomic et al., 2004; McKenzie et al., 1994; Roberts et al., 1991, 1994; Smith et al., 2003), and increased amyloidogenic (A β -producing) processing of APP has been postulated as a major cause of brain accumulation of A β (Thinakaran and Koo, 2008; Turner et al., 2003). Other factors contributing to A β deposition include impaired enzymatic degradation of A β (Johnson et al., 2009; Miners et al., 2008), alterations in brain efflux systems (Hawkes et al., 2014; Iliff et al., 2012), apolipoproteins (Castellano et al., 2011), and receptors involved in A β trafficking and clearance (Deane et al., 2004a, 2004b). Accordingly, in TBI patients with A β plaques, there is increased brain concentration of physiologically soluble (monomeric and oligomeric) A β 1–42 peptide (DeKosky et al., 2007), which could be related to reduced cerebral spinal fluid A β concentrations detected after TBI (Kay et al., 2003), similar to what occurs in AD patients (Blennow et al., 2015) (Fig. 1E). A β may be acutely neurotoxic (Emre et al., 1992; Smith et al., 1998) and could initiate a cascade of pathophysiological events leading to more advanced AD pathology and dementia later in life (Roberts et al., 1994). The outcome of these pathological changes, particularly in the aging brain, is progressive

impairment of neuronal function, inefficient repair of damaged synapses, and cognitive dysfunction.

In contrast to severe TBI, rmTBI has been connected more closely to tau than A β pathology. For example, a histological study of autopsy brains from boxers with dementia pugilistica (DP) reported tau pathology in the absence of A β plaques (Corsellis et al., 1973). However, Roberts and colleagues re-examined the same cases using antigen retrieval methods and A β immunohistochemistry and demonstrated widespread A β plaques in all of the DP cases (Roberts et al., 1990). Importantly, both A β and tau pathology in DP cases differ from the classic A β plaques and neurofibrillary tangles (NFT) of AD. In DP, A β plaques are mainly diffuse and difficult to detect using standard histological techniques (Roberts et al., 1990), as in severe TBI (see Section 3.2). In addition, tau-immunoreactive “NFT” in DP have different laminar distribution patterns than those in AD (Hof et al., 1992). Geddes and colleagues suggested that after rmTBI tau pathology may precede A β plaques, based on their findings of intracellular tau aggregates with a perivascular distribution and absence of A β plaques in four autopsy brains (Geddes et al., 1999). This finding was replicated by others (McKee et al., 2009; Omalu et al., 2005; Schmidt et al., 2001) and deep sulcal and perivascular distribution of tau-immunoreactive neurons and astrocytes has been designated the key pathological characteristic of CTE, providing the basis for its current neuropathological staging (McKee et al., 2015). Accordingly, CTE was defined as a “tauopathy”, however new research demonstrated A β plaques in 52% of CTE cases (Stein et al., 2015), which exceeds the reported 30% incidence of A β plaques in severe TBI. The incidence of A β plaques after rmTBI may be greater, because not all who suffer rmTBI develop CTE. Collectively, these observations demonstrate overlap in the pathology of severe TBI, rmTBI (including CTE), and AD, and emphasize that polyopathy, rather than just tauopathy or amyloidopathy, more accurately underlies the chronic neuropathological course of TBI (Turner et al., 2016; Washington et al., 2016). In this regard, evidence is emerging that other proteins, such as alpha-synuclein and TDP-43, can accumulate in the brain after TBI (Crane et al., 2016; Johnson et al., 2011; McKee et al., 2010).

2.2.2. Animal studies—Experimental studies of TBI-induced A β accumulation/toxicity as a risk of AD pathology have been methodologically diverse and often have produced conflicting results (Bird et al., 2016). These studies have been challenging, mainly because the amino acid sequence of the A β peptide differs between humans and commonly used experimental animals such as rats and mice. However, several animals produce A β with an amino acid sequence identical to that in humans and have utility in studies of the TBI-AD connection. After non-impact head rotational acceleration injury in pigs, A β accumulation was observed in injured axons and plaque-like structures (Smith et al., 1999). In aged guinea pigs, fluid percussion injury (FPI) resulted in diffuse A β plaques, and immunoreactivity to APP and tau increased with more advanced age over longer survival periods in this model (Bates et al., 2014). To study human A β response in brain injured mice, many investigations focused on transgenic mouse models of amyloidosis where APP is continually over-expressed, producing supra-physiologic brain concentrations of APP and A β . Brain injury experiments using these models produced varying outcomes. In Tg2576 mice (Hsiao et al., 1996), rmTBI at 9 months of age (prior to A β plaque formation in this model) increased

brain A β concentrations and A β plaque deposition at survival intervals up to 16 weeks (Uryu et al., 2002). In contrast, PDAPP mice (Games et al., 1995) with cortical impact brain injury at 4 months of age (prior to A β plaque formation in this model) had acute, transiently increased brain A β concentration (Smith et al., 1998). In aged PDAPP mice (24 months old, with robust plaque pathology), severe CCI injury resulted in fewer A β plaques, particularly in the hippocampus ipsilateral to injury compared to the contralateral hippocampus (Nakagawa et al., 2000). This “regression” of A β plaques could be due to extensive neuropil loss in the hippocampus, because unlike the rmTBI model, severe CCI injury induces a profound cortical cavitation lesion. Using the PSAPP transgenic mouse model of AD (Holcomb et al., 1998) and moderate-severe controlled cortical impact (CCI) injury at three months of age (time of A β plaque pathology onset in this transgenic model), Tajiri and colleagues observed greater A β plaque load six weeks after injury which also produced significant cell loss in the hippocampus (Tajiri et al., 2013). Using 5–7 month old 3 \times transgenic mice which over-produce both human A β and human tau (Oddo et al., 2003), Brody and colleagues (Tran et al., 2011) reported that severe CCI resulted in axonal accumulation of A β and tau. Interestingly, blockade of A β accumulation in this model did not affect tau immunoreactivity, leading the authors to suggest independent courses of these two AD pathologies after TBI (Tran et al., 2011). Another study used 3 \times Tg mice at ages prior to plaque deposition and reported that CCI injury produces acute increases in both insoluble (fibrillar) and soluble (oligomeric) A β , while changes in tau were not examined (Washington et al., 2014). The use of animal models in research of tau changes after TBI has been reviewed extensively by Abisambra and Scheff (Abisambra and Scheff, 2014). Collectively these animal studies demonstrate that formation of AD-like pathology after TBI is dependent on animal model, type and severity of injury, age at injury, and length of survival period. Furthermore, transgenic models over-expressing APP/A β and/or tau may be more suitable for studies of individuals with genetic predisposition for neurodegenerative diseases. To avoid confounds associated with transgene-driven APP overexpression, TBI studies by our group (Abrahamson et al., 2013, 2006, 2009) and others (Webster et al., 2015) utilized a human A β knock-in mouse model (hA β KI mice) where APP expression is under control of the endogenous promoter. CCI injury in hA β KI mice consistently produced significant increases and accumulation of A β and phosphorylated tau (Fig. 2).

3. Effect of aging on A β -induced risk for developing AD after TBI

3.1. The “two-hit” hypothesis of A β toxicity

The two-hit hypothesis has been formulated separately in the fields of TBI and AD, to explain the pathogenic role of A β . Related to TBI, Smith and colleagues (Smith et al., 1998) argued that neurons have a potential or latent vulnerability to A β toxicity at a given brain concentration (“first hit”) and that only after a “second hit”, such as TBI, is this potential manifested. Accordingly, “A β is necessary but not sufficient to cause neuronal death until a second pathological process potentiates its neurotoxicity” (Smith et al., 1998). In the context of AD as a chronic clinical-neuropathological sequela of TBI, amyloidogenic APP metabolism plays a role in both immediate (primary) and delayed (secondary) effects of TBI, while brain aging-related dysfunction (and non-A β -related secondary injury processes

resulting from TBI) could be a second insult exacerbating these pathological pathways and contributing to other pathologies, such as tau, and clinical dementia onset.

3.2. Aging as a modifying factor in the relationship between TBI and AD

In younger subjects with severe TBI, accumulation of A β does not fully replicate the pathology seen in AD dementia patients. Diffuse A β plaques are detected shortly after injury, when neuritic A β plaques are absent or rare (Gentleman et al., 1997; Graham et al., 1995; Ikonomic et al., 2004; Roberts et al., 1991). In addition, the acute phase after severe TBI is not associated with prominent cortical tau pathology (Ikonomic et al., 2004). However in aged subjects with TBI and longer survival periods, widespread A β plaques (both diffuse and neuritic) and classic NFT can be detected (Johnson et al., 2012). A β and tau changes are also seen in some professional athletes with rmTBI, however these two pathologies can present with different proportions and time of onset. For example, rmTBI can produce a pathological feature of CTE which is characterized primarily by tau changes (McKee et al., 2015), while in aged people with same type of injury tau pathology frequently co-presents with A β plaques (Stein et al., 2015), more typical of AD. Thus, aging can modify the chronic post-TBI course by providing a second insult that drives the neuropathological outcome to more closely resemble the neuropathology of AD. Differential time course of induction and progression of A β and tau pathologies after severe TBI or rmTBI may be also influenced by genetic susceptibility and epigenetic mechanisms. The effect of these multiple factors on pathological mechanisms contributing to patient's outcome after TBI is beginning to be understood. Advanced age is also a significant factor contributing to impaired recovery after TBI (Coronado et al., 2005; Czosnyka et al., 2005; Hukkelhoven et al., 2003) including increased risk for developing AD/dementia. This is particularly important in the context of growing aged populations of civilians and Veterans (Ortman et al., 2014), greater numbers of geriatric patients with chronic survival after head trauma (Adams and Holcomb, 2015), and increasing burden of elderly TBI patients on the health care system (Thompson et al., 2006). Recently, there is an indication of reduced inpatient mortality after TBI (Maxwell et al., 2015). Though encouraging from the standpoint of acute medical care, this will increase the number of aging TBI survivors at risk for developing chronic neurodegenerative diseases and dementia towards the end of their life. Notably, age alone is not a significant predictor of TBI outcome (Joseph et al., 2014), and aging-related comorbid states such as cerebrovascular disease may be superimposed on or work in synergy with TBI to worsen neurological outcomes (Plassman and Grafman, 2015).

4. Neurovascular unit and the TBI-AD link

The relationship between altered vascular responses after TBI and risk for developing chronic neurodegenerative diseases is not well understood (Logsdon et al., 2015). Defining the molecular mechanisms or vulnerable cell types which drive vascular impairment in TBI patients could facilitate treatment interventions aimed at preventing or ameliorating chronic pathology and neuropsychological impairment. Specifically, maintaining the functional integrity of cerebral neurovascular unit (NVU) after TBI is critical, and perhaps equally important as current neurocentric "neuroprotection" strategies (Logsdon et al., 2015), for

preventing chronic accumulation of toxic proteins and for promoting the restoration of neuronal homeostasis and functional recovery. Cerebrovascular consequences of TBI are in part determined by the type of TBI and include cerebral vasospasm, hemorrhage (epidural, subdural, subarachnoid, and intraparenchymal), and vasogenic edema all of which can result in brain ischemia. TBI involves complex changes in cerebral blood flow (CBF), with some areas (typically proximal to the site of TBI) showing profound hypoperfusion and other areas (typically distal or contralateral to the site of TBI) showing hyperemia (Abrahamson et al., 2013; Akbik et al., 2016). As discussed below, accumulations of A β peptides (both oligomeric and fibrillar assemblies) affect cellular components of the NVU and can foster secondary injury processes including activation of cell death pathways (apoptosis), oxidative stress, and inflammation. These effects are likely exacerbated by aging, contributing to the risk of AD.

4.1. Endothelial cells

Tight junctions between endothelial cells of blood vessels form the blood brain barrier (BBB) at the interface between the vasculature and brain parenchyma. Endothelial cells also function as a conduit for molecules to access the brain through receptor mediated transport. In the context of A β , the receptor for advanced glycation end products (RAGE) is an important mediator of A β transport from the vasculature into brain parenchyma (Zhao et al., 2015a; Zlokovic, 2011). Dysfunction of endothelial cells in TBI and aging results in BBB breakdown and increased brain penetrance of toxic molecules (Price et al., 2016). Similarly, receptor-mediated transport of toxic molecules such as A β (via low density lipoprotein receptors) *out* of the brain is dependent on endothelial cells, disruption of which leads to accumulation of A β . Zlokovic and colleagues (Zhao et al., 2015b) demonstrated that phosphatidylinositol-binding clathrin assembly protein (PICALM, a genetic factor linked to AD (Harold et al., 2009) expressed in endothelial cells (Baig et al., 2010)) is an important mediator of LRP-bound A β transcytosis and clearance from the brain. Because enhancement or restoration of PICALM function could counteract detrimental effects of A β accumulation at the NVU, it will be important to define changes in PICALM expression after TBI and during aging.

Endothelial cells can be affected by high concentrations of A β in the brain, such as in AD (Kelleher and Soiza, 2013) but also after TBI (DeKosky et al., 2007). Moreover, endothelial cell aging likely increases their susceptibility to toxic effects of A β (Brandes et al., 2005). This toxicity occurs via stimulation of cell death pathways involving caspase-3 and caspase-8, TNF-related-apoptosis-inducing-ligand (Ghiso et al., 2014; Xu et al., 2001), ASK1-JNK/p38 apoptotic signaling pathways (Hsu et al., 2007), death receptors DR4 and DR5 (Ghiso et al., 2014), oxidative stress pathways, and intracellular calcium ion overload (Koizumi et al., 2016). Additional pathways involve altered endothelial nitric oxide synthase (eNOS) and nitric oxide (NO) production (Suhara et al., 2003), and disruption of vascular proliferation (Grammas et al., 1995), potentially through effects on vascular endothelial growth receptor (Patel et al., 2010). Specifically, age-related changes in eNOS and NO production (Barton et al., 1997) could potentiate A β -induced impairment in endothelium-dependent vasodilatation after TBI.

Endothelial cells produce endothelin-1 (ET-1), a potent vasoconstrictor that is upregulated by A β (Palmer et al., 2012) and could contribute to vascular impairment in aging and AD (Love and Miners, 2016), but also after TBI. A β can upregulate at least one of the enzymes that regulate production of ET-1, endothelin-converting enzymes 1 and 2 (ECE-1 and ECE-2; (Palmer et al., 2009)), which interestingly also can degrade A β (Eckman et al., 2001). Love and colleagues (Palmer et al., 2009) demonstrated upregulation of ECE-2 mRNA and protein as well as increased activity of ECE-1 in AD brain tissue. This could be detrimental, through enhanced production and vasoconstrictor activity of ET-1, but also protective through degradation of A β . ET-1 is also upregulated acutely after TBI (Armstead and Kreipke, 2011), however its suppression through receptor pharmacology (Kreipke et al., 2010) or through mRNA silencing (Petrov, 2009) can restore CBF in TBI models. Since both endothelial cells and pericytes express ET-1 receptors, ET-1-induced changes in the NVU function might be mediated by both cell types (Dore-Duffy et al., 2011).

In addition to enhancing ET-1 induced vasoconstriction (Paris et al., 2003), A β could also impair CBF via loss or uncoupling of NO signaling (Austin et al., 2013). In an aged rat model of chronic brain hypoperfusion, de la Torre and colleagues reported that eNOS inhibition impaired behavioral outcome, leading these authors to conclude that eNOS (and NO production) might be a critical factor in maintaining at least a certain degree of cerebral perfusion even in the compromised state (hypoperfusion) (de la Torre and Aliev, 2005). This is relevant to aging and AD, where cerebrovascular impairment with hypoperfusion is related to brain accumulation of A β which is both toxic to endothelial cells (Thomas et al., 1996) and produces vasoactive effects (Iadecola, 2004; Townsend et al., 2002). Our work in the hA β KI mouse model, which has little if any fibrillar A β but produces increased concentrations of physiologically soluble (monomeric and oligomeric) human A β after TBI, provides additional evidence for vasoactive effects of A β . CCI injury produced significantly greater impairment of CBF in hA β KI mice compared to their wild type counterparts (C57Bl/6) (Abrahamson et al., 2013). This suggests that compared to murine A β , soluble human A β has stronger vasoconstriction effects after TBI.

4.2. Pericytes

Pericytes are components of the NVU (Winkler et al., 2014) and important regulators of BBB formation and maintenance, neurovascular coupling, and clearance of molecules, including soluble A β , from the brain (Bell et al., 2010; Winkler et al., 2014). Pericyte cell death, migration, and altered phagocytic and metabolic activity is reported in a wide variety of pathological conditions, including TBI and AD (for reviews see (Castejon, 2011; Winkler et al., 2014)). The effects of experimental TBI on pericytes is complex and dependent on the TBI model used and length of survival after injury. An ultrastructural study in adult rats with closed head injury demonstrated that within hours after injury pericytes migrated away from vessel cell walls in the vicinity of the lesion (Dore-Duffy et al., 2000). It is unclear whether this is a protective response or if the loss of capillary-associated pericytes further contributes to BBB breakdown and subsequent vasoactive edema after TBI. In mice subjected to a more severe, penetrating CCI injury model, pericyte cell death was observed at three days post injury in the ipsilateral hippocampus and perilesional cortex (Choi et al., 2016) whereas at five days post injury pericyte proliferation was detected in perilesional cortex (Zehendner et

al., 2015). The complex response of pericytes to TBI requires further characterization, particularly in aging brain where these cells are involved in BBB disruption. Using an in vitro model of accelerated senescence, Yamazaki and colleagues (Yamazaki et al., 2016) observed an association of endothelial cell and pericyte senescence with breakdown of the BBB. This idea is supported by Zlokovic and colleagues (Montagne et al., 2015) who demonstrated BBB breakdown in the hippocampus of aged people. Moreover, pericyte senescence could potentiate TBI-associated BBB breakdown which can persist lengthily after injury (Hay et al., 2015). Pericytes undergo constriction after ischemia (Hall et al., 2014), and under pathological conditions such as TBI and AD, their dysfunction could contribute to chronic changes in neurovascular coupling. In AD, molecular signaling between pericytes and other cell components of the NVU is compromised (Winkler et al., 2014) and pericyte loss is accelerated, likely related to disrupted A β clearance (Halliday et al., 2016). In support of this, an association between pericyte loss and accumulation of soluble A β was demonstrated in transgenic APP^{swe} mice (Sagare et al., 2013). Whether a similar relationship between pericyte changes and A β accumulation exists in chronic TBI needs to be investigated and may identify novel mechanisms contributing to risk for AD after TBI.

4.3. Astrocytes

Astrocytes exhibit changes in gene expression and phenotypic changes in the presence of oligomeric and fibrillar A β (Hu et al., 1998; Mulder et al., 2012). This is exemplified in their association with classic A β plaques in AD (Dickson, 1997; Thal, 2012; Wisniewski and Wegiel, 1991) where they may have a role in A β degradation (Wegiel et al., 2001) and glial scarring (Nagele et al., 2004). The relation between astrocytes and TBI-induced changes in A β is not well understood, particularly in the acute stages after severe TBI in young adults when diffuse A β plaques are predominant. A study examining pathology in frontal cortex biopsy samples from a subject with DP demonstrates a close correspondence between the laminar distribution of A β plaques, tangles, and GFAP-immunoreactive astrocytosis (Saing et al., 2012). A particularly striking feature of this case study is the conspicuously greater association of astrocytes with blood vessels in the DP case compared to cases with either AD or frontal temporal dementia, suggesting interplay between A β , astrocyte activation, and cerebral vasculature in brain injury. In addition, perivascular clustering of tau-immunoreactive astrocytes (and neurons) is a pathological feature of CTE. Astrocytes play critical role in the maintenance of the BBB through vasoactive endothelial growth factor signaling mechanisms (Argaw et al., 2012) and interactions with extracellular matrix proteins. Astrocytic regulation of the BBB responds to, and could mediate, leukocyte trafficking (Lecuyer et al., 2016). Astrocytes are also involved in neurovascular coupling and functional hyperemia, in part through glutamate or ATP signaling-induced release of vasoactive substances, including arachidonic acid metabolites such as 20-HETE (Howarth, 2014). With age, astrocytes increase expression of glial fibrillary acidic mRNA and shift to a pro-inflammatory phenotype (reviewed in (Garwood et al., 2016)), and exhibit signs of oxidative damage and expression of the senescence associated secretory phenotype (Garwood et al., 2016; Simpson et al., 2010). Astrocytic dysfunction could result in impaired A β clearance, increased release of pro-inflammatory molecules, and enhanced leukocyte trafficking at the BBB which all relate to neuroinflammatory processes (discussed in Section

5.6) and could contribute to AD pathology with aging and after TBI. The relation of these factors to functional changes of the NVU in aging and TBI needs to be investigated.

5. Role of A β and aging in primary and secondary effects of TBI and risk of AD

Primary pathology of TBI results from mechanical forces. Severe and penetrating brain injury causes immediate cell lysis with release of intracellular ions, neurotransmitters, and peptides/proteins, axonal damage and disconnection. Dysfunction of neurovasculature, including disruption of the BBB and consequent influx of peripheral proteins and immune cells into brain parenchyma is another important consequence of severe TBI. In rmTBI, the effects of mechanical forces are more subtle but nevertheless result in axonal and vascular pathology. Secondary injury processes occur following primary injury and develop over a longer timescale, and include oxidative stress, excitotoxicity, activation of cell death pathways, and neuroinflammation. In the aging injured brain, these secondary injury processes are exacerbated, and recovery processes (synaptogenesis and angiogenesis) are compromised. Thus, secondary injury effects are likely important mechanistic connections between TBI and AD, particularly in the aging brain (see schematic in Fig. 3), and they can be modified by genetic and epigenetic factors. In the following sections we discuss pathological consequences of primary and secondary TBI effects in the context of altered A β metabolism and the aging brain, and how this can contribute to increased risk for AD later in life.

5.1. Diffuse axonal injury

Mechanical forces of TBI disrupt intra-axonal cytoskeletal structure and increase axolemmal permeability with subsequent pathological influx of Ca²⁺ ions and activation of caspases, calpain-mediated spectrin proteolysis, and mitochondrial damage (Buki et al., 2000; Buki and Povlishock, 2006). Axonal swellings, a pathological hallmark of diffuse axonal injury (DAI) visualized histologically as axonal bulbs (retraction balls), accumulate cell organelles, vesicles, and proteins. Among the proteins normally undergoing fast axonal transport, APP accumulates within hours after TBI in axonal swellings, where it co-localizes with A β (Smith et al., 2003). Accordingly, axonal APP immunoreactivity is considered a reliable marker of DAI (Gentleman et al., 1993b; Stone et al., 2000) and precedes the appearance of silver staining positivity, a marker of neuronal/axonal degeneration (McKenzie et al., 1996; Sherriff et al., 1994). APP immunoreactive axonopathy is also seen in long-term survivors of blast TBI (months to years), in a pattern described by Koliatsos and colleagues as spheroids and varicosities with perivascular distribution in cortical white matter (Ryu et al., 2014). Thus, axonal injury results from multiple forms of TBI and involves an interplay between brain injury and APP/A β that are likely amplified, or at least persist, with aging (Chen et al., 2009).

The relationship between axonal accumulation of APP/A β and parenchymal A β plaque deposition after TBI is not clear. APP-immunoreactive deposits are prevalent in areas of axonal injury (Graham et al., 1996; Ikonomovic et al., 2004) and APP-immunoreactive swollen axons associate with A β plaques at least acutely after TBI (Ikonomovic et al., 2004;

Smith et al., 2003, 1999) (see Fig. 1). This suggests that injured axons may be the source of A β in plaques, however in an autopsy study of subjects with remote brain injuries (three years prior to death), lack of widespread plaque pathology despite axonal accumulation of A β led Smith and colleagues to suggest that TBI-induced plaques may regress over time (Chen et al., 2009). Interestingly, APP/A β deposition is more frequently seen in aged people who suffer a TBI, most typically as a consequence of a fall, the leading cause of head injury in the elderly (Faul and Coronado, 2015), thus more advanced age may exacerbate AD pathological processes after TBI.

There have been significant recent advances in detecting and monitoring axonal injury and A β deposition in living TBI patients, using imaging techniques typically applied in clinical studies of aging, MCI, and AD: MRI of axonal injury and connectivity (diffuse tensor imaging (DTI) and high definition fiber tractography) (MacDonald et al., 2007, 2011; Presson et al., 2015) as well as amyloid PET (Eisenmenger et al., 2016; Gatson et al., 2016; Hong et al., 2014; Kawai et al., 2013; Mitsis et al., 2014; Scott et al., 2016). Several of these clinical analyses replicate data from histopathology studies. Kawai and colleagues (Kawai et al., 2013) reported [C-11]PiB retention in 27% (3/11) of imaged patients, reminiscent of the percent of severe TBI cases with histological evidence of A β plaques. Jack and colleagues (Mielke et al., 2014) found that among the MCI subjects undergoing [C-11]PiB PET imaging in the Mayo Clinic Study of Aging, those with self-reported TBI had greater PiB-PET retention. In a study of long-term survivors of moderate-severe TBI, increased PiB-PET was associated with DTI evidence of altered connectivity involving the posterior cingulate cortex (Scott et al., 2016), a cortical area vulnerable to A β accumulation in AD. It will be important to use these imaging modalities in conjunction with imaging measures of vascular dysfunction to assess the relation between amyloid lesions and CVD after TBI, particularly in the aging brain as has been investigated in non-TBI subjects (Marchant et al., 2013).

5.2. Synapse loss

As discussed above, DAI disrupts axonal transport (both retrograde and anterograde) which, in addition to accumulation of proteins in axonal swellings, results in disconnection/deafferentation (see (Povlishock and Katz, 2005) for review). The time course of this process differs between experimental animals and humans and is associated with alterations in synapses (Povlishock et al., 1992). While axonal disruption can be extensive after TBI, Povlishock and colleagues pointed out that “the amount of degenerating nerve terminals far exceeds the number of identified damaged fibers” (Povlishock and Katz, 2005) underlining the importance of synapse degeneration in TBI. Detection of synapse degeneration/loss in TBI can be confounded by ongoing restorative processes including synapse regeneration, a phenomenon that could reflect brain compensatory response or an aberrant response to loss of synapses. Experimental studies by Cotman and colleagues revealed that this process is active in the hippocampus after brain injury (Cotman et al., 1981) and can be influenced by aging. This is most clearly demonstrated in the entorhinal cortex lesion (ECx) model. After complete unilateral ECx, greater loss of synapse density in the outer molecular layer of the dentate gyrus and slower synapse replacement was observed in aged compared to young rats (Hoff et al., 1982). Loss of synapses is a structural correlate of cognitive impairment in AD (Scheff and Price, 2006), and it could contribute to increased risk for dementia after TBI,

particularly chronically with aging. When synapses are quantified in clinical groups with no cognitive impairment, MCI and mild AD, synapse loss occurs in a stepwise fashion in some neocortical areas (inferior temporal gyrus and posterior cingulate cortex (Scheff et al., 2015, 2011)) while in others (e.g., precuneus) synapse loss is seen only in mild AD (Scheff et al., 2013). Synapse loss chronically after experimental TBI might recapitulate regional vulnerability patterns seen in AD. For example, cortical impact injury produces secondary injury with extensive synapse loss in the underlying hippocampus, a region vulnerable to synapse loss in AD (Scheff et al., 2005). The role of A β in synapse loss after experimental TBI remains to be investigated. We demonstrated that CCI injury produced greater loss of pre- and post-synaptic markers in hA β KI mice compared to wild type counterparts expressing endogenous (mouse) A β (Fig. 4). This suggests that human A β oligomers play a role in synapse degeneration after TBI, similar to what occurs in AD (Walsh et al., 2002). Advanced age, particularly >65 years involves synapse loss (Masliah et al., 2006, 1993), and this could contribute to late-onset AD dementia in some aging survivors of TBI since any significant synapse loss could lower the threshold for clinical manifestation of AD.

5.3. Oxidative stress

Detrimental effects of reactive oxygen species (ROS) due to mitochondrial leakage or accumulation of A β have been posited to underlie oxidative damage and cellular dysfunction in aging (Indo et al., 2015) and AD (Swomley and Butterfield, 2015), respectively. Studies by Scheff and colleagues demonstrate an association between oxidative stress and loss of synaptic proteins in the presence of A β pathology in preclinical and prodromal AD (Scheff et al., 2016). Although the cause and effect relationship between ROS and A in cellular/synaptic dysfunction is still a matter of debate in the field of neurodegenerative disorders (Mattson, 2011), both variables likely influence outcome, including risk for AD, after TBI. ROS production increases after TBI and could contribute to DNA damage, protein and lipid peroxidation, mitochondrial dysfunction and cell death (Hall, 2015). At the level of the NVU, pathological levels of ROS can induce cell death and disrupt the BBB (von Leden et al., 2016). In aging, mitochondria dysfunction and reductions in antioxidant enzymes increase oxidative stress at the NVU, in part through peroxynitrite formation (van der Loo et al., 2000) resulting from the interaction of endothelial cell derived NO and superoxide. These mechanisms could be exacerbated in the presence of A β or, conversely, promote brain accumulation of A β . The connection between A β and oxidative stress after TBI was examined in nine month old Tg2576 mice (prior to plaque deposition in this model) and wild type littermates subjected to rmTBI. In this study, Trojanowski and colleagues (Uryu et al., 2002) detected increased A β concentrations and deposition, increased levels of lipid peroxidation, and cognitive impairment in transgenic but not wild type mice (Uryu et al., 2002) and suggested that brain A β accumulation and oxidative stress could work synergistically after TBI to increase the risk for AD (Uryu et al., 2002). Collectively, ROS appear to be pathologically active in TBI, aging, and AD and should be targeted by therapies aiming to break the link between brain injury and AD.

5.4. Apoptosis

Apoptosis is an important cell death mechanism in TBI (reviewed in (Bramlett and Dietrich, 2015)). Pro-apoptotic molecules such as cytochrome-c and apoptosis inducing factor are

released from damaged mitochondria and activate caspases in injured axonal segments, contributing to cytoskeletal damage. Increased A β production after TBI could contribute to the induction of apoptosis through caspase activation (Allen et al., 2001; Nishimura et al., 2002; Uetsuki et al., 1999) which could, in turn, promote amyloidogenic processing of APP (Gervais et al., 1999). Enhanced caspase cleavage of APP after TBI or in aging leads to A β over-production and could contribute to the pathological link between TBI and AD (Stone et al., 2002; Zhao et al., 2003). Interestingly, Koliatsos and colleagues reported that in subjects with no cognitive impairment (NCI), there is little if any evidence of apoptosis in the absence of A β pathology, however apoptosis is present in NCI cases with A β plaques (a sign of pre-clinical AD) and is markedly increased in AD brains, (Troncoso et al., 1996). Although unexplored, the implications of these observations are that TBI patients who develop A β plaques could exhibit greater neuronal loss, and with aging this could lower the threshold for clinical manifestation of AD. We investigated, albeit indirectly, the effects of caspase-cleaved APP and human A β on outcome after TBI (Abrahamson et al., 2006), and observed increased levels of APP, caspase-cleaved APP, and A β monomers/oligomers after severe CCI injury in hA β KI mice. Pan-caspase inhibition immediately after CCI injury reduced levels of both caspase-cleaved APP and A β and improved histological outcome (Abrahamson et al., 2006), suggesting that targeting caspases after TBI could reduce injury-induced AD-like pathology. Aging, when superimposed on TBI, could enhance apoptotic response to brain injury and this could impair neurological outcome. In support of the notion that aging can exacerbate injury-induced neuronal degeneration, FPI produced higher number of TUNEL positive neurons in aged rats when compared to juvenile rats (Sun et al., 2013).

5.5. Neuroinflammation

Aging is associated with a shift to a pro-inflammatory state (Godbout and Johnson, 2009; Sandhir et al., 2008), enhanced microglia reactivity (Yu et al., 2002), and microglia senescence (Neumann et al., 2009; Streit et al., 2008). Microgliosis and reactive astrocytosis accompany amyloid lesions in AD, and they are potentially involved in A β -related neurodegeneration after TBI. Astrocyte signaling mechanisms are activated after TBI, and are associated with heterogeneous morphological changes determined in part by injury severity (reviewed in (Burda et al., 2016)). Van Eldik and colleagues observed that closed head injury produced a delayed but enhanced and persistent astrocytic response in hA β KI mice with the PS1 mutation compared to wild type mice (Webster et al., 2015). Moreover, greater plaque load was detected in hA β KI/PS1 mice after TBI compared to sham-operates, and the degree of astrocyte activation was also greater in injured transgenic mice compared to transgenic sham operates and injured wild type mice. These results suggest a relation between injury-induced A β changes and astrocyte activation after TBI. These processes could contribute to clearance of cell debris and neurovascular remodeling (Burda et al., 2016) and involve several receptors including toll-like receptors (TLRs) and RAGE. Astrocytes are capable of internalizing and metabolizing A β (Wyss-Coray et al., 2003), possibly through A β binding to the low density lipoprotein receptor-related protein 1 (Thal, 2012). After TBI astrocytes release inflammatory mediators including cyclo-oxygenase-2 and metalloproteinases, also active in AD (Phillips et al., 2014), and could play a role in sequestering toxic A β .

Microglia have the potential to be beneficial or detrimental after TBI, depending on their polarization/characterization as M1 (pro-inflammatory) or M2 (immunosuppressive), reviewed in (Loane and Kumar, 2016). Different phenotypes of microglial activation and related neuroreparatory versus neurotoxic processes need to be explored in relation to A β changes after TBI. In adult hA β KI mice subjected to CCI injury we observed a rapid (hours) and sustained (weeks) increase in microglia immunoreactive for ionized calcium binding adaptor molecule 1, and the course of this reactive process corresponded to increased accumulation of human A β and loss of synaptophysin immunoreactivity in the cortex and hippocampus (Abrahamson et al., 2009). Similarly, more pronounced microglia reaction and more sustained memory impairment after closed head injury were reported in hA β KI/PS1 mice compared to wild-type mice (Webster et al., 2015). Recent research supports combined effects of TBI and aging on microglia function. Aging can affect microglia function after TBI (Lourbopoulos et al., 2015), possibly reflected by morphological changes (Harry, 2013), which could influence outcome at different stages of recovery (Hefendehl et al., 2014; Norden et al., 2015). For example, in the aging brain the microglia profile changes into a primed (inflammatory) state which involves an exaggerated cytokine (IL-1 β) response and increased expression of inflammatory (IL-1 β , TNF- α) as well as immune (MHC II) markers, similar to what occurs after TBI and in AD (reviewed in (Norden et al., 2015)). Furthermore, aging impairs the ability of microglia to internalize A β , despite their preserved ability to adhere to A β fibrils both in situ (plaques) and isolated in vitro (Floden and Combs, 2011). Aging-related impairment in A β clearance from brain may explain greater vulnerability to neurodegenerative processes after injury in the aging brain (Harry, 2013). Animal studies also demonstrate that after TBI, peripheral monocyte infiltration and activation is greater in aged mice (Morganti et al., 2016). Thus, inflammatory processes activated after TBI may be exacerbated by aging-related pathophysiology and this could result in chronic neuroinflammation conferring greater risk of developing AD later in life.

6. Summary and conclusions

There is substantial evidence linking TBI to increased risk for AD and supporting a role for disordered APP metabolism and aging in this relationship. It is also becoming clear that both severe TBI and rmTBI involve complex polypathologies, with A β and tau changes occurring in different proportions at different time points after injury, and can also include aggregates of other proteins linked to chronic neurodegenerative diseases (e.g., TDP-43, alpha-synuclein). In this regard, future studies should strive to explore a wider array of aggregation-prone molecules, and employ more diverse assessment approaches to investigate pathological molecular changes not readily detectable in routine diagnostic neuropathology workups (e.g., soluble A β and tau oligomers). Studies of TBI should also define the time window of opportunity for treatments prior to advanced age when risk is greater for sustained accumulation of pathological protein aggregates, neuronal degeneration, and cognitive and behavioral changes. These treatments should aim to suppress prolonged accumulation of A β and tau, and also prevent or attenuate pathological effects of these molecules on cellular components of the NVU. Ideally such strategies would supplement

neuroprotection-focused therapies and advance the efforts to break the link between TBI and AD.

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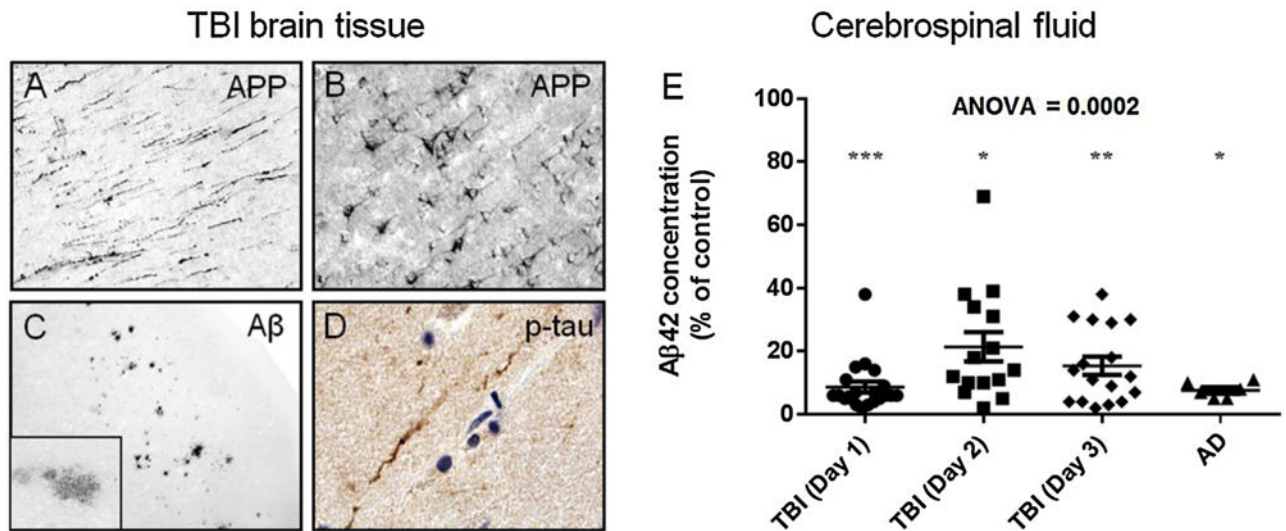


Fig. 1.

A–D: Brain tissue sections from a temporal cortex biopsy resected 12 h after severe TBI in a 39-year old subject from the University of Pittsburgh Brain Trauma Research Center (BTRC) were processed for immunohistochemistry using antibodies against the A β precursor protein (APP; polyclonal antibody anti-6, Athena), A β (antibody clone 10D5, Elan), and p-tau (antibody clone PHF-1, P. Davies, Albert Einstein College of Medicine). After severe TBI, APP accumulates in axons in the white matter (A), in cell bodies of pyramidal neurons in the grey matter (B), and A β deposits in diffuse A β plaques (C and inset). Rare profiles of phosphorylated tau (p-tau) immunoreactive fibers are detected in the gray matter (D; brown color is p-tau immunoreactivity, blue color is hematoxylin histological counterstain). E: A β 1–42 peptide (A β 42) concentrations (ELISA, Biosource) in cerebral spinal fluid (csf) from severe TBI patients (from the University of Pittsburgh BTRC; average age = 35.8 ± 15.7 , range 17–65) at one, two, and three days after injury and from end-stage AD patients (from the University of Pittsburgh Alzheimer’s Disease Research Center; average age = 76.3 ± 10.2 , range 63–91) are similarly reduced relative to levels in csf from cognitively normal control subjects (average age = 56.8 ± 14.5 , range 25–78). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ (Bonferroni multiple comparison post hoc test). Abbreviations: A β , amyloid- β ; APP, A β precursor protein; p-tau, phosphorylated tau.

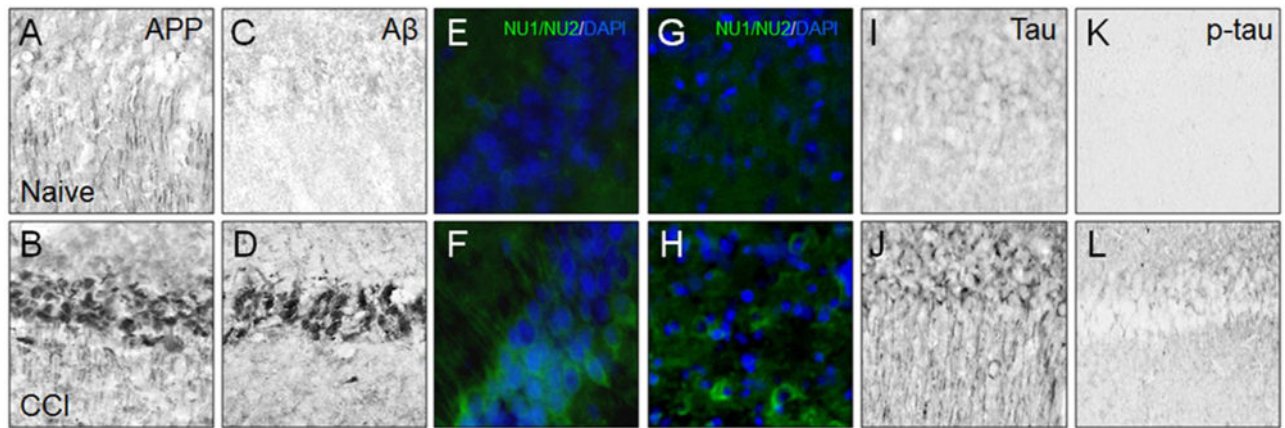


Fig. 2. Immunohistochemical analysis of hippocampus CA1 (A–F; I–L) and pericontusional somatosensory cortex (G, H) in human A β knock-in mice free of TBI (Naïve; A, C, E, G, I, K) and two weeks after severe controlled cortical impact injury (CCI; B, D, F, H, J, L). Tissue sections were immunoreacted with antibodies recognizing amyloid precursor protein (polyclonal anti-APP antibody CT695, Biosource; A, B), A β peptide (polyclonal anti-A β 42 antibody, Millipore; C, D), A β oligomers (antibodies clones NU1/NU2, generous gift from W. Klein, Northwestern University; E, F and G, H), total tau (polyclonal anti-Tau antibody, Dako; I, J), and phosphorylated tau (biotinylated antibody clone AT8, Thermo, p-tau; K, L). Each marker is detected at low levels in naïve mice and prominently after CCI injury.

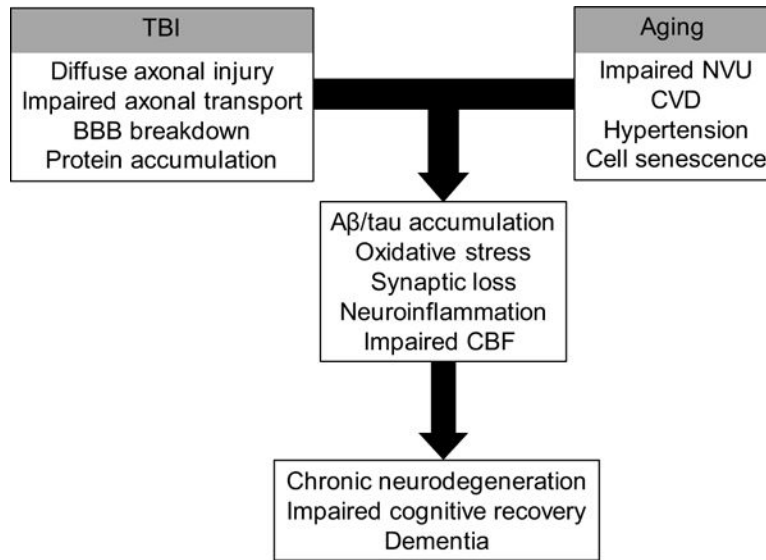


Fig. 3. Flow diagram illustrating concepts discussed in the current review, including the interaction between TBI and aging in relation to neurovascular dysfunction as precursors to, or risk factors for AD. In addition, genetic predisposition and epigenetic factors can influence pathways toward recovery or chronic pathology. Abbreviations: A β , amyloid- β ; BBB, blood brain barrier; CBF, cerebral blood flow; CVD, cerebrovascular disease; NVU, neurovascular unit; TBI, traumatic brain injury.

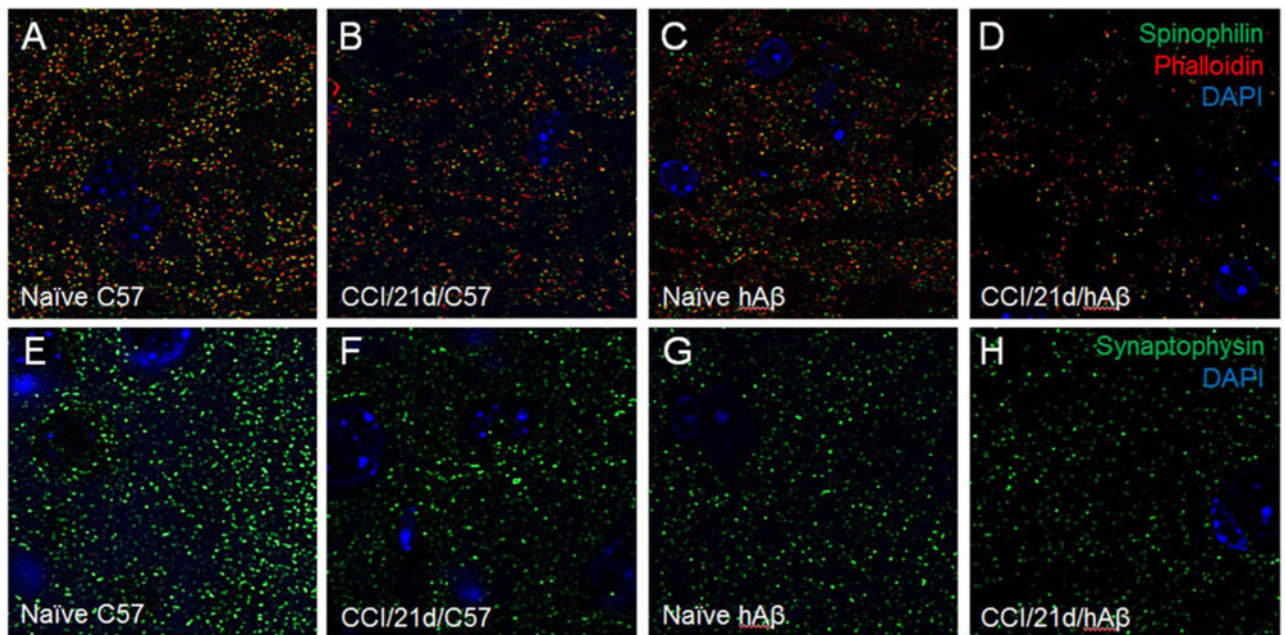


Fig. 4.

Confocal microscopy analyses of dendritic spines double immunolabeled using antibodies against spinophilin (polyclonal anti-spinophilin antibody, Millipore; green, A–D) and phalloidin (f-actin probe, Thermo; red, A–D) and presynaptic terminals immunolabeled with anti-synaptophysin antibody (polyclonal anti-synaptophysin antibody, Thermo; green, E–H) in the hippocampus of naïve (uninjured) wild type mice (line C57Bl/6, A, E) and naïve (uninjured) human A β (hA β) knock-in mice (C, G) compared to CCI injured wild type mice (B, F) and hA β mice (D, H) with 21 days survival. Blue fluorescence is DAPI counterstain. CCI injury results in loss of both spinophilin/phalloidin positive dendritic spines and synaptophysin positive presynaptic terminals, and the extent of this loss is greater in hA β mice when compared to wild type mice.