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Review

Traumatic Brain Injury and Alzheimer's Disease: The Cerebrovascular Link

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ABSTRACT

Traumatic brain injury (TBI) and Alzheimer's disease (AD) are devastating neurological disorders, whose complex relationship is not completely understood. Cerebrovascular pathology, a key element in both conditions, could represent a mechanistic link between Aβ/tau deposition after TBI and the development of post concussive syndrome, dementia and chronic traumatic encephalopathy (CTE). In addition to debilitating acute effects, TBI-induced neurovascular injuries accelerate amyloid β (Aβ) production and perivascular accumulation, arterial stiffness, tau hyperphosphorylation and tau/Aβ-induced blood brain barrier damage, giving rise to a deleterious feed-forward loop. We postulate that TBI can initiate cerebrovascular pathology, which is causally involved in the development of multiple forms of neurodegeneration including AD-like dementias. In this review, we will explore how novel biomarkers, animal and human studies with a focus on cerebrovascular dysfunction are contributing to the understanding of the consequences of TBI on the development of AD-like pathology.

Contents

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1. Introduction

Traumatic brain injury (TBI) is a significant public health problem associated with both acute and long-term disabilities, which are mediated by multiple, not entirely understood, molecular cascades. In addition to debilitating acute effects, severe TBI, and especially repeated mild TBI (Blennow et al., 2016) can initiate long-term neurodegeneration processes leading to pathological features that have similarities with Alzheimer's disease (AD)(Washington et al., 2016; Blennow et al., 2016; Mendez, 2017).

The term 'Punch drunk' was introduced by Dr. Martland in 1928, when describing the variety of syndromes present in contact-sport players after repeated loss of consciousness, years after retiring from boxing. Symptoms reported were "facial characteristics of the parkinsonian syndrome" and "marked mental deterioration" (Martland, 1928). Martland described the presence of hemorrhages near the "corpora striata" and "corona radiata", that were later replaced by gliosis and degenerative progressive lesions. Although he described his theory as "insusceptible of proof", he already showed a relationship between vascular injury and the presence of lesions later in life in nearby brain locations. Since then, a large body of epidemiological studies has shown that having a history of previous TBIs is associated with the development of numerous types of dementia later in life (Mendez, 2017; Gardner et al., 2014). Other recent studies have suggested that TBI is not linked to AD but to other types of neurodegeneration such as Lewy body accumulation and Parkinsonism (Crane et al., 2016) (Weiner et al., 2017), highlighting the need to better understand the pathological mechanisms activated after TBI and their relationship with neurodegeneration.

Evidence that will be discussed throughout this review shows that cerebrovascular dysfunction (CVD) is a key element for the development of dementia after TBI. Exploring biomarkers of CVD will help understand the contribution of TBI-induced vascular damage to AD-like pathology and improve diagnostic and therapeutic approaches for both disorders. We propose a shift in focus from a "neuronal" to a "neurovascular" point of view, pointing to CVD after TBI as a possible causal contributor to Aβ/tau deposition, neurodegeneration, and early initiation of AD-like pathology.

2. Pathological Relationship Between TBI and Dementia

Multiple pathological processes link TBI with neurodegeneration and dementia. The term chronic traumatic encephalopathy (CTE) describes neuropathological changes that occur later in life in patients subjected to repeated concussive head injuries, and can present with symptoms and pathology mimicking neurological diseases including AD, Parkinson's disease (PD), frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS). Some pathological features typically observed in AD have been found in postmortem brains of TBI and CTE (McKee et al., 2013), such as increases in hyperphosphorylated tau (P-Tau) and in some cases amyloid beta (Aβ) and TDP-43 deposits (Washington et al., 2014; Abisambra and Scheff, 2014). Indeed, recent consensus criteria consider CTE as a tauopathy (McKee et al., 2016).

2.1. Aβ Pathology in TBI and its Relationship With Vascular Dysfunction

Autopsies of relatively young TBI patients who died during the acute phase after injury show diffuse Aβ plaques similar to those found in AD patients located in the areas surrounding the lesion sites in both gray and white matter regions (reviewed in (Perry et al., 2016, Johnson et al., 2010)).

It is still unclear which mechanisms lead to Aβ accumulation in TBI. TBI, through vascular shear stress, can induce acute blood brain barrier (BBB) disruption, which is known to contribute to both ischemic damage and Aβ accumulation (Iadecola, 2013; Pluta et al., 2013). Hypoperfusion, vascular dysfunction and ischemia after TBI may all contribute to Aβ deposition (Iadecola, 2013; Pluta et al., 2013; De Silva and Faraci, 2016; Wolters et al., 2017). Previous studies showed a relationship between brain ischemic stress and Aβ-deposition (Wisniewski and Maslinska, 1996) and we previously reported that plasma Aβ42 levels are increased after transient hypoxia during static apnea in healthy subjects (Gren et al., 2016), indicating that general hypoxia may cause mild neuronal dysfunction or damage and stimulate Aβ production. Indeed, under blood flow reduction (hypoperfusion), β and γ-secretases are activated, leading to increased Aβ production (Gupta and Iadecola, 2015; Pluta et al., 2013). Additionally, trauma-induced brain heat/cooling alterations can modulate brain metabolism (Mrozek et al., 2012). Metabolic acidosis after TBI could also potentially contribute to Aβ accumulation, as it is known that Aβ, like other proteins, is prone to aggregation in a pH-dependent manner (Acharya et al., 2016). The formation Aβ aggregates in the perivascular spaces induced by these acute events after TBI may play a role in secondary injury cascades, including cerebrovascular damage, oxidative stress, mitochondrial damage, and endothelial cell dysfunction/death. Accordingly, our group has demonstrated the role of oligomeric species of Aβ in the activation of mitochondria- and death receptor-mediated pathways of endothelial cell stress and death (Fossati et al., 2010, Fossati et al., 2012a, Fossati et al., 2012b, Ghiso et al., 2014, Fossati et al., 2013). This cascade of neurovascular stress events induced by Aβ could be particularly exacerbated after repeated TBIs, and contribute to the development of AD-like pathology and dementia later in life.

2.2. Tau Pathology in TBI and its Relationship With Vascular Dysfunction

Tau is well known for its role in neurofibrillary tangle formation in AD. Neuropathological data indicates that CTE is a tauopathy intimately linked to CVD and characterized by the deposition of hyperphosphorylated tau protein as NFTs and pre-tangles in clusters, particularly around small blood vessels of the cortex, and typically in the depths of the sulci (Omalu et al., 2005; Goldstein et al., 2012; McKee et al., 2013; Smith et al., 2013; DeKosky et al., 2013; Blennow et al., 2012). NFTs in CTE typically follow the penetrating small cortical vessels as linear accumulations extending from the surface of the brain to the lowest layers of the cortical gray matter or, when observed in cross-section, as clusters, pre-tangles and dot-shaped and thread-like neuropils in a penumbra around small arterioles (McKee et al., 2015). Multiple forms of CVD are found in nearly all tauopathies (Michalicova et al., 2017). Interestingly, vessel wall remodeling, an early-onset process that precedes cerebral amyloid angiopathy (CAA), which may contribute to downstream microvascular pathology in AD, is also tau-associated (Merlini et al., 2016).

Studies in animal models show that acceleration/deceleration injury causes tau to become phosphorylated, misfolded, aggregated, and cleaved, generating neurotoxic tau peptide fragments (Huber et al., 2013; McKee et al., 2015). Recent data suggests that tau accumulation alone induces chronic dysfunction of the cerebral vasculature (Merlini et al., 2016; Blair et al., 2015), contributing to neurodegeneration.

The process leading to tau accumulation is unclear, however it has been proposed that mechanical stress beyond certain thresholds after TBI can disrupt microtubule networks within axons leading to diffuse axonal injury (DAI), tau release, hyper-phosphorylation and extracellular accumulation (Johnson et al., 2013; Kawata et al., 2016). While this option is plausible, other options should be considered, such as oxidative stress, which is known to modulate tau phosphorylation patterns *in vitro* (Katai et al., 2016). Studies in animal models of cerebral ischemia show altered tau gene expression in the infarct core after stroke (Ramos-Cejudo et al., 2012) or hyper-phosphorylated tau deposits in the hippocampus after middle cerebral artery occlusion (Xu et al., 2015). Accordingly, CSF tau levels are transiently increased in stroke patients (Hesse et al., 2001) as well as in TBI (Ost et al., 2006; Shahim et al., 2014) (Olivera et al., 2015). While increased brain, CSF and plasma tau levels after TBI could be merely the result of axonal injury, we propose that trauma-induced CVD also contributes to tau release, hyperphosphorylation and early accumulation after TBI. Indeed, recent literature directly implicates the

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