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COMMENTARY

Traumatic brain injury: a platform for studies in Aβ processing

Commentary on: "Rapid Aβ oligomer and protofibril accumulation in traumatic brain injury"

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Traumatic brain injury (TBI) offers a unique opportunity to examine amyloid-beta (Aβ) pathology since the moment of head trauma is the triggering event of aberrant Aβ genesis. This commentary highlights a study by Abu Hamdeh and colleagues in this issue of *Brain Pathology* (xxx) in which the authors show surprisingly rapid formation of amyloid oligomers and protofibrils within hours of severe TBI, with higher levels of these potentially toxic Aβ species found in individuals with the APOE e4 genotype. This study provides a window into the very early events of amyloid pathogenesis after TBI, and serves as a platform for future studies to follow the temporal mischief that the Aβ species wreak in the injured brain.

Long recognized as a hallmark pathology of Alzheimer's disease (AD), plaques composed of amyloid-beta (Aβ) peptides are now widely acknowledged as a common consequence of both acute and late survivals from traumatic brain injury (TBI) (1). However, while in all practical terms it is impossible to determine the precise time of onset of abnormal amyloid processing in AD, in contrast, for TBI the moment of head trauma is essentially "time zero" as the triggering event of aberrant production of Aβ peptides. As such, TBI provides a unique opportunity to study the processes contributing to abnormal Aβ pathologies in neurodegeneration.

Previous studies using autopsy acquired or surgically excised tissues have shown that moderate to severe levels of TBI can trigger the formation of diffuse plaques in approximately 30% of individuals (2–5); risk in turn influenced by genetic susceptibility (APOE and neprilysin polymorphisms) (6, 7). Remarkably, these plaques can form within hours of injury, even in young individuals. While the sources of Aβ genesis following TBI remain to be fully characterized, diffuse axonal injury (DAI) presents a strong candidate (8). Common to all severities of TBI, DAI results in axonal transport interruption leading to massive accumulation of amyloid precursor protein (APP) and its cleavage enzymes in axonal swellings in stereotypical locations throughout the white matter. In this pathological milieu, Aβ is thought to be cleaved from APP, with the resulting Aβ reservoir released by lysis of the injured axons (9) (Figure 1). However, the ensuing events leading to Aβ aggregation and the rapid deposition of diffuse plaques or other pathological mischief have only been partially explored (10–14).

In this issue of *Brain Pathology*, Abu Hamdeh and colleagues provide striking insight into post-TBI amyloid pathogenesis. Particularly laudable in their study is the use of human brain tissue acquired during surgical intervention from 12 patients with severe TBI (Glasgow Coma Scale 8 or less), thereby providing samples for parallel immunohistochemical and biochemical analyses in many of their cases. While this number of subjects is understandably small due to the unique source, the findings are nonetheless

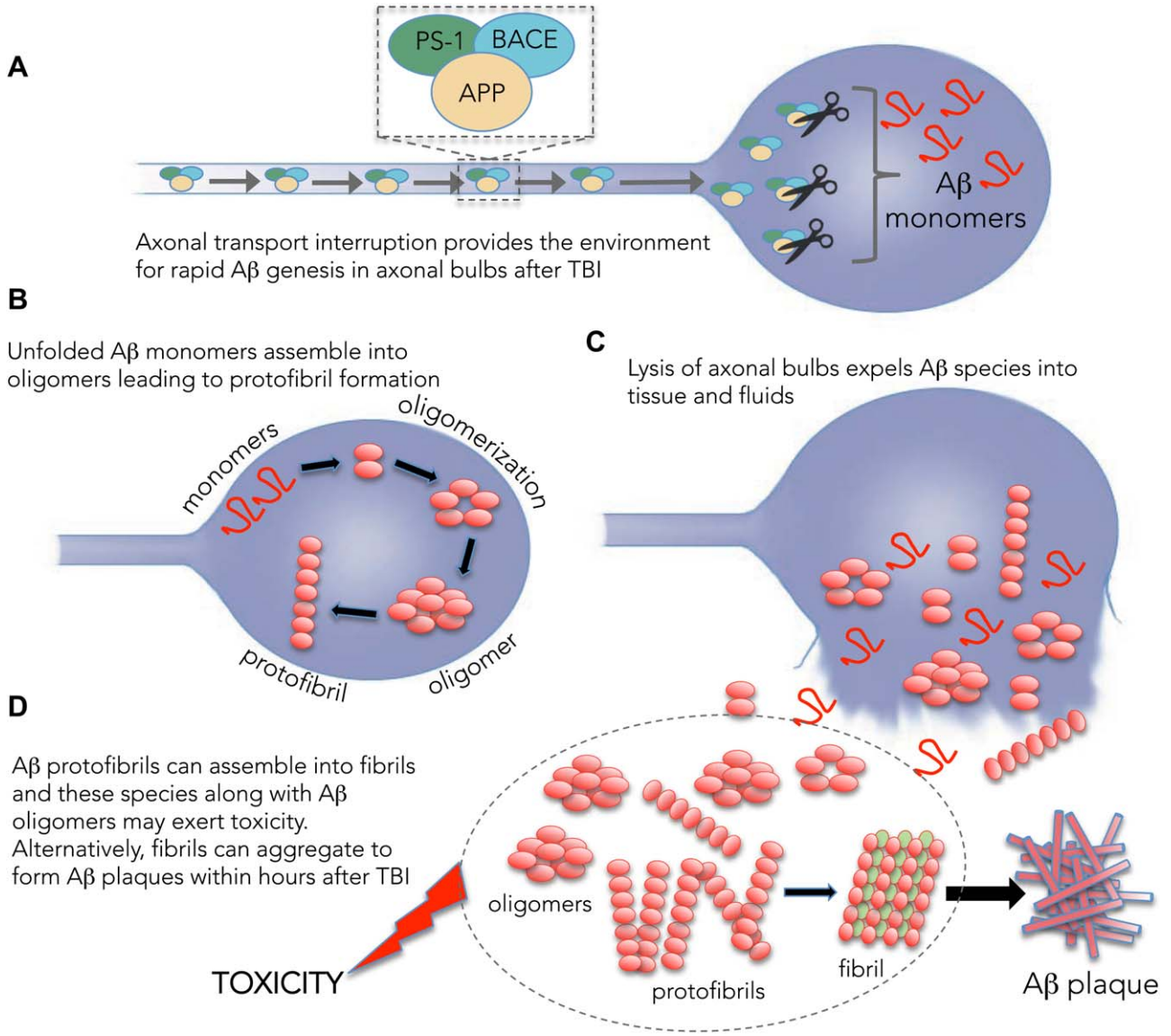

Figure 1. One potential source for rapid genesis of amyloid-beta (Aβ) species after traumatic brain injury (TBI). **A.** Widespread damage to axons induces transport interruption and accumulation of amyloid precursor protein (APP) and the secretases, PS-1 and BACE that can cleave it to form Aβ peptides within axonal swellings. **B.** Accumulating Aβ assembles into oligomers and protofibrils, that are (**C**) released into the brain when the axonal bulb is lysed. **D.** Free Aβ oligomers, protofibrils and developing fibrils may exert toxicity to the brain and/or form plaques that can be observed within hours after TBI.

compelling. As with earlier studies in amyloid post-TBI, this group observed plaque pathology in the excised tissue shortly after injury in around a third of the case material they examined. However, for their biochemical examinations on these as well as the apparently "non-plaque" cases, the authors report the first evidence of rapid accumulation of Aβ oligomers and protofibrils in a matter of just hours after injury. Notably, while these soluble Aβ aggregates are thought to be integral to AD pathogenesis (15), pushing the disease to progress over many years, this new study demonstrates that these potentially toxic Aβ species can form extremely rapidly after TBI. As such, their appearance perhaps provides a substrate for the initiation or acceleration of processes leading to late post-TBI neurodegeneration, which might provide insight to similar pathways driving AD.

Interestingly, in common with previous studies in amyloid plaque deposition after TBI, the authors found an association between appearance of these Aβ oligomers and protofibrils and APOE genotype (6, 7). Specifically, higher levels of Aβ species were detected in patients with the high risk APOE ε4 allele (in this series all ε3/ε4 genotype), known to be more prone to developing Aβ plaques after TBI, than in non-ε4 carriers. Since it remains unknown whether the there is an increased generation of Aβ or decreased capacity to clear it, further biochemical and genetic analyses are warranted to further elaborate on this

observation. For example, this appearance of increased amyloid pathologies after TBI in APOE ε4 carriers may reflect a decreased capacity to traffic Aβ. It would also be interesting to examine the role of the Aβ degrading enzyme, neprilysin, and polymorphisms of its gene in this population of cases (6).

Aβ oligomers and protofibrils are implicated in a growing number of pathological processes, such as interrupting long-term potentiation and memory function and increasing inflammation (16–19). As such, their processing to and deposition as plaques might conceivably represent an amyloid pathology of lesser concern, since the otherwise toxic Aβ species are literally "bound up (Figure 1)." Nonetheless, acute plaque formation does not appear to be the final chapter as TBI has been shown to be an "injury that keeps on taking." Indeed, approximately 30% of patients go on to have progressive neuropathological processes, including the late re-emergence of widespread amyloid plaque pathologies and further protein misfolding pathologies, including striking pathologies in tau, and persistent and evolving neuroinflammation; pathologies common to many neurodegenerative diseases (1, 20, 21). Therefore, as this work illustrates, TBI provides an intriguing and informative platform to explore events springing from "time zero" that are directed toward identifying candidate pathological processes responsible for converting an initial traumatic event into a progressive neurodegenerative disease.

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