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Review Article

Mechanical stress models of Alzheimer's disease pathology

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Abstract

Introduction: Extracellular accumulation of amyloid-β protein and intracellular accumulation of tau in brain tissues have been described in animal models of Alzheimer's disease (AD) and mechanical stress-based diseases of different mechanisms, such as traumatic brain injury (TBI), arterial hypertension (HTN), and normal pressure hydrocephalus (NPH).
Methods: We provide a brief overview of experimental models of TBI, HTN, and NPH showing features of tau-amyloid pathology, neuroinflammation, and neuronal loss.
Results: "Alzheimer-like" hallmarks found in these mechanical stress-based models were compared with AD features found in transgenic models.
Discussion: The goal of this review is, therefore, to build on current concepts of onset and progression of AD lesions. We point to the importance of accumulated mechanical stress in brain as an environmental and endogenous factor that pushes protein deposition and neuronal injury over the disease threshold. We further encourage the development of preventing strategies and drug screening based on mechanical stress models.

Keywords: Alzheimer's disease; Animal models; Mechanical stress; Brain injury; Normal pressure hydrocephalus; Hypertension; Amyloid pathology; Tauopathy

1. Transgenic Alzheimer's disease models: Hallmarks and limitations

Neuropathologically, Alzheimer's disease (AD) is characterized by the extracellular accumulation of amyloid-β (Aβ) peptides in the core of the amyloid plaques and the intracellular accumulation of hyperphosphorylated tau protein in the form of neurofibrillary tangles (NFTs) and neuropil threads. In addition to the tau-amyloid signature, oxidative damage, neuroinflammation, widespread synaptic loss, and neuronal death have been considered hallmark features of AD [1]. The amyloid cascade hypothesis initially proposed that Aβ is the principal etiopathological event in AD because it triggers a cascade of processes leading to tauopathy, neuronal injury, and cognitive impairment [2].

Animal models of AD have played a major role in defining critical disease-related mechanisms and have been at the forefront of how novel therapeutic approaches are evaluated. Many treatments currently tested in clinical trials stem from studies initially performed in rodent models [3]. Current transgenic models of AD are derived from the familial forms of the disease (FAD) that are indistinguishable from sporadic AD histopathologically [4]. On the other hand, the mechanisms underlying sporadic AD, more complex and numerous than the monogenic dominant mutations responsible for FAD, remain less well known and modelled [4]. Transgenic models of Aβ accumulation overproducing mutant amyloid precursor protein (APP) develop an amyloid

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pathology that is mostly similar to that found in the human brain. Doubly PS1-APP–mutated transgenic models of Aβ accumulation develop the lesions earlier [5–7]. Neurofibrillary tangles, in contrast, are practically only found in transgenic mice overexpressing mutated tau [8] (whereas mutations of microtubule-associated protein tau do not lead to AD in human but in other neurodegenerative diseases such as frontotemporal dementia). Albeit mixed transgenic models with both Aβ and tau accumulation recapitulate the histological changes seen in AD, the genetic changes needed for the expression of these pathological hallmarks differ from those found in FAD [9]. In addition, many AD models do not recapitulate the neuronal and/or synaptic loss as observed in the human condition [4]. Inflammation, in turn, is not precisely modeled in mice, as there are differences between humans and AD transgenic mice with respect to the nature and severity of the inflammation. A number of mediators, such as complements, cytokines [10], Cdk5, and reactive oxygen species [11], associated with the activation of microglia and astrocytes surrounding Aβ plaques, have been found in both humans and AD transgenic mice.

Because of the complexity of the disease, none of the transgenic lines was able to recapitulate all aspects of AD pathology. It probably suggests the limitation in using a transgenic system to reproduce a human disease process. Another issue with transgenic models of AD is the fact that the overproduction of Aβ alone drives the pathological process consistently with the amyloid cascade hypothesis [2]. So these transgenic models reproduce FAD, whereas most people have sporadic AD [4]. In sporadic AD, the disease is rather linked to an imbalance between production and clearance of Aβ leading to its accumulation over time. But the mechanisms leading to this imbalance remain poorly known. From a practical point of view, there is discordance in results between preclinical animal models and human clinical trials. Although they are highly useful in understanding AD pathogenesis, transgenic models have some limitation that leads to the need to explore new venues in the scope of animal modeling of AD [4].

2. AD pathology and brain mechanics

Physical forces, both from the external and the internal environment of the body, constantly influence organs. Neuronal tissues are continuously affected by physical stressors including gravity, temperature, electromagnetism, and pressure. The influence of mechanical energy on the brains of living organisms is omnipresent, as all cells are susceptible to mechanical forces. These stressors could be the cause, the consequence, and/or might also simultaneously interact with neurobiological processes. For example, neuroglial proteins could be twisted, turned, ratcheted, flexed, compressed, expanded, and bent [12]. Consequently, these nanoscopic changes in neuron stress and tension can influence cell division, gene expression, cell migration, morphogenesis, cell adhesion, fluid homeostasis, ion channel gating, and vesicular transports [13–15]. The source of mechanical energy in the brain is, for example, provided by cerebrovascular blood flow accompanying every heartbeat in humans, which generates forces that can displace the brain tissue by tens of micrometers [16]. Consequently, the brain is not only an electrically sensitive organ but also a mechanically sensitive one [12], whose properties allow endogenous forces to regulate many aspects of the neuronal function. Over the past decades, the mechanical forces that influence neuronal processes have largely remained unexplored.

Epidemiological and neuropathological data have suggested a tight association between neurodegenerative diseases and the history of exposure to mechanical stress factors. Extracranial mechanical stressors predisposing an individual to AD later in life can be observed in traumatic brain injury (TBI) [17], whereas occupational exposure can be observed in athletes (boxers, football, and soccer players) and military personnel [18]. Changes in intracranial dynamics may also result in an increased risk of AD as seen in normal pressure hydrocephalus (NPH) [19] because AD pathology is often present in cortical biopsies of NPH patients. Neuropathological confirmation of AD in NPH cases may also indicate that NPH is an overdiagnosed syndrome [20]. The expansion of cerebrospinal fluid (CSF) compartments in NPH alters brain dynamics through shrinkage of the parenchyma and reduced CSF turnover. Finally, cerebrovascular hemodynamic changes, caused by atherosclerosis, heart diseases, and arterial hypertension (HTN), also affect cognition and are among the most important risk factors for AD [21].

Surprisingly, many of these mechanical stress-based diseases carry pathological tau-amyloid hallmarks of AD, as observed in both humans and animal models. These AD-like features have been found in TBI, HTN, and NPH models, which share a key common mechanical stress-based mechanism.

3. AD pathology in mechanical stress-based models

3.1. Brain injury

Pathological analysis of TBI tissues in humans has led to notable findings regarding AD pathological features. Amyloidosis, for example, can be induced after TBI. It is manifested by amyloidogenic APP processing [22,23], increased levels of soluble Aβ42 [24], and an accumulation of diffuse and dense-cored amyloid deposits [25]. Tauopathy could also be induced by brain injury and manifested by increased phosphorylated tau protein levels [26] and the presence of NFT [27] with gliosis [28]. Moreover, TBI has been associated with neuroinflammation [29] and neuronal loss [30] in the patients' brains. Neurocognitive syndromes associated with chronic traumatic encephalopathy include personality change, memory impairment, dementia, pyramidal and extrapyramidal dysfunction, and cerebellar impairment [31].