Mechanical Stress Models of Alzheimer's disease Pathology

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Abstract:

Introduction: Extracellular accumulation of beta-amyloid 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.

Transgenic AD models: hallmarks and limitations

Neuropathologically, 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 (NFT) 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, since 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 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] (while mutations of MAPT 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 pathologic hallmarks differs 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.

Due to 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 pathologic process consistently with the amyloid cascade hypothesis [2]. So these transgenic models reproduce FAD, while 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 which leads to the need to explore new venues in the scope of animal modeling of AD [4].

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 TBI [17], while 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], since AD pathology is often present in cortical biopsies of NPH patients. Neuropathological confirmation of AD in NPH cases may also indicate that NPH is overdiagnosed syndrome [20]**.** The expansion of 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, 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 traumatic brain injury, arterial hypertension, and NPH models, which share a key common mechanical stress based-mechanism.

AD pathology in mechanical stress-based models

Brain injury

Pathological analysis of traumatic brain injury (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] as well as 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 (CTE) include personality change, memory impairment and dementia, as well as pyramidal and extrapyramidal dysfunction and cerebellar impairment [31].

As observed in humans, several defining pathological hallmarks of AD are also present in numerous models of TBI using mice, rats, rabbits, pigs, and monkeys. Rodent models of TBI exhibit amyloidosis, tauopathy, neuroinflammation, and neuronal loss [32]. Each one of these AD hallmarks, in turn, could be induced by different mechanisms of injury. Focal injury [33], controlled cortical impact [34], closed head trauma [35], mild compression contusion [36], lateral fluid percussion [37], traumatic axonal injury [36], electro-coagulation [38] and penetrating needlestick injury [39] can prompt amyloidogenic APP processing and/or Aβ accumulation in rodents. Tauopathy can be exhibited in rodent models of mild repetitive trauma [40], blast injury, concussion [41], lateral fluid percussion [42] and penetrating needlestick injury [39]. Even if unspecific, neuroinflammation and/or neuronal loss have also been induced in these models by the mechanisms of controlled cortical impact [43,44], fluid percussion injury [45,46], weight-drop impact [47], and repetitive mild trauma [40]. Cognitive dysfunction, such as memory and object recognition impairment [48–52], as well as behavioral disturbances (anxiety and depression-like symptoms) [53–57] and sensorimotor deficits [58], has also been described in TBI models of different mechanisms. Repetitive mild TBI (rmTBI) models have shown temporal dynamics of total tau and phospho-tau levels consistent with development of learning, memory and motor impairments, as well as anxiety-like disorders [59]. However, since rmTBI models have also revealed cognitive deficits independent of increased Aβ or tau phosphorylation [60], it remains to be elucidated how these pathological hallmarks precisely correlate with behavioral dysfunction in TBI models [61].

Hydrocephalus

Normal pressure hydrocephalus (NPH) is characterized by an excessive enlargement of the brain ventricles leading to parenchymal shrinkage, while cerebrospinal fluid (CSF) pressure measurements usually remain within the normal range. A clinical triad of gait disturbance, cognitive impairment, and urinary incontinence is variably present [62]. The pathophysiological cause of these findings has not been clarified in detail and the most commonly accepted hypothesis is that transient intracranial pressure peaks lead to chronic mechanical stress on the ventricular walls, ultimately resulting in ventricular dilatation and clinical impairment [63]. Several studies have demonstrated neuropathologic evidence of AD in NPH [19,64–66]. The frequency of AD features through cortical biopsies taken during shunt placement has been shown to be greater than that of the general population,

suggesting the existence of an AD-NPH syndrome [67] or indicate misdiagnosed NPH in pathologically confirmed AD cases.

Animal models of NPH have revealed amyloid accumulation in aged rats in which hydrocephalus was induced by cisternal kaolin injection [68]. Furthermore, amyloid accumulation was revealed to be temporally and spatially related to hyperphosphorylation of tau in a manner similar to what is described in human NPH with associated AD pathology [69]. However, there is no evidence that tauopathy could be a consequence of NPH. It has been suggested that the underlying mechanisms of reduced Aβ clearance could explain amyloid accumulation in hydrocephalic rats. Although nonspecific feature of AD, neuronal death has also been described in experimental models of compensated [70] and non-compensated hydrocephalus in rats [71,72]. Neuroinflammation manifested by glial reaction has also been demonstrated in rat and dog models of hydrocephalus [68,73,74], also exhibiting impaired memory [74]. Adult rats with chronic kaolin hydrocephalus manifest decreased learning and spatial memory performances, gait ataxia and bradykinesia, comparable to NPH patients [75–78].

Arterial hypertension models

Arterial hypertension increases brain mechanical (hemodynamic) stress as a result of pulsating shock waves (some 30 million/year) produced by the external surface of the arterial wall in contact with the brain parenchyma [79]. Carnevale et al. [80] have found that mice that have been subjected to high levels of blood pressure show an accumulation of amyloid aggregates, as well as an initiation of the glial response in brain tissues. In this work, hypertension was mechanically induced by transverse aortic coarctation. Schreiber et al. [81] demonstrate age-dependent extracellular deposition of Aβ and phospho-tau accumulation in a hypertensive rat model. Spontaneously hypertensive models, also useful for investigating the effects of hypertension on the cognitive function, have shown impaired learning and memory in rats but only with the presence of white matter and focal brain lesions. Aged hypertensive mice induced by infusion of angiotensin II have exhibited spatial memory object recognition impairments, yet tau and Aβ pathology was not reported in this model [82].

Accumulation of Aβ in mechanical stress models

Aβ plaques without NFT found in the brains of AD transgenic mice are structurally similar to those in the human brain. They initiate as diffuse plaques consisting mainly of Aβ42, develop a dense Aβ42 core, and then incorporate Aβ40 as well as numerous other non-Aβ components, such as ubiquitin and α-synuclein [83], found in Lewy Body Disease cases. As in the human brain, these plaques stain positive with both thioflavin and Congo red, and show similar fibrillar structures in electron microscopy. Several models have been used in an attempt to clarify the mechanisms of plaque appearance after TBI. Aβ accumulation in rats was observed in axonal bulbs, and partially around them, one month to one year posttraumatically in rats [37]. A pig model of rotational head injury developed quite rapid diffuse deposits of Aβ three days after trauma, not increasing with time [84].

While TBI models have proved useful in characterizing the accumulation of diffuse Aβ deposits, they failed in manifest mature dense plaques found in transgenic AD models (table 1). This is likely due to the fact that these TBI animal models have a relatively low abundance of misfolded Aβ species that do not reach a critical threshold for aggregation [36,37,42,85–89]. While acute Aβ deposits following TBI are typically diffuse in nature, similar to those seen in early AD, those observed in long-term survivors from single TBI were more frequently fibrillar and dense, i.e. similar to those of established AD [27] This raises the question of whether AD amyloid dense deposits follow the pattern of diffuse (posttraumatic) Aβ pathology [90].

Unlike their wild-type counterparts used as TBI models, HTN rats exhibited increased cortical age-dependent extracellular ovoid cortical AβPP deposits and parenchymal eosinophilic material suggestive of amyloid “plaque-like” accumulation [81], suggesting that HTA drives Aβ accumulation in brain tissues [91]. In hydrocephalic rats, Aβ42 immunostaining was characterized by small, medium, and large Aβ42 granular accumulations, reflecting the progressive aggregation [69] (table 1).

Tauopathy in mechanical stress models

Unlike humans with AD, transgenic mouse models based on Aβ accumulation do not develop NFTs, yet many do show increased tau hyperphosphorylation [92] (table 1). NFTs are practically only found in transgenic mice

overexpressing mutated human tau. Although blast-exposed wild-type mice recapitulated cellular accumulation of phospho-tau and pretangle tau protein neuropathology, it is notable that mature NFTs were not detected in these mice [32]. This apparent discrepancy with human TBI/AD tauopathy was explained by the early time points chosen for evaluation in TBI mouse studies or, alternatively, by the resistance of wild-type murine tau protein in forming neurotoxic aggregates in vivo [41]. Mice expressing human tau isoforms after repetitive TBI show increased phospho-tau immunoreactivity [40] and NFTs [93], commonly found in human TBI. Phosphorylated tau intracellular accumulation could be labeled in the brain of hypertensive rats [81,94]. In hydrocephalic rats, accumulated coarse phospho-tau granules appeared margined around the periphery of the neurons, in the proximal dendritic tree and at the axon hillock, seemingly representing “excess pTau” inclusions [69]. No tangle/pretangle pathology has been reported in hydrocephalus and hypertension rat models (table 1).

Expanding possibilities: radiation and metabolic stress-based models of AD pathology

Different physical stress mechanisms have been shown to induce tau-amyloid pathology. Exposure to electromagnetic pulses leads to oligomeric Aβ overexpression and long-term memory impairment in wild-type rats [96]. Ionizing radiation causes increased tau phosphorylation in primary neuron cultures, which involved oxidative stress-dependent and independent activation [97]. In humans, prophylactic cranial irradiation induces altered amyloid metabolism and increased CSF tau levels [98]. Such findings suggest the possibility that a broad spectrum of physical stressors could induce and accelerate amyloidosis and tauopathy. Even from a molecular point of view, physical stressors may also influence the biological pathways of AD. The high-temperature environment favors the formation of tau fibril structures by providing enough time and space for peptides to rearrange during the aggregation process [99].

Physical stressors cause direct structural damage to neurons, initiating a secondary mechanism of stress signals involving inflammation and oxidative structural damage [100]. Oxidative stress can cause toxic effects by producing peroxides and free radicals that damage all components of the cell, resulting in a traffic of electrons

from one atom or molecule to another, a change in electric potential and hence energy. Accelerated senescence rat models (OXYS rats) show increasing mitochondrial aberrations and dysfunctions with age, which is followed by an accumulation of oxidative stress. Accumulation of Aβ deposits, hyperphosphorylation of the tau protein and neuronal loss was observed in the hippocampus and brain cortex. No plaque or neurofibrillary pathology was reported [101]. Spontaneous senescence accelerated mice models (SAMP8) show early oxidative damage, overproduction of Aβ with late amyloid plaques, phosphorylated tau (NFTs not reported), neuron loss, gliosis, and memory impairment [102]. Table 2 compares five hallmark features from transgenic, mechanical stress and metabolic rodent models of AD pathology. Amyloidosis, tauopathy, gliosis, neuronal loss or cognitive impairment could be present in at least four of the five mechanisms of mechanical stress selected.

Hypothesis behind AD pathology induced by mechanical stress

Effects related to endogenous mechanical energy in AD pathology have been widely overlooked in hypotheses involving a postulated molecular amyloido-centric pathway such as the amyloid cascade theory [106] derived from reductionistic transgenic animal mutation models that do not account for the principles of mechanics. A more complex picture seems to progressively replace the unitary view of AD as a disease with a single sequential pathological pathway. Independent pathological processes (Aβ, tau, and possibly others) may be influenced by independent and common risk factors [107]. A great number of AD biomarker studies have suggested that Aβ and tau-related pathologies may occur in parallel and their onset and rate could be under the influence of a series of environmental risk factors [107].

Several authors have already suggested the hypothesis that AD pathology is being driven by mechanical forces. Wostyn et al. and Silverberg et al. were the first to bring up the causative link between intracranial pressure and AD [108–112]. It has been shown that mechanical impedance (a measure of how much a structure resists motion when subjected to a given force) of the intracranial cavity and vessels plays a role in the pathophysiology of AD [113]. Some have set forth that the strength of the pulse waves induced by the vascular tree in the craniospinal cavity is the underlying vascular pathophysiology behind AD and other conditions like vascular dementia and NPH [114–117]. Barz et al. [118] set forth that mechanical changes accumulate in neuronal membranes and

cytoplasm in old age, in a similar fashion to how vessel walls stiffen and change in arteriosclerosis. With age, the impact of the hemodynamic pulses provided by the cerebral vasculature becomes increasingly destructive to brain parenchyma because of the age-related stiffening of the aorta, carotids and intracranial arteries [119].

Changing mechanical factors are not only related to tau-amyloid pathology but the reverse is also true, apparently AD pathology also changes the mechanical properties of brain tissues. Neurodegenerative disorders are characterized by the accumulation of very dense deposits that settle in the environment of cytoskeleton and in the extracellular matrix. In AD, these slow cumulative changes in the microarchitecture of the brain could impact its mechanical properties [120,121]. In general, biological tissues adapt to higher levels of stress by changing cross-sectional area, density, or volume. Another example of how they adapt consists in changes in the material properties of tissues. The elasticity and stiffness of the brain varies substantially in normal humans as well as with age and the state of the disease [12]. Cerebral stiffness, which can be measured by magnetic resonance elastography (MRE) [122], decreases when AD pathology is present in both humans and transgenic mice models [120,123]. MRE has also shown that it may have the merit of providing physical insights into a biological process.

The extent to which mechanical dynamics influence AD pathology and even normal aging remains a mystery. AD deposits could increase the resilience of neuronal tissues to mechanical stressors and consequently increase the tolerance to subsequent stresses. Like muscle fibers, neuronal tissues may adapt to physical stresses by altering their structure and composition to best meet the biological requirements of routine energy loads. As opposed to musculoskeletal tissues, the neuro-glial environment may have a very low tolerance to subsequent mechanical stresses. It raises the possibility that mechanical stress levels, which exceed the maintenance range of brain tissues, could trigger and accelerate protein misfolding, spreading/diffusion, aggregation, and deposition. Furthermore, continuous and repetitive exposure to environmental mechanical stress, mostly in an unnoticed manner, is inevitable in daily life and, thus, it becomes a potential driving force for the amyloid cascade. Tau-amyloid aggregates most likely constitute the end stage of a molecular cascade, whose earlier steps may be more directly related to pathogenesis than the deposits themselves [124]. The higher the exposure to mechanical stress, the more likely an early onset of the disease will be [125].

Conclusion and outlook

Various types of animal models can contribute to our growing understanding of the molecular pathways involved in developing and screening therapeutic targets in AD. The conclusions drawn from animal models largely depend on the validity of the model in representing the human condition. The perfect model would account for etiology, symptomatology, treatment, and physiological basis. Animal models in general do not meet all of these criteria. Nevertheless, the mechanical stress models described in this review may increase our knowledge of how different mechanical factors, from both the external and the internal environment, could influence pathophysiological mechanisms underlying AD. Beyond the scope of this review, methods and tools for studying mechanobiology have been proposed in order to test the influence of mechanical forces in neurodegenerative processes [12].

Newly developed treatment strategies have been tested in mechanical stress models of AD pathology. Hypertensive rats were used to assess the impact of N-acetil-cysteine [126], an antioxidant agent, and of Telmisartan [94], an angiotensin receptor blocker, on AD tau-amyloid pathology. A TBI model protocol shows a beneficial effect of lutein, a naturally occurring flavonoid, on reducing the charge of tau-amyloid deposits and inflammation in brain [127]. In another TBI model, post-injury treatment with lithium appears to alleviate the Aβ load and improve the spatial memory in mice [34]. Another relevant outlook is the development of animal models to enable future studies at the crossroads of mechanical stress-based diseases and AD research. TBI, NPH, vascular cognitive impairment, and AD will require early identification in the form of imaging or biomarkers to allow for therapeutic intervention at the earliest possible stages. These common features of AD and mechanical stressors stress the need to improve the primary prevention for head traumas and HTN in the general population.

Table 1: Mechanical stress-based models of AD pathology in rodents

Model	Examples of mechanisms	Amyloid pathology	Tau pathology	References
Traumatic brain injury	Controlled cortical impact, fluid percussion injury, weight drop / repetitive mild trauma, needlestick injury	Aβ diffuse, Aβ-related and plaque-like deposits No dense/mature plaques	P-tau and pretangle tau protein deposits. Mature NFTs not detected, except in mice expressing human tau isoforms.	[33–37,39–42,85]
Hypertension	Transverse aortic coarctation, spontaneously hypertensive stroke-prone rats.	"Plaque-like" accumulation characterized by extracellular ovoid cortical Aβ deposits and parenchymal eosinophilic material.	Phosphorylated tau intracellular deposits. No tangle/pretangle pathology.	[80,81,94]
Hydrocephalus	Cisternal kaolin injection	Small, medium and large Aβ42 granular accumulations. No plaque.	P-Tau granules, seemingly representing "excess p-Tau" inclusions. No tangle/pretangle pathology.	[68–74,95]

Table 2: Selected rodent models displaying AD pathological hallmarks

Rodent models	Transgenic			Mechanical stress						Metabolic
				Traumatic brain injury				HTN	HPN	Oxidative stress
	APP	Tau	APPxTau	CCI	FPI	NSI	rmTBI/WD			
Amyloidosis	++	-	+	++	+	+	++	++	+	++
Tauopathy	?[a]	++	+	++	+	+	+	+	+	+
Neuroinflammation	++	+	+	++	+	+	+	++	+	+
Neuronal loss	?[b]	?[b]	-	++	+	+	++	?[c]	+	++
Cognitive impairment	++	++	+	++	++	?	++	+	+	++
References	[4,8,9]		[4,8,9, 103]	[34,36,40,43,44, 84,89,104,105]	[37,42,45 ,46,86,87]	[39]	[36,40,47,59,60,93]	[80–82,94]	[68–78,95]	[101,102]

Comparison between transgenic, mechanical stress, and metabolic rodent models as a function of 5 hallmark features of AD pathology. **(+)** Feature present in mice or rat models. **(++)** Feature present in both mice and rat models. (-) Absence. (?) Unknown/uncertain evidence. (a) Only increased p-tau but no tau deposits. (b) Only present in a few models. (c) Only when associated with white matter and focal lesions. APP: Amyloid precursor protein. CCI: Controlled cortical impact. FPI: Fluid percussion injury. NSI: Needlestick injury. RmTBI: repetitive mild traumatic brain injury. WD: Weight drop. HTN: arterial hypertension. NPH: normal pressure hydrocephalus.

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