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Featured Article

Mechanical stress increases brain amyloid β, tau, and α-synuclein concentrations in wild-type mice

Marcel Levy Nogueira[a,b,c,e,*], Minoo Hamraz[d,e], Mohammad Abolhassani[d,e], Erwan Bigan[c,e], Olivier Lafitte[d,e], Jean-Marc Steyaert[c,e], Bruno Dubois[a,b,e,f], Laurent Schwartz[c,e]

[a]*Institut de la Mémoire et de la Maladie d'Alzheimer (IM2A), Département de Neurologie, Hôpital de la Pitié-Salpêtrière, AP-HP, Paris, France*
[b]*Institut de Recherche Translationnelle en Neurosciences (IHU-A-ICM), Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France*
[c]*Laboratoire d'informatique (LIX), UMR 7161, École Polytechnique, Université Paris-Saclay, Palaiseau, France*
[d]*Nosco Pharmaceuticals, Paris, France*
[e]*LAGA, UMR 7539, Université Paris 13, Sorbonne Paris Cité, Villetaneuse, France*
[f]*INSERM, CNRS, UMR-S975, Institut du Cerveau et de la Moelle Epinière (ICM), Paris, France*

Abstract

Introduction: Exposure to traumatic brain injury is a core risk factor that predisposes an individual to sporadic neurodegenerative diseases. We provide evidence that mechanical stress increases brain levels of hallmark proteins associated with neurodegeneration.

Methods: Wild-type mice were exposed to multiple regimens of repetitive mild traumatic brain injury, generating a range of combinations of impact energies, frequencies, and durations of exposure. Brain concentrations of amyloid β 1–42 ($A\beta_{1-42}$), total tau, and α-synuclein were measured by sandwich enzyme-linked immunosorbent assay.

Results: There was a highly significant main effect of impact energy, frequency, and duration of exposure on $A\beta_{1-42}$, tau, and α-synuclein levels ($P < .001$), and a significant interaction between impact energy and duration of exposure for $A\beta_{1-42}$ and tau ($P < .001$), but not for α-synuclein.

Discussion: Dose-dependent and cumulative influence of repetitive mild traumatic brain injury–induced mechanical stress may trigger and/or accelerate neurodegeneration by pushing protein concentration over the disease threshold.

Keywords: Alzheimer's disease; Parkinson's disease; Animal models; Mechanical stress; Repetitive mild traumatic brain injury; Amyloid; Tau; α-synuclein

1. Background

While aging is the greatest risk factor for dementia, several pieces of evidence suggest that exposure to traumatic brain injury (TBI) increases the likelihood of developing neurodegenerative diseases later in life, including Alzheimer's disease and Parkinson's disease [1,2]. A common denominator among these neurodegenerative disorders is the abnormal accumulation of misfolding proteins, such as 42 amino acid-long form of the amyloid β peptide ($A\beta_{1-42}$) and tau protein, hallmark proteinopathies of Alzheimer's disease [3], and α-synuclein, a key neurodegenerative biomarker in Parkinson's disease. First described nearly a century ago in boxers as "punch drunk" or "dementia pugilistica" [4], chronic traumatic encephalopathy is a progressive neurodegeneration characterized by a widespread brain deposition of Aβ, tau, and α-synuclein [5–7]. The frequent association found between chronic traumatic encephalopathy and other neurodegenerative disorders suggests that repetitive mild TBI (rmTBI), the most common form of head injury in humans, can promote the accumulation of multiple proteins

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*Corresponding author. Tel.: +33 1 42 16 75 67; Fax: +33 6 42 16 75 41.

E-mail address: marcel.levy@psl.aphp.fr

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and trigger the development of TBI-induced neurodegenerative disease [8].

As it remains unclear how abnormal protein accumulation after TBI relates to the reported increased risk of Alzheimer's disease and Parkinson's disease, we speculate on the potential relevance of mechanical stress triggering neurodegeneration as a direct consequence of cascades initiated at the time of impact, reflected by initial changes in Aβ, tau, and α-synuclein concentrations in brain tissues [9]. Preclinical rmTBI studies using transgenic mice models of amyloidosis or tauopathy produce elevated brain $A\beta_{1-42}$ or tau levels, respectively, with increased protein deposition [10,11]. To further elucidate how mechanical stress triggers neurodegeneration, we propose an rmTBI-induced mechanical stress model that can significantly increase brain levels of multiple proteins associated with the development of neurodegenerative diseases. To this end, we expose wild-type BALB/c mice to multiple paradigms of rmTBI using a weight-drop mechanism [12] and long-term exposure to mechanical stress. Post-injury brain levels of $A\beta_{1-42}$, tau, and α-synuclein were measured by sandwich enzyme-linked immunosorbent assay (ELISA).

2. Methods

2.1. Animal care and maintenance

The subjects of these experiments were 5 to 6-week-old male BALB/c mice, weighing 19–24 g (n = 156; Nosco Pharmaceuticals, Paris, France). Animal handling and experimentation were performed in accordance with the European Community's guidelines regarding the care and use of laboratory animals. Mice were housed in a vivarium (10 per cage) under a 12 h light/12 h dark cycle and given access to pellet food and water *ad libitum*. Mice were allowed to adapt to the vivarium for at least 1 week before the experimental procedures. They were randomized into injured and sham mice groups (six mice per group). After the injury, animals were rapidly returned to their home cages for recovery.

2.2. Mechanical stress model of rmTBI

To assess the impact of mechanical stress on changes in brain levels of Aβ, tau, and α-synuclein, a mice model of human rmTBI was used as previously described [13,14]. Animal models of rmTBI approximate the conditions associated with repeated concussion encountered in contact sports [14]. Major modifications were implemented to test multiple injury paradigms in mice [12] without causing skull fracture, intracranial bleeding, or seizures [14] after long-term exposure to injury. The essential components and overall arrangement of the rmTBI apparatus consist of a simple weight-drop device illustrated in Fig. 1. Animals were placed into 50-mL conical polypropylene tubes, 30 mm in diameter and 115 mm in length, and featuring an opening of ~1 × 1 cm, large enough to allow for ventilation and exposure of the cranial scalp. The head was positioned at the cone end [15], subtending a narrow angle of 60° that restrained head mobility. At the caudal end of the tube, a flat-top screw cap restrained the mouse from moving, and a hole kept the tail out of the tube. The head and body were thus carefully stabilized, obviating the need for anesthesia [16]. The tube was held by a frame and placed at an angle, so that the midline of the scalp was perpendicular to a vertical hollow guide tube 17 mm in caliber placed right above it. The falling weights consisted of stainless steel marbles weighing 13.5 or 20 g that were dropped vertically through the hollow guide tube, 20 or 40 cm in height, delivering the impact to the dorsal aspect of the skull.

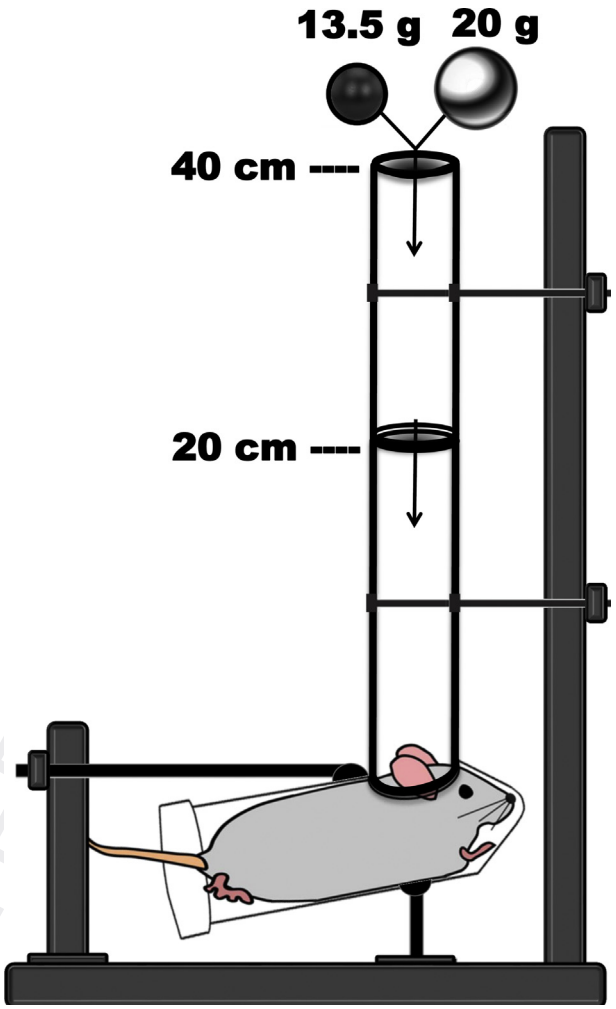

Fig. 1. Schematic illustration of the weight-drop device showing the essential components of the apparatus that comprised a vertical guide tube for the dropped weight situated above the mouse stage. Mice were restrained in a 50-mL conical polypropylene tube of 30 mm in diameter and 115 mm in length equipped with an ~1 × 1 cm opening large enough to expose the cranial scalp. The falcon tube was held by a frame and oriented at an angle, so that the scalp midline was perpendicularly oriented under a vertical hollow guide tube. Stainless steel marbles of 13.5 or 20 g drop vertically through the path of the hollow guide tube of 20 or 40 cm in height delivering the impact to the dorsal aspect of the skull.