Micromechanics of brain tissue measured with atomic force microscopy in Alzheimer's disease mouse model

Maria José Menal[1,#], Ignasi Jorba[1,2,#], Isaac Almendros[1,3,4], Ramon Farré[1,3,4], Daniel Navajas[1,2,3,*]

[1]Unitat Biofísica i Bioenginyeria, Facultat de Medicina, Universitat de Barcelona, Barcelona, Spain.

[2]Institut de Bioenginyeria de Catalunya, Barcelona, Spain.

[3]CIBER de Enfermedades Respiratorias, Madrid, Spain.

[4]Institut Investigacions Biomediques August Pi Sunyer, Barcelona, Spain.

[#]Contributed equally to this work.

*Corresponding author: Daniel Navajas, dnavajas@ub.edu

Introduction

Cells sense and respond to the mechanical properties of their microenvironment. Several diseases including cancer and fibrosis are associated with alterations of tissue stiffness. However, stiffness changes in brain diseases remains poorly known. Alzheimer's disease (AD) is the most prevalent neurodegenerative disease and the first cause of dementia worldwide, being a considerable public health problem. Preliminary results obtained by Magnetic Resonance Elastography (MRE), a non-invasive technique based in externally exploring the whole organ, suggest that brain tissue stiffness is reduced in AD. Nevertheless, MRE estimation of tissue stiffness is indirect since it requires the use of invers-model based algorithms mapping the 3D structure of the whole organ. To date there are no data providing a direct measure of brain tissue stiffness in AD. The aim of the study was to directly measure and compare the local stiffness of the brain cortex of AD-mutant and normal mice by using atomic force microscopy (AFM).

Materials and methods

Mice (6-8 month old) bearing a mutation (APPswe/PSEN1dE9) mimicking human AD and their littermates wild type (N=8 and N=9, respectively) were investigated. After anesthesia and euthanasia by exsanguination, the brain was excised and 200-micron coronal slices were cut with a vibratome. As previously described in detail [1], brain slices were subjected with a 3D printed ring with a compliant mesh (2 mm spacing) of silicone thread (0.2 mm in diameter) (Fig. 1) and placed on the stage of a custom-built Atomic Force Microscope to measure the local stiffness of the cortex. Force-indentation curves were obtained with a 25 µm diameter polystyrene bead glued to the end of a tipless cantilever (nominal spring constant k= 0.01 N/m). The Young's modulus (E) of the cortex in each animal was computed as the median from 9 randomized force-indentation curves.

Results

E [median (IQR)] of the cortex in AD-mice was considerably reduced as compared with the stiffness of their wild type littermates: 325 (194-513) Pa and 666 (416-985) Pa, respectively. This difference was statistically significant (Mann-Whitney analysis, p-value=0.049).

Discussion

Mice having the APPswe/PSEN1dE9 mutations, which develop an AD-like phenotype, show a significant decrease in local cortical stiffness. These local measurements by AFM provide a direct evidence of previous indirect estimations by MRE and pave the way for studying the mechanisms determining brain tissue mechanics in AD.

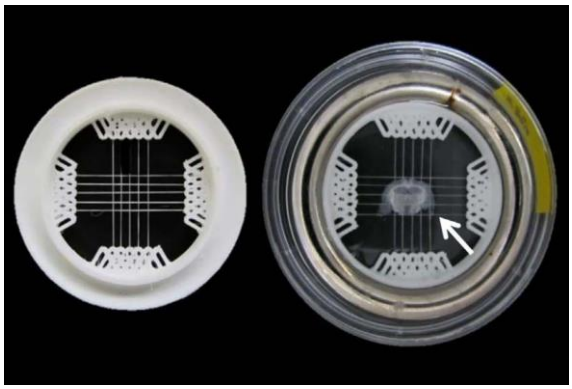

Figure 1. Customized mesh-system to subject the brain tissue slices (white arrow) on the surface of the Petri dish.

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[1] Jorba I, Menal MJ, et al. J Mech Behav Biomed Mater. 71:106-113 (2017).