

2023 Annual Research Day – Oral session
April 19th, 2023, 2:00 p.m. – 4:30 p.m., PHAB 2A

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Enzymatic Removal of Hyaluronan Slows Down Extracellular Diffusion of Molecules With Physiologically Relevant Sizes in Mouse Brain

Brain extracellular space (ECS) serves as a pathway for transport of many biological molecules like neurotransmitters, neuromodulators, proteins, as well as therapeutics. This transport primarily happens via diffusion. Hyaluronan (HA) is a major component of the extracellular matrix, and it was reported that enzymatic removal of HA enhances the diffusion of 490-780 nm long thread-like carbon nanotubes through the ECS (Godin et al, 2017). However, many physiologically relevant molecules and therapeutics that diffuse through the ECS are smaller, typically less than 15 nm in diameter. In this study, we have investigated the effect of enzymatic removal of HA on the diffusion of molecules with sizes in the physiologically relevant range of 0.5 to 12 nm. Contrary to the carbon nanotubes, diffusion of molecules used in this study was more hindered after HA depletion in the mouse somatosensory cortex, both in the acute brain slices and in vivo. Moreover, this HA depletion led to an increase in the ECS volume by 50%. The enzyme used to cleave HA was specific to HA, and yet, enzymatic HA depletion also led to a partial loss of other extracellular matrix molecules that are bound onto the HA scaffold. In conclusion, the molecules used in this study were more hindered despite an increase in the space available for their diffusion after HA depletion and the associated matrix changes. The contradictory results for the small molecules used in this study and the large carbon nanotubes highlight a size-dependent effect of HA on the diffusional transport of molecules through the ECS. Together, these results indicate that the HA-based extracellular matrix has a role in maintaining extracellular transport of biologically important molecules, like neurochemicals and therapeutics. These intriguing findings can potentially provide new insights into the changes in cellular communication and drug delivery in some neuropathologies that involve the breakdown of HA-based matrix.