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**Hyaluronan is involved in maintaining the volume of brain extracellular space and diffusion of small molecules**

Hyaluronan (HA) is a ubiquitous, long, linear, and highly hydrated extracellular matrix molecule, which is known to hinder the diffusive spread of molecules in the skin tissue, owing to its intricate mesh-like arrangement in the extracellular space (ECS). Even in the brain ECS, HA forms a meshwork and other matrix molecules are attached onto the HA scaffold. This meshwork is arranged in the narrow pores between brain cells. Due to its large size, intrinsic ability to occupy a large volume and other matrix molecules attached to it, we hypothesized that HA can affect the volume available for diffusion in the narrow pores of the brain ECS. We also hypothesized that the HA meshwork can hinder diffusion in the brain ECS, based on its role in the skin ECS. We tested these hypotheses by measuring ECS volume available for diffusion and the hindrance experienced by diffusing molecules in the mouse somatosensory cortex, following cleavage of HA by hyaluronidase. As hypothesized, the ECS volume available for diffusion was affected by removal of HA— it significantly increased by 50%. Surprisingly, as the available volume increased after HA cleavage, the diffusion of molecules with diameters less than 1 nm became even more hindered, while the diffusion of other molecules (with diameters ranging from 1-12 nm) was unaffected. These results point to a more complex role of HA in the brain ECS. HA appears to be important in maintaining the volume available for diffusion and seems to be essential for supporting diffusion of small molecules— possibly by formation of low-hindrance tunnels with small diameters within the meshwork that can be accessed only by small molecules. Thus, the presence of HA matrix could be critical for functionally appropriate diffusion of ions and small neurotransmitters in the brain tissue.