Erasure of Neural Extracellular Matrix to Ameliorate Aging-Dependent Cognitive Decline

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The proportion of the world's population aged 65 years and older is expected to double from 8% to 16% within the next 35 years. This is expected to result in a concomitant increase in aging-related disorders, such as cognitive decline, which affects executive function, e.g. working memory, reference memory, motor skill learning, and mental flexibility. Aging- related decline in neural plasticity may underlie cognitive decline. In the brain the neural extracellular matrix (ECM) accumulates in an aging-dependent manner and is a critical regulator of plasticity. Thus, targeting the neural ECM may be a viable strategy to attenuate aging-related cognitive deficits. We hypothesize that modulation of neural ECM via pharmacologic methods can reverse the decline in plasticity associated with aging. We have shown that aged mice (22 months) have significant impairments in motor skill learning, working memory, adaptive learning, and reference memory compared to their younger counterparts (7 months). Intrastriatal injections of chondroitinase ABC (ChABC), an enzyme that degrades ECM chondroitin sulfate proteoglycans, can improve motor skill learning and reference memory in aged mice.

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