Therapeutic Effects of Arachidonoyl Methionine on Cerebral Edema and Fiber Density across Neurodegenerative Contexts

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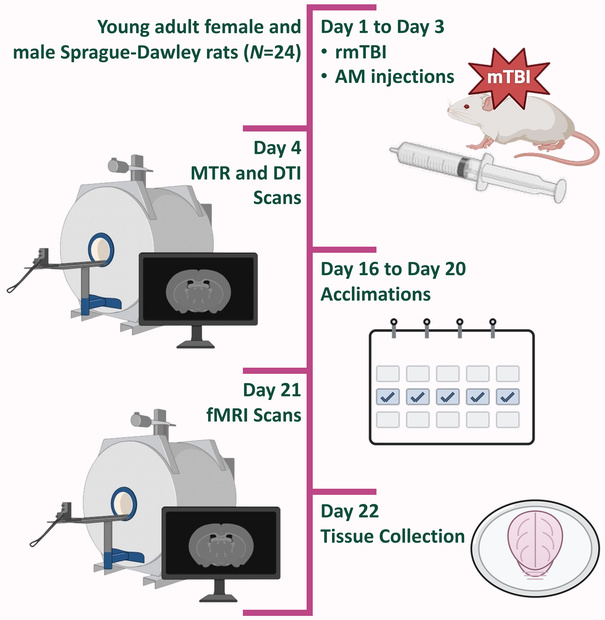
Introduction

Repetitive mild traumatic brain injury (rmTBI) is a leading risk factor for later neurodegeneration, yet no treatment addresses its acute microstructural and vascular consequences.

Our lab has shown that psilocybin (PSI), a 5-HT_{2a} agonist, reduces cerebral edema, restores cerebrovascular reactivity and strengthens functional connectivity after rmTBI in female rats. Screening 87 small signaling lipids across multiple cohorts, arachidonoyl methionine (AM), an endogenous lipoamino acid, was the single most robustly affected molecule, falling three-fold after injury and returning to control levels after PSI in both middle-aged and older adult animals.

That AM tracks the therapeutic effect so closely raises the question of whether it marks recovery or mediates it. We hypothesized that AM alone reproduces the effects of PSI as a non-hallucinogenic alternative for rmTBI in young adults and Alzheimer's disease in older adults.

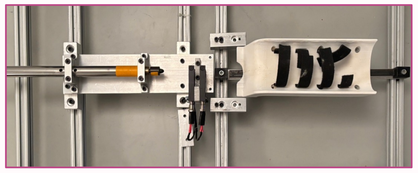
Experimental Design

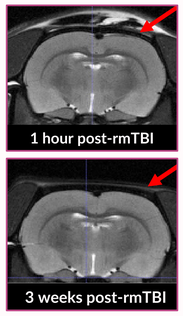


Momentum Exchange Model

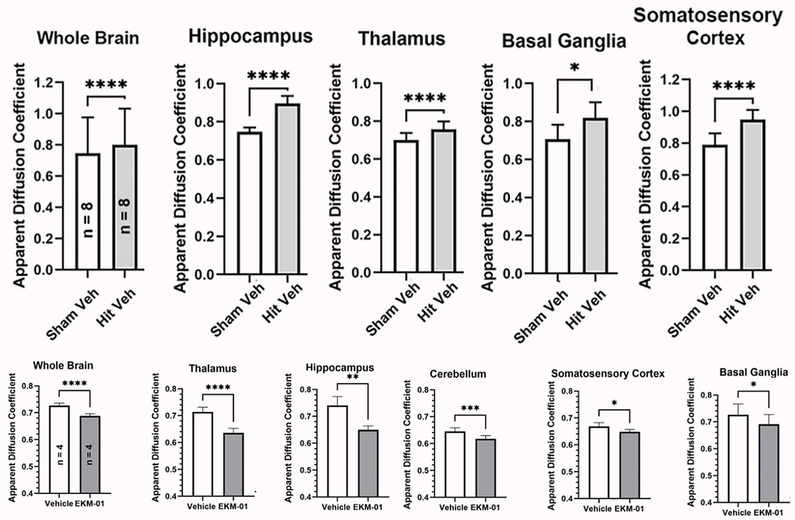
The momentum exchange method ranks highly among preclinical mTBI models in translational value for its ability to generate tightly regulated, ecologically valid closed-head injury in awake, active-phase rats. Upon impact (7.4 m/s), the cradle accelerates backward along its track, so the head is free to move as forces resemble those of a human concussion rather than a fixed-skull severe traumatic brain injury.

Radiography indicates no skull fracture or gross anatomical damage. Edema of the tissue overlying the skull at the site of impact is shown on the third day of rmTBI.



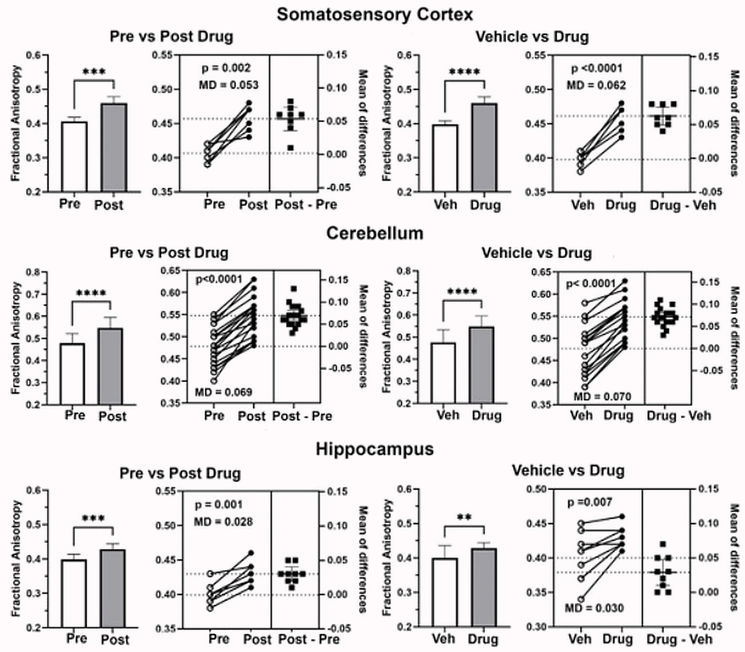


AM reduces cerebral edema after rmTBI



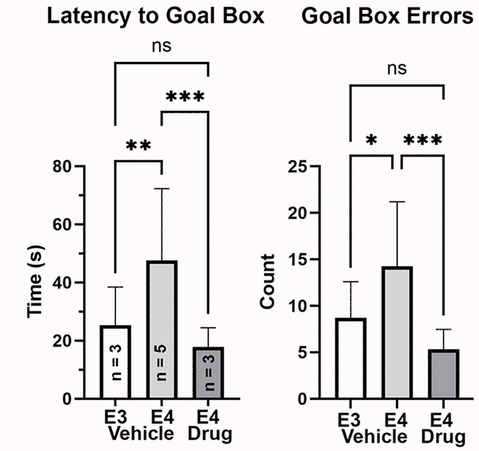
Apparent diffusion coefficient on Day 4, a proxy for free water and therefore for vasogenic edema. **Top:** rmTBI raised ADC above sham in whole brain, hippocampus, thalamus and somatosensory cortex (****) and basal ganglia (*), *n*=8. **Bottom:** AM lowered ADC against vehicle in whole brain and thalamus (****), cerebellum (***), hippocampus (**), somatosensory cortex and basal ganglia (*), *n*=4.

AM increases fiber density in older adult APOE4 knock-in rats

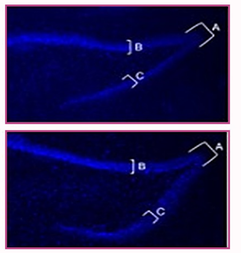


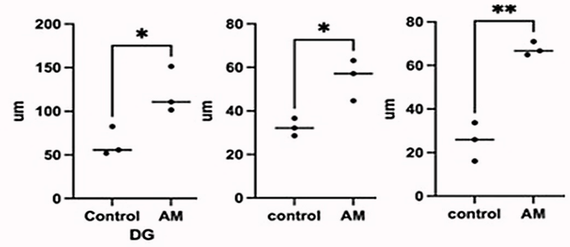
Fractional anisotropy in older adult APOE4 knock-in rats, pre versus post drug (**top**) and vehicle versus drug (**bottom**). Higher FA indicates more directionally coherent fibers. Brain areas comprising the cerebellum showed the largest effect, with mean difference 0.069 and 0.070, both p<0.0001 (paired t-test), then somatosensory cortex (0.053, p=0.002; 0.062, p<0.0001) and hippocampus (0.028, p=0.001; 0.030, p=0.007).

AM improves spatial memory and dentate gyrus thickness in older adult APOE4 knock-ins



Left: Barnes maze, a hippocampus-dependent spatial task. E4 vehicle took roughly twice as long to reach the goal box as E3 vehicle (48 s versus 25 s, **, unpaired t-test) with more errors (14 versus 9, *). AM returned both to E3 levels, at 18 s and 5 errors, better than E4 vehicle (***) and not different from E3 (ns). **Below:** dentate gyrus thickness nearly doubled with AM (57 to 110 µm, *), with gains in two further subregions (*, **); *n*=3/group.





Discussion

While AM treatment alone is not sufficient to reproduce the robust neuroplastic effects of PSI, it may have age- and sex-dependent benefits, particularly for older females.

Cerebral Edema: DWI indicates vasogenic edema is induced by Day 4 after rmTBI, and that AM lowers ADC against vehicle in every region measured. Edema is therefore the component of the psilocybin profile that AM reproduces.

Fiber Density: DWI indicates fractional anisotropy is elevated by AM in aged APOE4 knock-ins, both within animals and relative to vehicle. The effect was greatest in the cerebellum ($p<0.0001$), followed by the somatosensory cortex ($p<0.0001$) and hippocampus ($p=0.007$).

Functional Imaging: In prior cohorts PSI restored connectivity beyond control levels in prefrontal cortex, basal ganglia, hippocampus and the midbrain dopaminergic system; AM produced no comparable reorganization. Further research will be needed to determine whether this was the result of an unexplored sex difference.

Limitations: The drug comparison rests on four animals per group, the APOE4 cohort on three to five, and the MTR analysis of in vivo myelination remains ongoing.

Future Directions

Remaining work will complete the MTR analysis to test whether AM elevates myelination; explore the sex-dependence of the edema finding in a powered mixed-sex cohort; establish whether a cerebrovascular overshoot exists and whether it carries a functional cost; examine protein markers of neurodegeneration, neuroinflammation and neuroplasticity; and test AM against PSI directly in aged APOE4 animals.

Acknowledgements

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