Mitophagy was impaired after rotenone exposure, as TOM-20 levels increased 40% indicating mitochondria accumulation, whereas physical training during early neurodegeneration prevented that increase. PINK1 levels showed a tendency of decrease in substantia nigra of aged rats exposed to rotenone, which was not present in exercised rats. Physical activity also prevented H2O2 increase during early neurodegeneration, although the mechanism involved remains to be elucidated, since the antioxidant enzymes evaluated did not changed. TrkB levels and its anterograde trafficking in substantia nigra seem not to be influenced by moderate treadmill running during early neurodegeneration. In conclusion, moderate physical training could prevent early neurodegeneration in substantia nigra through the improvement of autophagy and mitophagy.

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Board Number: B476

Decoupling the effect of mutant amyloid precursor protein (APP) from the effect of plaque on axonal transport dynamics in the living mouse brain: A correlation MRI-microscopy study.

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The parent protein for amyloid plaques, amyloid precursor protein (APP), mediates cargo-motor attachments for intracellular transport. Axonal transport is decreased and the distal location of accumulation is altered in transgenic mice expressing human APP with the Swedish and Indiana mutations (APPSwInd) linked to Familial Alzheimer's Disease, as detected by time-lapse magnetic resonance imaging (MRI) of transport in living mouse brains (Bearer et al. 2017). Transport is also altered in brains of Down syndrome mice with 3 copies of APP gene. Questions now become whether expression of mutated APP effects transport dynamics independent of plaque, and do plaques alone contribute to transport defects? To address these we used the Tet-Off system to decouple expression of APPSwInd from presence of plaques, and then studied transport using our MRI technique in three experimental groups of transgenic mice in which the timing and duration of APPSwInd expression, and thereby plaque formation, was altered with doxycycline: Group A (+ plaques, + APPSwInd); Group B (+ plaques, no APPSwInd), and group C (no plaques, + APPSwInd). Manganese-enhanced MRI (MEMRI) allows us to perform cell biological experiments in live animals with T1-weighted MRI in a Bruker 11.7T scanner (Medina et al 2016). Time-lapse MR images were captured before and after stereotactic injection of Mn2+ (3-5nL) into CA3 of the hippocampus at successive time-points. Images of multiple individuals were aligned and processed with our automated computational pipeline (Medina et al. 2017) and statistical parametric mapping (SPM) performed. After MRI brains were harvested for histopathology or biochemistry. Results show that within group between time-point have altered transport locations as well as diminished transport in all groups compared to wildtype ($p<0.05$ FDR n= 36). Preliminary ANOVA between-group comparisons both by SPM and by region of interest measurements of images support the visual impression that APPSwInd expression alone may compromise transport. Groups A and B displayed plaques, but not C, and Western blots showed APPSwInd expressed 3.2-fold over normal at sacrifice in Groups A and C but not B, with Aβ detected only in Groups A and B, where phospho-tau was also present in dystrophic neurites surrounding plaques. Cholinergic neurons that project to hippocampus from the medial septal nucleus were decreased in Group C ($p=0.0006$ by ANOVA, n=15). Isolated hippocampal vesicles contained Mn2+, as well as Trk (NGF receptor), Rab 5 and 7 (associated with transport vesicles), suggesting a distinct vesicle population is

affected by these APP mutations. These surprising results implicate mutated APPSwInd in transport defects, separable from the effect of plaque. Supported NS062184 and MH096093.

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Transcription derepression of Fuz triggers apoptosis and contributes to polyglutamine neurodegeneration.

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Planar cell polarity (PCP) describes a cell-cell communication process through which individual cells coordinate and align on a tissue plane. In this study, we demonstrated that overexpression of Fuz, the human orthologue of the Drosophila melanogaster PCP gene fuzzy (fy), triggered neuronal apoptosis via the Dishevelled (Dvl)/Rac1 GTPase/MEKK1/JNK/caspase signalling axis. We further discovered that endogenous Fuz expression was upregulated in patients with spinocerebellar ataxia type 3 (SCA3), one of nine polyglutamine (polyQ) neurodegenerative disorders. Interestingly, Fuz gene induction was consistently observed in models of other polyQ diseases, including Huntington's disease. And downregulation of Fuz expression rescued polyQ-associated cytotoxicity, and neurodegeneration in Drosophila. At a mechanistic level, we demonstrated that the transcriptional regulator Yin Yang 1 (YY1) associates with Fuz promoter, such that overexpression of YY1 caused hypermethylation of Fuz promoter, leading to transcriptional repression of Fuz. Soluble YY1 protein level was reduced in polyQ diseases. Such reduction perturbed the function of YY1, and led to induction of Fuz expression followed by neuronal apoptosis. In summary, our findings unveil a polyQ pathogenic pathway that involves YY1-mediated Fuz induction-promoted apoptotic cell death in polyQ diseases. Targeting this novel pathway may be of therapeutic potential.
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GPRC6A signaling impacts mTORC1 activation and tau clearance.

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Tauopathies are a group of neurodegenerative diseases characterized by pathognomonic protein inclusions formed by abnormal accumulation of microtubule-associated protein named tau. Clinical phenotypes of tauopathies manifest as cognitive impairment and behavioral disturbance. The aggregation of tau remains a central target for drug discovery, however no disease-modifying treatments exist. The mechanistic target of rapamycin (mTOR) signaling has emerging evidence in regulating cellular proteostasis through the uncovered cytosolic and lysosomal L-arginine sensing pathways. Our group has previously discovered a unique interaction between tau aggregation and mTOR signaling linked to L-arginine metabolism. In both human Alzheimer's disease patient samples and tau transgenic mice, we observed dysregulated L-arginine metabolism and uncoupled mTOR signaling proteins associated with tau pathology. G protein coupled receptor family C, group 6 member A