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Ghalayini's journal club captures the gist of our recent study tying neuronal PTP1B activation with neurodegeneration and cognitive decline in the hAPP-J20 mouse model of Alzheimer's disease (Ricke et al., 2020). We agree that neuronal PTP1B activation likely affects BDNF signaling in this model. Although we did not specifically pursue this angle in the Ricke et al. paper, we have just reported that mice lacking the endogenous inhibitor of PTP1B, the small LIM domain only protein LMO4 in glutamatergic neurons have impaired signaling through the BDNF receptor trkB and deficits in trkB-dependent endocannabinoid signaling (Qin et al., 2020). A key unanswered question in the Ricke et al. (2020) study is how expression of mutant human amyloid protein in the hAPP-J20 mice activates PTP1B in neurons. PTP1B is an endoplasmic reticulum (ER)-tethered enzyme that associates with and is inhibited by LMO4 through a mechanism that involves palmitoylation of the C-terminus of LMO4 and its retention at the ER (Pandey et al., 2013). Palmitoylation of amyloid precursor protein is also required for the generation of β -amyloid (Bhattacharyya et al., 2013). Might the expression of mutant amyloid precursor protein affect palmitoylation of LMO4 and thereby prevent its interaction with and inhibition of PTP1B? Alternatively, mutant amyloid precursor protein could trigger an ER stress response, and this could suffice for PTP1B activation. In any case, restoring PTP1B inhibition has therapeutic potential to limit the progression of Alzheimer's disease, at least in the hAPP-J20 mouse.

Bhattacharyya R, Barren C, Kovacs DM (2013) Palmitoylation of amyloid precursor protein regulates amyloidogenic processing in lipid rafts. *J Neurosci* 33:11169-11183.

Pandey NR, Zhou X, Qin Z, Zaman T, Gomez-Smith M, Keyhanian K, Anisman H, Brunel JM, Stewart AF, Chen HH (2013) The LIM domain only 4 protein is a metabolic responsive inhibitor of protein tyrosine phosphatase 1B that controls hypothalamic leptin signaling. *J Neurosci* 33:12647-12655.

Qin Z, Zhang L, Cruz SA, Stewart AFR, Chen HH (2020) Activation of tyrosine phosphatase PTP1B in pyramidal neurons impairs endocannabinoid signaling by tyrosine receptor kinase trkB and causes schizophrenia-like behaviors in mice. *Neuropsychopharmacology*.

Ricke KM, Cruz SA, Qin Z, Farrokhi K, Sharmin F, Zhang L, Zasloff MA, Stewart AFR, Chen HH (2020) Neuronal Protein Tyrosine Phosphatase 1B Hastens Amyloid beta-Associated Alzheimer's Disease in Mice. *J Neurosci* 40:1581-1593.