Stimulation of ET_B receptors with IRL-1620 improves both acquisition (learning) and retention (memory) on water maze task in APP/PS1 transgenic mice. IRL-1620 enhances the expression of neurogenic and synaptogenic markers by maintaining mitochondrial dynamic balance leading to functional recovery.

P4-505 SIRT1 ENHANCES AUTOPHAGIC RESPONSE AND NON-AMYLOIDOGENIC PROCESSING OF APP IN OLIGOMERIC $A\beta_{1-42}$ INDUCED RAT MODEL FOR ALZHEIMER'S DISEASE

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Background: Epigenetic mechanism has been widely discussed in etiopathology of metabolic disorders like Diabetes. However, epigenetics in neurodegeneration is least studied. SIRT1, a homeostatic regulator and widely known epigenetic factor seems to be suppressed in conditions like Alzheimer's disease. Deficient SIRT1 is closely associated with Aβ accumulation and disease progression that results in synaptic dysfunction. Therefore, the current study tends to observe the effect of Resveratrol (RSV) mediated SIRT1 activity on altered epigenetic regulation on major pathways like APP metabolism and autophagy gene response in oligomeric Aβ (oAβ_{1-42}) induced rat model for AD. **Methods:** Oligomeric Aβ_{1-42} (oAβ_{1-42}) was injected bilaterally (bregma: -4.0mm, mediolateral: ± 3.0mm and dorsoventral: -3.6mm) into the hippocampus of adult rats using stereotaxic surgery, following intraperitoneal administration of resveratrol (RSV), 30 mg/kg body weight for 14 days. The mRNA expression of Sirtuins (1-7) and autophagy regulated genes (ATG5, 6, 7, 12, 16L1), mTOR and BACE1 level were analysed using RT-PCR analysis. ADAM10, BACE1, PS1 & 2, GSK3β and SIRT1 levels were measured in hippocampal tissue of rat brain using Western blotting analysis. **Results:** Single Intra-hippocampal injection of oAβ_{1-42} impaired the Sirt1, 4 and 7 mRNA levels and autophagy regulated genes with a simultaneous decrease in ADAM10 expression in hippocampus of adult rats. Further oAβ_{1-42} increased the expression of BACE1 mRNA and protein levels, with increasing extracellular accumulation of Aβ in hippocampus and entorhinal cortex. Resveratrol administration caused significant increase in autophagy related genes, include Atg5, 6 and 7 mRNA levels depicting positive epigenetic mechanism of SIRT1 in preventing Aβ accumulation. Interestingly, SIRT1 activation increased α-secretase activity, decreasing BACE1 and GSK3β expression that facilitate non-amyloidogenic processing of APP. **Conclusions:** Present study concludes that RSV mediated SIRT1, facilitated autophagic response and provoked non-amyloidogenic processing of APP through epigenetic regulation.

P4-506 ROLE OF P38α MAP KINASE IN AMYLOID-β DERIVED DIFFUSIBLE LIGAND (ADDL) INDUCED DENDRITIC SPINE LOSS IN HIPPOCAMPAL NEURONS

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Background: We recently described a p38 MAP kinase-dependent synaptotoxic signaling pathway that is activated by prions (Fang et al. 2018, PLoS Pathog. 14:e1007283). Although there is evidence that p38 MAPK also plays a role in the toxicity of Aβ oligomers (Birnbaum et al, 2015, Cell Death Dis, 18;6:e1791), we reported previously that a non-selective chemical inhibitor of all four p38 isoforms (SB239063) did not prevent dendritic spine retraction caused by synthetic ADDLs (Fang et al. 2018). To further explore the relationship between p38 activation and ADDL-induced synaptotoxicity, we evaluated the effect of neflamapimod (VX-745), a selective inhibitor of the α isoform of p38 MAPK (p38α), on ADDL-induced spine degeneration in cultured hippocampal neurons. **Methods:** Primary mouse hippocampal neurons were treated with 500 nM ADDLs and 0, 10, 50 or 100 nM concentrations of neflamapimod for 24 hrs, and were then fixed, and spine number was quantitated after staining with Alexa 488-labeled phalloidin to visualize F-actin (which is enriched in dendritic spines). We chose neflamapimod because it is a highly selective p38α inhibitor that improved Morris water maze performance in aged rats (Alam 2015, J. Alzheimers Dis. 48:219-227); and it demonstrated potential to improve episodic memory function in early AD patients (Scheltens et al. 2018 Ann. Clin. Transl. Neurol. 5:464-473). As a positive control, we conducted a dose-response analysis of neflamapimod for its ability to prevent spine retraction induced by purified PrP^{Sc}, the infectious form of the prion protein. **Results:** Neflamapimod reduced ADDL-induced spine retraction starting at the lowest concentration tested (10 nM) and fully blocked the effect at 50 nM (see Figure 1). Consistent with our previous report (Fang, et al. 2018), neflamapimod reduced dendritic spine retraction after exposure to PrP^{Sc} starting at 25 nM, and fully blocked spine retraction at 100 nM (EC_{50}=30 nM). **Conclusions:** The results suggest that Aβ oligomers and PrP^{Sc} may trigger overlapping synaptotoxic signaling pathways that have in common activation of p38α MAP kinase. The results of an ongoing placebo-controlled clinical trial of neflamapimod in patients with early AD, which has episodic memory as a primary endpoint, may inform on the clinical translatability of our findings.

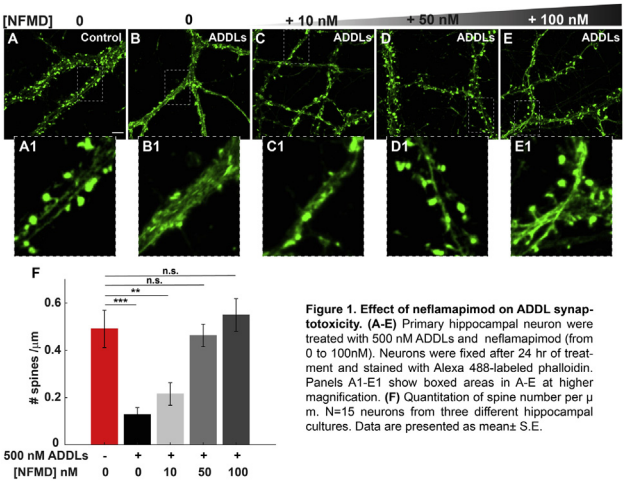

Figure 1. Effect of neflamapimod on ADDL synaptotoxicity. (A-E) Primary hippocampal neuron were treated with 500 nM ADDLs and neflamapimod (from 0 to 100nM). Neurons were fixed after 24 hr of treatment and stained with Alexa 488-labeled phalloidin. Panels A1-E1 show boxed areas in A-E at higher magnification. **(F)** Quantitation of spine number per µm. N=15 neurons from three different hippocampal cultures. Data are presented as mean± S.E.

P4-507 INHIBITORY EFFECT OF RECEPTOR PROTEINS ON Aβ AGGREGATION PROCESS

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