critical branch-point, which dictates several outcomes: nitric oxide generation from nitric oxide synthases (NOS) or polyamine production from arginine (Arg1). Several reports show that nitration of tau impacts tau metabolism and increases aggregation, thus biasing one or more pathways may dictate tau fate. Depletion of arginine may also lead to increased autophagy through amino acid sensing. **Methods:** Utilizing gene therapy (adeno-associated virus), cellular, animal models of tauopathy (rTg4510 and PS19 mice), and recombinant protein experiments we tested each of these potential mechanisms: 1) decrease tau nitration (**shiftinig arginine metabolism away from the NOS pathway**); 2) arginine depletion (and activation of autophagy); and 3) polyamine production. **Results:** We find dysregulation of the polyamine pathway in tau transgenic mice. Our data indicates that Arg1 overexpression in mouse models of tauopathy reduces the many aspects of the tau phenotype including reduced phospho-tau and nitrated tau, reduced tangle pathology, reduced atrophy, reduced high molecular weight tau, reduced markers of inflammation, reduced inhibitors of autophagy, and reduced protein kinase activation. We find similar outcomes in cell lines overexpressing tau with parallel Arg1 manipulations. Importantly, we identified that higher-order polyamines at physiological concentrations directly block tau aggregation and facilitate tubulin polymerization but acetylated forms fail to mimic this affect. **Conclusions:** These data suggest arginine metabolism and the polyamine pathway as therapeutic targets that may arrest or slow the progression of the tau pathology in models of tauopathies.

**P3-049**

**EFFECTS OF REHABILITATION TRAINING ON THE ALTERATION IN TAU MODIFICATION BY PHOTOTHROMBUSA-INDUCED ISCHEMIC STROKE**

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**Background:** Ischemic stroke is one of the leading causes of disability and a cause of vascular dementia. Physical rehabilitation is an important intervention for functional recovery and helps to realign the affected part of brain by ischemic stroke. However, studies for the relationship between ischemic stroke and Alzheimer’s disease (AD) pathology and for the effects of rehabilitation on the AD-related protein expression in stroke region are limited. **Methods:** Focal cortical infarction was induced by photothermrobus using Rose Bengal dye in the dominant side of sensorimotor frontal cortex. One group of infarcted rats housed in standard cages received once daily session of rehabilitation by single pellet reaching training of the dominant forelimb for four weeks, while another group was remained in the standard cages without training. After the motor and novel recognition test. **Results:** One day after stroke, expression levels of acetyl-tau, p-tauS396/205 and short form of tau in infarcted side of the cerebral cortex were significantly higher than those in contralateral side. On the contrary, the expression of p-tauS396 and long form tau were significantly down-regulated in ipsilateral region. Interestingly, the expression of SIRT1 and the activity of AMPK (p-AMPK_T172/AMPK) in ipsilateral side were significantly lower, while α-synuclein oligomer and COX-2 expression were higher in infarcted region than contralateral side. Rehabilitation for 4 weeks greatly improved functional performance in the motor and novel recognition test. The down-regulation of p-AMPK_T172 and p-GSK3β and p-tauS396 were observed in ipsilateral cortex of rehabilitation group, compare with the untreated control group. **Conclusions:** We found that ischemic stroke induced tau modification, suppressed the expression of SIRT-1 and AMPK activity, and concurrently upregulated the expression of acetyl-tau and α-synuclein oligomer. The improvement of cognitive function by rehabilitation in ischemic stroke model involves the activity of AMPK, GSK3β, and phosphorylation of p-tauS396, and further investigations to clarify the role of tau-related signaling pathway in development of vascular dementia are needed. This work was supported by NRF grant (Mid-career Researcher Program 2013R1A2A201008223 and MRC program 2014009392), Korea.

**P3-050**

**EXTRACELLULAR TAU OLIGOMERS AFFECT ENDOGENOUS TAU DISTRIBUTION IN AN ISOFORM-DEPENDENT MANNER**

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**Background:** Tau is a microtubule-associated protein enriched in axons in the central nervous system, where its functions include the binding and stabilizing of microtubules, and regulating axonal transport. Neuronal inclusions composed of the six naturally occurring isoforms of tau are a major histopathological feature of a series of neurodegenerative disorders known collectively as tauopathies, the most prominent and well-known of which is Alzheimer’s disease. While the clinical and histological presentation of these disorders is extremely heterogeneous, most share the common hallmarks of loss of normal axonal distribution of tau and accumulation of insoluble, fibrillar tau aggregates in neurites and the soma. There is also evidence that these disorders progress throughout the brain by a prion-like mechanism, in which misfolded tau is taken up by neurons, confers this pathological phenotype to the endogenous “normal” protein, and is eventually released by the cell, perpetuating the cycle. While early research focused on the fibrillar inclusions of tau as the “toxic” species, recent research has shown that oligomeric species composed of two or more tau molecules are in fact much more potent with regards to neuronal dysfunction and death. In this study we set out to analyze the role of tau oligomers and their isoform composition in tauopathy pathogenesis, and to investigate possible mechanisms of oligomer toxicity. **Methods:** Tau oligomers of varying isoform composition were applied extracellularly to mouse primary cortical neurons. Distruption of intracellular tau distribution was analyzed by immunofluorescence and quantified utilizing ImageJ. Axonal transport was quantified by kymograph analysis of live-imaged neurites. **Results:** We demonstrate that externally applied oligomers of tau, but not monomers or fibrils, lead to loss of normal tau distribution within primary cortical neurons, and that the extent of this effect is dependent on the isoform composition of the exogenous tau. This mislocalization of tau is concomitant with changes in axonal transport velocity of various cargoes. **Conclusions:** Extracellular tau oligomers have the ability to affect the intracellular distribution of endogenous tau, indicating a possible prion-like mechanism in oligomer toxicity. This disruption in turn leads to alterations of axonal transport, a precursor to synaptic dysfunction and cell death.