FENS Regional Meeting

Belgrade, Serbia, July 10–13, 2019

ДНС SNS Друштво за неуронауке Србије Serbian Neuroscience Society

National Neuroscience Society of Romania

Neuroscience Society of Turkey

Abstract Book

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Thursday, July 11, 2019

13:45-15:00

Room Atlantic 1
Room Atlantic 2

POSTER SESSION 2

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THE PROTECTIVE ROLE OF AMPK AND AUTOPHAGY IN NEUROTOXICITY CAUSED BY EXTRACELLULAR ALPHA-SYNUCLEIN

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Alpha-synuclein (ASYN) is regarded as one of the key culprits in pathogenesis of synucleinopathies, including Parkinson's disease, and impaired regulation of autophagy is associated with the ASYN aggregation. Autophagy is regulated by complex mechanisms, including AMP activated protein kinase (AMPK), a key energy sensor regulating cellular metabolism to maintain energy homeostasis. The aim of our study was to investigate the role of AMPK and autophagy in neurotoxic effect of secreted ASYN, as well as dopamine-modified and nitrated recombinant wild-type ASYN oligomers, on retinoic acid (RA)-differentiated SH-SY5Y cells.

The culture supernatant from neuroblastoma cells stably expressing wt ASYN was collected and used as conditioned medium (CM). The presence of wt ASYN in CM was confirmed by immunoblot, following lyophilisation.

The CM, as well as recombinant dopamine-modified or nitrated ASYN, all reduced viability in differentiated SH-SY5Y cells. This decrease in viability was accompanied by reduced AMPK activation, increased conversion of LC3-I to LC3-II and increase in Beclin-1 level, as demonstrated by immunoblot. Pharmacological activators of AMPK and autophagy (metformin and AICAR) significantly increased the cells' viability in the presence of CM and modified ASYN forms. Pharmacological inhibitors of autophagy (chloroqine, bafilomycin A1 and ammonium-chloride), further reduced cell viability in the presence of extracellular ASYN. The shRNA-mediated LC3 downregulation, as well as the RNA interference-mediated knockdown of ATG7 gene, both important for autophagosome biogenesis/maturation, increased sensitivity of SH-SY5Y cells to the extracellular ASYN-induced toxicity.

These data demonstrate the protective role of AMPK and autophagy against the toxicity of extracellular ASYN, suggesting that their modulation may be a promising neuroprotective strategy in Parkinson's disease.