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Serbian Neuroscience Society



National Neuroscience
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ABSTRACT BOOK

1. PLENARY LECTURES
2. SYMPOSIA
3. SPECIAL INTEREST SYMPOSIA
4. NANO SYMPOSIA
5. HISTORY POSTERS
6. POSTER SESSION
7. BRAIN AWARENESS WEEK POSTERS

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Saturday, July 13, 2019

8:30–10:10

Room Atlantic 1

SYMPOSIUM 31

AUTOPHAGY REGULATION AND ITS ROLE IN NEURONAL FUNCTION, SURVIVAL, AND DEATH

Organizers: Vladimir Trajkovic (Belgrade, RS)

AUTOPHAGY REGULATION AND ITS ROLE IN GLUTAMATE EXCITOTOXICITY DURING NUTRIENT STRESS

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We investigated the effect of excitotoxic glutamate on nutrient starvation-induced autophagy, a process of lysosome-mediated degradation of cellular macromolecules and organelles. Incubation of SH-SY5Y human neuroblastoma cell line in glucose/amino acid/serum-free Hank Balanced Salt solution synergized with glutamate in causing energy stress and excitotoxic necrosis. Glutamate inhibited starvation-induced autophagy, as demonstrated by decreased intracellular acidification, lower LC3 punctuation, reduced conversion of LC3-I to LC3-II, reduced expression of autophagy activators beclin-1 and ATG5, increased levels of the selective autophagic target NBR1, and decline in the number of autophagic vesicles observed by transmission electron microscopy. NMDA antagonist memantine restored LC3B-II accumulation in starved cells exposed to glutamate, indicating that glutamate exerts its inhibitory role on autophagy by activating NMDA receptors. The modulation of mTOR, the negative regulator of autophagy, was not responsible for glutamate-mediated autophagy inhibition during starvation. On the other hand, glutamate downregulated starvation-induced activation of the intracellular energy sensor AMP-activated protein kinase (AMPK). This was associated with reduced mRNA expression of autophagy transcription factors FOXO3 and ATF4, as well as molecules involved in autophagy process (ULK1, ATG13, FIP200, ATG14, beclin-1, ATG5, ATG12, SQSTM1). The ability of glutamate to repress transcription of autophagy genes in starved cells was partly mediated by AMPK downregulation. Genetic or pharmacological AMPK activation by AMPK overexpression or metformin, as well as genetic or pharmacological autophagy induction by TFEB overexpression or lithium chloride, rescued cells from glutamate-mediated excitotoxicity. These data indicate that transcriptional inhibition of AMPK-dependent autophagy is involved in glutamate-mediated excitotoxicity during nutrient deprivation *in vitro*.