



3rd Nordic Autophagy Society (NAS) Conference

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Venue: St. Bartholomeus Gasthuis, Lange Smeestraat 40, 3511 PZ Utrecht
(<https://www.bartholomeusgasthuis.nl/>)

Local organizers

Paul Coffey (University Medical Center Utrecht)
Muriel Mari (University Medical Center Groningen)
Fulvio Reggiori (University Medical Center Groningen)

Nordic Autophagy Society (NAS)



<https://nordicautophagy.org/>

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A24: Glutamate-mediated autophagy inhibition intensifies excitotoxic death of nutrient-deprived SH-SY5Y neuroblastoma cells

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We investigated the role of autophagy in glutamate excitotoxicity during nutrient deprivation *in vitro*. Lack of serum, amino acids, and glucose markedly increased the sensitivity of SH-SY5Y human neuroblastoma cell line to glutamate-induced excitotoxic necrosis. Glutamate suppressed starvation-triggered autophagic response, as confirmed by diminished intracellular acidification, lower LC3 punctuation and conversion of LC3-I to autophagosome-associated LC3-II, reduced levels of autophagy activators beclin-1 and ATG5, increased levels of the selective autophagic target NBR1, and reduced appearance of autophagic vesicles observed by transmission electron microscopy. Glutamate reduced starvation-triggered phosphorylation of the intracellular energy sensor AMP-activated protein kinase (AMPK), without affecting the activity of mammalian target of rapamycin complex 1 as a major negative regulator of autophagy. Similar results were shown on PC12 cells, which are often exploited as a model for excitotoxicity. We also detected reduced mRNA expression of autophagy transcription factors FOXO3 and ATF4, as well as molecules involved in autophagy initiation (ULK1, ATG13, FIP200), autophagosome nucleation/elongation (ATG14, beclin-1, ATG5, ATG12), and the autophagic cargo delivery to autophagosomes (SQSTM1/p62). Genetic or pharmacological AMPK activation by AMPK overexpression or metformin reduced the sensitivity of nutrient-deprived SH-SY5Y cells to glutamate excitotoxicity. These data indicate that transcriptional inhibition of AMPK-dependent autophagy is involved in glutamate-mediated excitotoxicity during nutrient deprivation *in vitro*.