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Blockade of the NMDA receptor in developing cortex induces autophagy-mediated death of migrating cortical GABAergic interneurons: An *ex vivo* and *in vivo* study in Gad67-GFP mice

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In neonates, excitotoxicity is a major process involved in hypoxic-ischemic brain lesions, and several studies reported neuroprotective effects of NMDA antagonists. However, there is more and more evidence indicating that, in the developing brain, glutamate exerts trophic effects on migrating GABAergic interneurons and that NMDA antagonists would present side effects. Consequently, characterizing mechanisms leading to these side effects would be therapeutically useful. Because macroautophagy is involved in the adaptive response to trophic deprivation, we investigated the impact of autophagy modulators on MK801-induced death of immature GABAergic interneurons. Using cortical slices from wild type and Gad67-GFP mice, we showed that blockade of the NMDA receptor resulted in an accumulation of autophagosomes due to the disruption of the autophagic flux. This effect preceded the activation of the mitochondrial apoptotic pathway, and the degeneration of immature GABAergic neurons present in the developing cortical layers II-IV. The autophagy inhibitor, 3-MA, prevented the apoptotic death of GABA interneurons whereas modulators of autophagy (3-MA, rapamycin) did not interfere with the anti-excitotoxic effect of MK801 observed in deep layers V and VI. *In vivo*, 3-MA blocked the rapid increase in caspase-3 cleavage induced by NMDA antagonists and prevented death of Gad67-GFP neurons in layers II-IV. Together, these data suggest that, in the developing cortex, blockade of the NMDA receptor in the developing cortex induces autophagy-mediated death of migrating cortical GABAergic interneurons. The use of autophagy modulators would create new opportunities to prevent side effects of NMDA antagonists used for neuroprotection or anesthesia.

Biography

Bruno J Gonzalez is PhD Researcher at the National Institute for Medical Research and Head of the NeoVasc Laboratory "Microvascular Endothelium and Neonatal Brain Lesions", Normandy University, France. He developed a research program on pathologic neurodevelopment in preterm and term neonates with a particular attention to neurovascular defects. His working hypotheses are (1) microvessels contribute to injurious mechanisms with age-dependent specificities, (2) microvessels are targets for therapeutic actions, and (3) brain microvessels release factors with biomarker potential. Focusing on NMDA receptors, his objectives consist of molecular and functional characterizations of endothelial and neuronal interactions (GABA interneurons) and of deleterious/side effects of drugs (alcohol, anesthetics).

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