

Nathalie Pierrot

Institute of Neuroscience (IoNS)/Alzheimer Dementia group

Université catholique de Louvain

Research Engineer, Institute of Development Biology, CNRS,
Marseille, France, 1998-1999

PhD Student, UCL, Brussels, Belgium, 2001-2007

Research Assistant, UCL, Brussels, Belgium, 2005-2008

Post-doctoral position, Chargé de Recherches FRS-FNRS, UCL,
Brussels, Belgium, since 2008



E-mail: nathalie.pierrot@uclouvain.be

Phone: +32 (2) 764 93 34

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Science: Alzheimer's disease is the most frequent form of progressive dementia, occurring predominantly in the elderly population. The accumulation of Aβ peptide is generally believed to be involved in the development of the disease. Aβ is proteolytically derived from the amyloid precursor protein (APP). Although APP processing by secretase activities has been extensively studied, the function of the protein remains unclear. To get a better insight into the neuronal function of APP, we decided to express human APP (hAPP) in primary cultures of rat cortical neurons or to down regulate endogenous APP expression using shRNA. Using this experimental model, we have recently demonstrated that APP plays a key role in neuronal excitability by controlling calcium oscillations of neuronal networks in culture (Santos et al. 2009). We have also recently demonstrated that APP controls the neuronal transcription of the HMG-CoA reductase gene, a key enzyme involved in the synthesis of cholesterol, by regulating the metabolism of sterol regulatory element binding proteins (SREBP) (Pierrot et al. submitted). In a very recent work, we have also observed that hAPP expression specifically decreased the ApoE mRNA levels in cultured rat cortical neurons but not in astrocytes. Experiments performed on brain lysates from APP knock-out mice (APP^{-/-}) showed an increase in ApoE protein when compared to wild type mice (APP^{+/+}) of the same genetic background. Since ApoE is a main lipid carrier playing a crucial role in brain cholesterol metabolism, our preliminary observations highlight a central role of APP in lipid metabolism. The aim of this project is to understand how APP regulates the transcription of the ApoE gene. We will analyze the transcriptional activity of the ApoE gene promoter in APP^{+/+} and APP^{-/-} neurons with ApoE-luciferase reporter genes. We will also investigate the stability of the ApoE mRNA in these cells. Based on our preliminary data, we will further study the epigenetic modifications of the ApoE gene, with a particular focus on DNA methylation, which has been proposed to play a key role in the control of ApoE gene expression.

Selected publications

Santos SF, **Pierrot N**, Morel N, Gailly P, Sindic C, Octave JN (2009) Expression of human amyloid precursor protein in rat cortical neurons inhibits calcium oscillations, *J Neurosci.* 29(15):4708-18.

Nathalie Pierrot, Donatienne Tyteca, Ludovic D'auria, Ilse Dewachter, Bernadette Tasiaux, Annie Laquerrière, Jean-Baptiste Demoulin, Dominique Campion, Jean-Pierre Brion, Pierre Courtoy, Pascal Kienlen-Campard and Jean-Noël Octave. Amyloid Precursor Protein regulates SREBP1-mediated neuronal lipid homeostasis in mice and humans, *Submitted*.