

Cortical cells reveal APP as a regulator of GABAergic neurotransmission

Anna Doshina¹, Florian Gourgue¹, Michiho Onizuka¹, Remi Opsomer¹, Peng Wang¹, Kunie Ando², Bernadette Tasiaux¹, Ilse Dewachter¹, Pascal Kienlen-Campard¹, Jean-Pierre Brion², Philippe Gailly¹, Jean-Noël Octave^{1*} and Nathalie Pierrot¹

- ¹ Université Catholique de Louvain, Belgium
- ² Université Libre de Bruxelles, Belgium

Besides its involvement in the pathophysiology of Alzheimer Disease (AD), the amyloid precursor protein (APP) has been reported to modulate neuronal activity which depends on the fine tuning between excitatory and inhibitory neurotransmission. GABAergic inhibitory neurotransmission is affected by modifications in intracellular chloride concentrations regulated by Na⁺-K⁺-2Cl⁻ cotransporter 1 (NKCC1) and neuronal K⁺-Cl⁻ cotransporter 2 (KCC2), allowing entrance and efflux of chloride, respectively. Changes in NKCC1 and KCC2 expression during maturation of cortical cells induce a shift in GABAergic signaling. Here, we demonstrated that APP affects this GABA shift. Expression of APP in primary cortical cultures decreased the expression of KCC2, without modifying NKCC1. Conversely, knocking down APP increased KCC2 expression in these cultures. Furthermore, in primary cortical cultures expressing APP, GABA response was less inhibitory and less hyperpolarizing. In addition, KCC2 was also downregulated in vivo following APP expression in neonatal mouse brain. Finally, KCC2 protein levels were decreased in the brains of sporadic AD patients. Our results outline a new important role of APP in KCC2 expression regulation which could influence GABAergic neurotransmission. This information advances our understanding of the physiological function of APP and sheds light on new mechanisms that could contribute to AD pathology.

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* **Correspondence:** Prof. Jean-Noël Octave, Université Catholique de Louvain, Brussels, Belgium, jean-noel.octave@uclouvain.be