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INFLUENCE OF INTRANEURONAL CALCIUM INCREASE ON THE METABOLISM OF THE AMYLOID PRECURSOR PROTEIN

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One hallmark of Alzheimer's disease (AD) is the deposition of amyloid plaques in the central nervous system. These plaques contain mainly beta-amyloid peptide (Abeta), which is produced by cleavage of the Amyloid Precursor Protein (APP). Two catabolic pathways process APP. The non-amyloidogenic pathway is mediated by the alpha-secretase activity cleaving APP within the Abeta sequence. This cleavage precludes formation of Abeta peptide and leads to the extracellular release of an amino-terminal fragment of APP called soluble alpha-APP (s-alpha-APPs). In the second amyloidogenic pathway, Abeta is produced by cleavage of APP by beta and gamma-secretase activities. It is thus essential to understand the intracellular mechanisms that control APP processing and Abeta production. Calcium homeostasis may play an important role in Abeta production as shown by data indicating that Abeta toxicity involves impaired calcium regulation. Moreover, the increase in intracellular calcium concentration itself enhances the secretion of Abeta from APP in HEK293 cells. The aim of our work is to study the processing modifications of APP after disrupting neuronal calcium homeostasis by K+-induced depolarization. In these conditions, we analyse the processing of APP in cultured rat cortical neurons expressing human APP 695. We observed a decrease of extracellular s-alpha-APP production and the accumulation of intracellular APP carboxy-terminal fragments. Moreover, neuronal depolarization triggers the extracellular and intracellular accumulation of a one isoform of Abeta, named Abeta 42. Altogether, our results suggest that calcium fluctuations resulting from neuronal depolarization could favour the amyloidogenic processing of human APP.