EFFECTS OF ALOISINES, A NEW FAMILY OF CDK/GSK3 INHIBITORS, ON APP PROCESSING

A. Noel, L. Barrier, B. Fauconneau, S. Ingrand
GREVIC (EA3808), University of Poitiers, Poitiers, France

According to their involvement in Aβ production, Tau hyperphosphorylation and neuronal death, Glycogen synthase kinase-3 (GSK3) and cyclin-dependent kinase 5 (CDK5) are the two latter enzymes implicated in Alzheimer's disease (AD) representing very promising targets in the therapeutic strategy of AD.

Among selective and potent inhibitors of these kinases, a new family of CDK/GSK3 inhibitors, named aloisines, was recently described by Mettey et al (2003). In vitro studies showed that these 6-phenyl[5H]pyrrolo[2,3-b]pyrazines act reversibly by competition for ATP binding with a IC50 at submicromolar range. Moreover, in vivo studies demonstrated that some of these molecules have anti-proliferative and antiviral effects (Mettey et al., 2003, Rowe et al., 2010) and reduce tau phosphorylation in tau transgenic mice (Uno et al., 2009). However, there is currently no data about aloisines action on APP processing. That is the reason why we proposed to evaluate the effects of several compounds of aloisines family on GSK3 and CDK5 activity, and to study their effects on APP processing in Human neuroglioma cells H4 overexpressing the double Swedish mutation (K595N/M596L) of human APP by western blotting. Interestingly, our results showed that among selective GSK3 inhibitors, some of these molecules have selective action on one of the two main isoforms of GSK3 (i.e. GSK3α or GSK3β). Moreover, we showed that aloisines have significative repercussions on APP processing.

Thus, this work confirms the implication of GSK3 and CDK5 on Aβ production and puts forward the therapeutic interest of modulation of GSK3 and/or CDK5 activity in AD.