Quinolinic Acid Provokes Hyperphosphorylation of Cytoskeletal Proteins of Neural Cells of Rats: Involvement of Glutamatergic System, Calcium and Protein Kinases

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Quinolinic acid (QUIN) is a metabolite of the kynurenine pathway that has been associated with many neurodegenerative diseases. QUIN act as an excitotoxic agonist of the N-metil-D-aspartate (NMDA) receptor. Intermediate filaments (IFs) are important constituents of the cytoskeleton and phosphorylation of their subunits is one of the main regulatory mechanisms of cellular functions. The present study investigates the in vitro effects of QUIN on cytoskeletal proteins in rat striatum and evaluates the participation of NMDA receptor, Ca\(^{2+}\) and protein kinases in these effects. Slices of striatum were incubated in the presence of \(^{32}\text{P}\) orthophosphate in the presence or absence of 100 µM QUIN and/or the NMDA antagonist DL-AP5, the L-VDCC receptor antagonist verapamil, the rianodine receptor antagonist dantrolene, the calcium chelators Bapta-AM or EGTA and the protein kinase inhibitors H-89 (protein kinase A-PKA), staurosporine (protein kinase C-PKC), KN93 (Ca\(^{2+}\)/calmodulin dependent-protein kinase II PKCaMII), PD98056 (MEK/ERK), SP600125 (c-JUN kinase-JNK), p38 MAPK IV inhibitor (p38) and roscovitine (Cdk5). Results showed that QUIN significantly increased the phosphorylation of the IFs of neural cells, and this effect was mediated by NMDA receptor, L-VDCC channel, Ca\(^{2+}\), PKA, PKC, PKCaMII and Cdk5. We also observed that QUIN-induced hyperphosphorylation was targeted at the Ser55 and Ser57 phosphorylating site and KSP repeats. We propose that QUIN activate signaling pathways that provoke hyperphosphorylation of IF subunits in astrocytes and neurons. Since the hyperphosphorylation of these proteins is related to neurodegeneration, these results are promising in the study of brain damage induced by QUIN.

Word keys: intermediate filaments, phosphorylation, quinolinic acid

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