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The Role of Piceatannol in Counteracting Glyceraldehyde-3-Phosphate Dehydrogenase Aggregation and Nuclear Translocation

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Abstract : In the pathogenesis of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease, protein and peptide aggregation processes play a vital role in contributing to the formation of intracellular and extracellular protein deposits. One of the major components of these deposits is the oxidatively modified glyceraldehyde-3-phosphate dehydrogenase (GAPDH). Therefore, the purpose of this research was to answer the question whether piceatannol, a stilbene derivative, counteracts and/or slows down oxidative stress-induced GAPDH aggregation. The study also aimed to determine if this natural occurring compound prevents unfavorable nuclear translocation of GAPDH in hippocampal cells. The isothermal titration calorimetry (ITC) analysis indicated that one molecule of GAPDH can bind up to 8 molecules of piceatannol (7.3 ± 0.9). As a consequence of piceatannol binding to the enzyme, the loss of activity was observed. Parallel with GAPDH inactivation the changes in zeta potential, and loss of free thiol groups were noted. Nevertheless, the ligand-protein binding does not influence the secondary structure of the GAPDH. Precise molecular docking analysis of the interactions inside the active center allowed to presume that these effects are due to piceatannol ability to assemble a covalent binding with nucleophilic cysteine residue (Cys149) which is directly involved in the catalytic reaction. Molecular docking also showed that simultaneously 11 molecules of ligand can be bound to dehydrogenase. Taking into consideration obtained data, the influence of piceatannol on level of GAPDH aggregation induced by excessive oxidative stress was examined. The applied methods (thioflavin-T binding-dependent fluorescence as well as microscopy methods - transmission electron microscopy, Congo Red staining) revealed that piceatannol significantly diminishes level of GAPDH aggregation. Finally, studies involving cellular model (Western blot analyses of nuclear and cytosolic fractions and confocal microscopy) indicated that piceatannol-GAPDH binding prevents GAPDH from nuclear translocation induced by excessive oxidative stress in hippocampal cells. In consequence, it counteracts cell apoptosis. These studies demonstrate that by binding with GAPDH, piceatannol blocks cysteine residue and counteracts its oxidative modifications, that induce oligomerization and GAPDH aggregation as well as it prevents hippocampal cells from apoptosis by retaining GAPDH in the cytoplasm. All these findings provide a new insight into the role of piceatannol interaction with GAPDH and present a potential therapeutic strategy for some neurological disorders related to GAPDH aggregation. This work was supported by the by National Science Centre, Poland (grant number 2017/25/N/NZ1/02849).

Keywords : glyceraldehyde-3-phosphate dehydrogenase, neurodegenerative disease, neuroprotection, piceatannol, protein aggregation
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