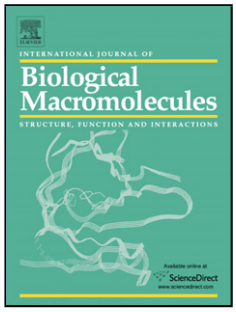

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Glyceraldehyde-3-phosphate dehydrogenase: aggregation mechanisms and impact on amyloid neurodegenerative diseases

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Abstract

The review analyses data on specific features of aggregation of glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and possible role of this enzyme in the development of neurodegenerative diseases. Different post-translational modifications of the enzyme are considered: oxidation, nitrosylation, and S-glutathionylation of the active site sulfhydryl groups, as well as phosphorylation, glycation and homocysteinylation of other amino acid residues. Modification of the sulfhydryl groups of the enzyme inhibits the enzymatic activity of GAPDH, resulting in slowdown of glycolysis, and may lead to the dissociation of the cofactor NAD from the active site of the enzyme. The resulting apo-GAPDH (without NAD) is less stable and prone to dissociation, denaturation, and subsequent aggregation. These processes could play a crucial role in the translocation of GAPDH subunits from the cytoplasm into the nucleus, which is linked to the induction of apoptosis. Phosphorylation and glycation of GAPDH are presumably involved in the regulation of protein-protein interactions and intracellular localization of the enzyme. Besides, glycation by dicarbonyl compounds and aldehydes may directly inhibit glycolysis. Homocysteinylation of GAPDH may stabilize aggregates of the enzyme by additional disulfide bonding. All types of post-translational modifications affect aggregation of GAPDH. A special attention is given to the role of chaperones in the amyloidogenic transformation of proteins and to confirmation of the hypothesis on blocking of the chaperones by misfolded protein forms. The denatured GAPDH forms were shown to interact directly with amyloidogenic proteins (alpha-synuclein and amyloid-beta peptide) and to play a crucial role in blocking of chaperone system.

Keywords

glyceraldehyde-3-phosphate dehydrogenase; aggregation; amyloidosis.