Activation of the fibrinolytic system by amyloid cross-β structure

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Conversion of plasminogen into plasmin by tPA requires a cofactor that acts as a scaffold bringing tPA and plasminogen into contact. Fibrin is the classical cofactor, but fragments of a large number of proteins as well as denatured proteins can also function as cofactor for tPA-mediated plasmin formation. We showed that fibrin-derived peptides adopt cross-β structure and form amyloid fibers. This correlated with tPA binding and stimulation of tPA-mediated plasminogen activation. Amyloid peptides, including amyloid β (associated with Alzheimer's disease), have no sequence similarity to fibrin peptides but bind to tPA and can substitute for fibrin in plasminogen activation. Our results classified tPA as a multiligand binding protein and show that the common denominator in tPA-binding ligands is the cross-β structure. We showed that proteins modified by advanced glycation endproducts (AGE) also gain tPA-binding capacity. Besides tPA, amyloid proteins and protein-AGE adducts bind multiligand receptors, such as RAGE and CD36. We tested the hypothesis that glycation induces refolding of globular proteins, accompanied by formation of cross-β structure. We demonstrate that glycated albumin condensates into fibrous or amorphous aggregates. The aggregates bind amyloid-specific dyes Congo red and thioflavin T, and tPA. Glycated albumin displays cross-β structure, as determined with X-ray fibre diffraction. We conclude that glycation induces the formation of cross-β structure in albumin. Our results may explain how glycated ligands and amyloid ligands can bind the same multiligand 'cross-β structure' receptors and tPA.
We studied the consequence of amyloid induced plasmin formation in cultures of neuronal cells and endothelial cells. As a result of excessive cell-associated plasmin generation the cells detach. Cell detachment can be prevented by carboxypeptidase B, an enzyme that cleaves off carboxyterminal lysine residues and that inhibits plasmin formation.
Our results support the idea that activation of the fibrinolytic system during (patho)physiological processes is mediated by the cross-β structure.

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