Non-enzymatic modification of hen egg white lysozyme by glycolaldehyde proves that intermolecular crosslinks are involved in the aggregation of glycated proteins

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Reactive carbonyl compound can modify proteins through a process known as protein glycation (PG). Diabetes-derived hyperglycemia triggers this process, which involves the development of diabetes-related diseases[1]. Moreover, PG boosts protein aggregation (PA) increasing the development of aggregation diseases in diabetic people[2]. Regardless its biological relevance, the mechanism that links PG with PA remains unclear.

To delve into this process, we have used a broad range of biophysical techniques (e.g. AFM, NMR, fluorescence, etc.) to study the glycation of hen egg white lysozyme (HEWL) with glycolaldehyde (GLA), a reactive α-hydroxyaldehyde that increases its physiological concentration under diabetes mellitus[3]. Our data prove that HEWL glycation occurs through two different concentration-dependent mechanisms. At low HEWL concentrations ([HEWL]≤2mM), its glycation results into the formation of non-crosslinking fluorescent advanced glycation end-products (AGEs). This process does not alter the HEWL native structure but depletes its enzymatic activity without inducing PA. However, upon increasing HEWL concentration, the mechanism gradually shifts towards the formation of intermolecular crosslinking AGEs, which trigger the formation of covalently linked insoluble spherical-like aggregates[4]. These results differ from the aggregation-modulation mechanism that we earlier described for HEWL glycated with ribose[5].

Altogether, our data provide new insights into the mechanism that links PG with PA, and demonstrates the strongly dependence of the glycated-protein aggregation mechanism on the chemical nature of the glycating agent.

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