HOTSPOTS SITES FOR GLYCATION OF HUMAN SERUM ALBUMIN AND EFFECT ON FUNCTIONAL ACTIVITY AND DEGRADATION

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Albumin is susceptible to glycation by glucose and reactive dicarbonyl glycating agents such as glyoxal, methylglyoxal and 3-deoxyglucosone (3-DG). Glycation of human serum albumin (HSA) by glucose in vivo forms glucose-derived Schiff's base and N\textsubscript{\alpha}-fructosyl-lysine (FL) residues. Degradation of fructosamine residues and glycation by reactive dicarbonyl metabolites forms advanced glycation endproduct (AGE) residues. In human subjects, steady state concentrations of glycation adduct residues in albumin (mol% total albumin) are: early glycation adducts - glucose-derived Schiff's base 1 - 5%, and FL 6 - 15%; and AGEs - hydroimidazolones, 2 - 7%, N\textsubscript{\alpha}-carboxymethyl-lysine (CML) 0.2 - 0.6%, N\textsubscript{\alpha}-carboxyethyl-lysine (CEL) 0.1 - 0.3%, glyoxal and methylglyoxal-derived bis (lysyl)imidazolium crosslink GOLD and MOLD 0.05 - 0.3%, and pentosidine 0.005 - 0.02%

Glycation of by glucose forms FL residues mainly at lys\textsuperscript{525}, lys\textsuperscript{439}, lys\textsuperscript{199} and lys\textsuperscript{281}. The most reactive site is lys\textsuperscript{525} where 33% of fructosamine adducts are present. These FL residues degrade oxidatively to form CML residues at the same sites. Methylglyoxal reacts with HSA to form mainly the hydroimidazolone AGE, N\textsubscript{\alpha}-(5-hydro-5-methyl-4-imidazolon-2-yl)-ornithine (MG-H1), with minor formation of CEL, MOLD and argpyrimidine residues. MG-H1 residue formation occurs on arg\textsuperscript{114}, arg\textsuperscript{186}, arg\textsuperscript{218}, arg\textsuperscript{410} and arg\textsuperscript{428} with the hotspot of modification at arg\textsuperscript{410}. Arg\textsuperscript{410} is located in drug binding site II and the active site of albumin-associated esterase activity. Hydroimidazolone formation at arg\textsuperscript{410} inhibits drug binding and esterase activity.

Glycation of HSA by the minimal extents found in vivo does not decrease the half-life or enhance degradation. With much higher, supraphysiological extents of glycation, as often found in HSA glycated in vitro, lead to scavenger receptor recognition and rapid removal of the highly glycated HSA from circulation in the liver. Removal of minimal glycated HSA in vivo rather appears to occur via uptake and proteolytic degradation in the kidney and other tissues with release and urinary excretion of mainly glycated amino acids (glycation free adducts) thereby formed and minor amounts of HSA-derived glycated peptides.

References: