GOLD-INDUCED STRUCTURAL SWITCH OF CYS34 IN ALBUMIN: COMPARISON OF AURANOFIN WITH AUROTHIOMALATE

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Albumin, a single-chain protein of ca. 580 amino acids (66.5 kDa), is the major protein in blood serum with a concentration of ca. 0.63 mM. The protein consists of three largely α-helical structurally-similar domains, each of which contains two sub-domains [1]. It plays a central role in the molecular pharmacology of gold drugs used for the treatment of rheumatoid arthritis, carrying ca. 80% of circulating gold in the body.

The primary binding site for Au(I) on albumin is known to be at the sulfur of Cys34 in domain I [2]. We have investigated the structural changes induced in bovine and human albumin by the oral drug auranofin, its deacetylated metabolite, Et_3PAuCl, the injectable drug aurothiomalate, and related thiols, using NMR spectroscopy.

In reactions of albumin with auranofin and tetraacetylthioglucose, cystine was detected as a product, whereas for deacetylated auranofin, thioglucose and glutathione, mixed disulfides with cysteine were produced. These reactions appear to involve reductive deblocking of albumin disulfides via thiol-disulfide interchange reactions [3].

The behavior of the $His^{\varepsilon 1}$ ^1H NMR resonance of His3 suggests that albumin exists in two distinct structural forms in solution dependent on whether the side-chain of Cys34 is buried or exposed. Modification of Cys34 by gold binding, disulfide formation or other oxidation, switches the conformation to the exposed form [4]. Such a structural change may influence the metabolism of albumin *in vivo*, as well as its other binding properties.

The buried-exposed conformational switch of Cys34 induced by aurothiomalate shows an interesting ionic strength dependence. In this case the gold -induced switch may require a concomitant anion-induced structural change in the protein. This interdependence may influence the uptake and transport of aurothiomalate by albumin *in vivo*.

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References

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