STRUCTURAL CHANGES AFFECT PHARMACOKINETICS OF HUMAN SERUM ALBUMIN
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Human serum albumin (HSA) possesses about 67% α-helix but no β-sheet and has relatively long plasma half-life, about 19 days. It has been suggested that the changes of size and charge of albumin affect its in vivo clearance. In previous studies using genetic variants of HSA, it was shown that mutations can affect structure and stability of HSA. However it is not clear whether changes in the structural stability of HSA affect its elimination. In the present study, we studied the pharmacokinetic properties of 13 HSA variants (V122E, C177F, K240E, K276N, D314V, E321K, E333K, D365H, D375H, E501K, K560E, E570K and K573E) and examined the relationships between pharmacokinetic and structural properties of these variants. To examine the pharmacokinetic properties, mice received tail vein injections of these ¹¹¹In-labeled samples. We calculated the plasma half-life (t₁/₂) and the organ uptake clearance (CLorg) using the nonlinear least-square program MULTI. Structural stability was evaluated by α-helical content using spectroscopic techniques. In all variants, mutations were found to affect pharmacokinetic properties (t₁/₂ ratio, CLorg ratio). Interestingly, the liver and kidney uptake clearance of HSA closely correlated with α-helical content (liver, r = 0.742, p < 0.01; kidney, r = 0.648, p < 0.05) in which the decrease of α-helix increased the organ uptake. However, the correlation between t₁/₂ and α-helix content was not obtained. In addition, no relationship was found between other organ uptake clearance and structural parameters. The above results suggest that single-residue substitutions of HSA can affect these pharmacokinetics, particularly, uptake of HSA in liver and kidney depending upon the structural changes.

IN VITRO ALTERATION ON THE CHIRAL INVERSION OF IBUPROFEN IN ADJUVANT-INDUCED ARTHRITIS RAT HEPATOCYTES
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The effect of adjuvant-induced arthritis (AA) on the chiral inversion of “profens”, a nonsteroidal anti-inflammatory drug (NSAID), has been little known. In this study, we investigated the effect of AA on the chiral inversion of ibuprofen using freshly isolated rat hepatocytes. S- or R-ibuprofen (0.5 mM) was incubated with rat hepatocytes and the amounts of both enantiomers in the cells and medium were determined with a stereoselective HPLC assay. The chiral inversion rate constant of R- to S-ibuprofen, estimated using the compartmental inversion model, was significantly decreased by 70% in AA rat compared to that in normal rat. The metabolite rate constants of R- and S-ibuprofen were also significantly decreased by about 60%. To clarify the alteration of the enzymes involved in chiral inversion in AA rats, the mRNA expression of acyl-coenzyme A synthetases (ACS) 1, 4 and 5, and 2-arylpropionyl-CoA epimerase (APCE) were quantified by RT-PCR method. The mRNA levels of ACS 1, 4 and 5 were decreased in rat liver of AA, but not APCE. These results suggested that the chiral inversion activity itself in AA rat was impaired due to the downregulation of ACS.