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Measurement of albumin synthesis in humans using stable isotopes

Erfassung der Albuminsynthese

Albumin is a plasma protein with a molecular weight of about 70,000 and a biological half-life of 3 weeks which is exclusively synthesized in the liver. Plasma albumin is widely used as a reflection of albumin synthesis although various factors such as an increase in transcapillary escape rate of albumin under inflammatory conditions or intravascular fluid overload may severely alter plasma albumin concentration without affecting hepatic synthesis. However, attempts to evaluate albumin synthesis in common pathological conditions, such as cirrhosis of the liver or nephrotic syndrome, produced conflicting results in part because of the complex and unreliable methods of measuring albumin synthesis. Using decay methods with radioactive albumin or tracers such as ^{14}C-carbonate require lengthy time intervals, high doses of radioactivity, and rely on metabolic and kinetic assumptions that are difficult to control.

Therefore, we have developed a new technique for measuring albumin synthesis by using stable isotopes, which is based on the flooding dose technique (1). After i. v. injecting a large, i.e., a flooding dose, of a stable isotope such as [^{13}C]leucine or [$^{2}H_5$ring]phenylalanine (2), all potential sources of amino acids for albumin synthesis are brought to similar isotopic enrichment which minimizes the compartmentation of amino acid precursor pools. Incorporation of labeled amino acid is then measured over 90 min which facilitates investigations in conditions with rapidly changing synthesis rates. In recent studies, we have i. v. injected 43 mg/kg body weight of [$^{2}H_5$ring]phenylalanine with 7.5 to 15 atom%. Blood samples were taken at regular intervals up to 90 min. Albumin was extracted from trichloroacetic acid (10% w/w) precipitated plasma proteins by differential solubility in absolute ethanol, and its purity was regularly checked by sodium dodecylsulfate gel electrophoresis and compared with a commercially available human albumin standard. After hydrolysis, phenylalanine was enzymatically converted to ß-phenethylamine, derivatized, and the enrichment measured by mass spectrometry. The plasma free phenylalanine enrichments were measured by gas chromatography mass spectrometry. Albumin synthesis was then calculated as a fractional synthesis rate (FSR), i.e., the percentage of the intravascular albumin mass synthesised per day. FSR equals the rate of increase in [$^{2}H_5$ring]phenylalanine enrichment in albumin divided by the area under the curve of the plasma free phenylalanine enrichment times 100, expressed as %/d. Multiplying FSR by the intravascular albumin mass, i.e., plasma albumin concentration times plasma volume, results in absolute synthesis rates of albumin, expressed in mg per kg body weight per day (for details see refs. 1 to 3). The plasma volume was measured by injecting ^{125}I-albumin or indocyanine green.

To illustrate the potential of the method, the results of a recent study are shown, where the influence of chronic metabolic acidosis (CMA) on albumin synthesis in human healthy volunteers was investigated (4). Two different levels of CMA were induced by oral ammonium chloride and albumin synthesis was measured before and during acidosis as described above. CMA significantly decreased FSR of albumin and induced negative nitrogen balance. The observed decrease in plasma concentration of insulin-like growth factor-I suggested that the effects of CMA may be mediated by suppression of IGF-I. In conclusion,

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measuring albumin synthesis by a flooding dose of stable isotopes is safe and convenient in the clinical environment and facilitates investigations of short-term regulatory mechanisms of albumin synthesis in humans. Also, repeat measurements of albumin synthesis can be easily performed, and, as recently shown (3), the method can be employed for measuring synthesis rates of other hepatic proteins such as fibrinogen.

References

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