DECREASED ESTERASE ACTIVITY IN SERUM OF PATIENTS WITH REACTIVE SYSTEMIC (AA) AMYLOIDOSIS

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ABSTRACT

Serum esterase activities were measured in patients with AA amyloidosis and in control subjects. Patients with rheumatoid arthritis + amyloidosis had significantly reduced activities of arylesterase and paraoxonase, but not cholinesterase, as compared to healthy subjects and to disease controls including patients with rheumatoid arthritis without amyloid and patients with various nonamyloid liver and renal diseases. A significant correlation was found between serum arylesterase and amyloid degrading activity (r = 0.51, p < 0.01).

INTRODUCTION

The major constituent of the amyloid fibrils deposited in tissues of patients with inflammation-associated (reactive) amyloidosis is amyloid A (AA) protein [1, 2] which is believed to be formed from a circulating precursor, serum amyloid A protein (SAA) [3, 4]. Direct proof for this is lacking, but SAA is structurally and immunologically closely related to AA, and serine proteases of monocytic origin can cleave SAA to an AA-like fragment [5, 6]. Moreover, in conditions associated with reactive amyloidosis, elevated SAA levels are found [7, 10] and persistently high SAA levels correlate with rapid progression of amyloidosis [11]. If the underlying disease is controlled, resolution of AA amyloid may occur [12]. The molecular mechanisms involved in the resolution process are largely unknown, but they may involve serine proteases [13, 14].

We recently described an albumin-associated serine protease/hydrolase activity that is reduced in patients with reactive amyloidosis [8, 15]. Because previous studies have shown the presence of an esterase-like activity (the "albumin esterase") [16, 17] and a protease activity [18] in albumin preparations, we studied the possible relationships between various serum esterase activities and amyloid degrading activity. Significantly reduced by arylesterase and paraoxonase, but no cholinesterase, activities were found in patients with reactive amyloidosis. The arylesterase activity correlated positively with amyloid degrading activity.
Fig. 1. Serum esterase activities in different groups of patients. Hatched area: Reference range of activity. Details of the patient groups are given in Methods section.

Patients and Methods

Group RA + A consisted of 31 patients (19 women, 12 men; mean age 53 years, range 31 to 84) with rheumatoid arthritis plus amyloidosis, which was histologically confirmed in all cases. Serum creatinine levels were 243 ± 41 \(\mu\text{mol/L} \ (\text{SEM})\), and mean proteinuria was 4.7 ± 0.7 gm/24 h. Group RA consisted of 26 patients (15 women, 11 men; mean age 52.2 years, range 26 to 80) with rheumatoid arthritis. None had clinical signs of amyloidosis. Their renal function was normal, and they had no proteinuria (<0.1/24 h). Because patients with liver disease may have changed esterase [19, 20] and AA degrading activity [21], a group of patients with liver disease was included. It consisted of 19 patients (10 women, 9 men; mean age 47.5 years, range 30 to 76) with histologically confirmed liver diseases. Chronic active hepatitis, liver cirrhosis, fatty liver degeneration, primary biliary cirrhosis, and metastatic liver disease. Because patients with amyloidosis had hypoalbuminemia and renal insufficiency, we included patients with renal diseases as an additional control group. The group consisted of 19 patients (8 women, 11 men; mean age 44.7 years, range 15 to 79) with various renal diseases, but not amyloidosis. Serum albumin level was 20.8 ± 1.3 gm/L, creatinine 363 ± 75 \(\mu\text{mol/L}\) and proteinurea 3.2 ± 0.6 g/24 h.

Serum arylesterase (EC 3.1.1.2) activity was measured with phenylacetate used as substrate; details of the assay have been described elsewhere [19]. The reference values for the assay are 55 to 180 kU/L. Serum paraoxonase activity was measured with diethyl-p-nitrophenyl phosphate as substrate. The reference value is >35 U/L. Serum (pseudo-)cholinesterase (EC 3.1.1.8) activity was measured with butyryl choline used as substrate according to the recommendation of the German Society for Clinical Chemistry. The reference values are 3000 to 8000 U/L. Amyloid degrading activity was assayed as described previously [8, 15, 24].

Previous studies have shown that the addition of inhibitors of serine hydrolases to serum (diisopropyl fluorophosphate, methylsulfonylfluoride) as well as physiologic inhibitors (\(\alpha_1\)-antitrypsin or \(\alpha_1\)-macroglobulin) inhibits the amyloid degrading activity [15]. Dialysis of sera with reduced amyloid degrading activity against physiologic saline solution (1 h), phosphate-buffered solution (1 h), and Tris HCl buffer with 2.5 mmol/L \(\text{Ca}^{2+}\) and 1.0 mmol/L \(\text{Mg}^{2+}\) addition (2 h) did not affect the degrading activity.