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Plasma Protease Inhibitors in α_1 -Antitrypsin-Deficient Children

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ABSTRACT. Seven plasma protease inhibitors were analyzed in 8-yr-old children—75 PiZ (severely deficient), one PiZ—(with a null gene), 32 PiSZ (moderately deficient), and 35 normals. In PiZ and PiSZ α_1 -antitrypsin-deficient children, significantly higher concentrations of α_2 -macroglobulin ($p < 0.001$) and antithrombin III ($p < 0.001$) were found and significantly lower concentrations of α_2 -antiplasmin ($p < 0.001$), C1-inactivator ($p < 0.01$) and plasminogen (PiZ $p < 0.02$, PiSZ $p < 0.01$). The inter- α -trypsin inhibitor concentrations differed in PiSZ children only ($p < 0.01$). At this age the high α_2 -macroglobulin levels may be of importance to protect the lung tissue against free proteolytic activity, while importance of the other differences are unknown or reflect changes of purely theoretical interest. (*Pediatr Res* 19: 834-835, 1985)

Abbreviations

α_1 AT, α_1 -antitrypsin
 α_1 ATD, α_1 -antitrypsin deficiency
 α_1 AC, α_1 -antichymotrypsin
 α_2 AP, α_2 -antiplasmin
 α_2 M, α_2 -macroglobulin
 ATIII, antithrombin III
 C1IA, C1 inactivator
 I- α -I, inter- α -trypsin inhibitor
 PG, plasminogen

In α_1 ATD, one important protease inhibitor is significantly reduced—in the PiZ state to 15% the PiSZ state to 40% and in the PiSZ-state to 7.5% of the normal plasma level (1). Plasminogen and seven protease inhibitors— α_1 AT, α_2 M, α_1 AC, α_2 AP, C1IA, ATIII, I- α -I—were studied in 8-yr-old children with α_1 ATD followed prospectively since birth (2).

MATERIALS AND METHODS

EDTA-plasma (vacutainer) was drawn from 75 PiZ, one PiZ—, 32 PiSZ, and 35 age-matched control children. The age of both α_1 ATD and control children was 8 yr 3 months $\pm$ 3 months. All were apparently healthy and had normal blood cell counts and sedimentation rates. None had clinical signs of liver disease. One-third of the PiZ, but none of the PiSZ children, had slightly increased plasma aminotransferase concentrations (2).

Plasma was stored at -20° C until analyzed. Protein concentrations were determined by electroimmunoassay using antibodies available at the laboratory of clinical chemistry (3). The concentrations are given as percentages of Seronorm (batch 103), except that of ATIII for which a standard pool of blood-donor plasma (EDTA) is used. One hundred percent corresponds to 1.5 g α_1 AT/liter, 2.5 g α_2 M/liter; the Seronorm protein concentrations of the other inhibitors are not properly known.

RESULTS

The protease inhibitor concentrations of the 8-yr-old α_1 ATD and control children are given in Table 1. α_1 ATD children (both PiZ and SZ) had significantly higher concentrations of α_2 M (p

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Table 1. The protease inhibitor concentrations of the 75 PiZ (A), the 32 PiSZ (B), and the 35 control children (C)*

Protein	Group		
	A	B	C
α_1 AT	17 $\pm$ 3	40 $\pm$ 7	113 $\pm$ 15
α_2 M	310 $\pm$ 38†	301 $\pm$ 35†	252 $\pm$ 36
α_1 AC	100 $\pm$ 22	106 $\pm$ 24	97 $\pm$ 23
I- α -I	116 $\pm$ 13	123 $\pm$ 16‡	111 $\pm$ 15
α_2 AP	105 $\pm$ 17†	104 $\pm$ 11†	125 $\pm$ 11
PG	98 $\pm$ 15§	95 $\pm$ 15‡	107 $\pm$ 18
ATIII	134 $\pm$ 17†	135 $\pm$ 19†	117 $\pm$ 13
C α IA	107 $\pm$ 18‡	110 $\pm$ 20‡	124 $\pm$ 31

* All values are given as percentages of adult concentrations (see "Materials and Methods").

† $p < 0.001$.

‡ $p < 0.01$.

§ $p < 0.02$.

< 0.001) and AT III ($p < 0.001$), and lower concentrations of α_2 AP ($p < 0.001$), PG (PiZ $p < 0.02$, PiSZ $p < 0.01$) and C α IA ($p < 0.01$). The I- α -I differed in PiSZ subjects only ($p < 0.01$). The respective concentrations for the PiZ- child were: α_1 AT 5, α_2 M 305, α_1 AC 148, I- α -I 132, α_2 AP 102, PG 89, ATIII 170, and C α IA 95%.

DISCUSSION

The plasma protease inhibitors control important physiological functions in the extracellular compartment associated with tissue turnover especially during inflammatory reactions, coagulation, fibrinolysis, and complement activation (4). Multiple enzyme interactions have been claimed for each inhibitor but several of the proposed reactions are too slow to be of biological importance. α_2 M is a polyvalent inhibitor, which preferentially inactivates proteases of all classes when they appear in the circulation. The others are serine inhibitors with the following known main specific target enzymes: α_1 AT—neutrophil elastase, α_1 AC—cathepsin G, α_2 AP—plasmin, ATIII—thrombin, C α IA—Clr and Cls (4). The functional role of I- α -I is not known.

The major inhibitor of elastase is considerably decreased in children with α_1 ATD, thus predisposing them to the develop-

ment of lung emphysema (5). α_1 AT is the major extravascular, monovalent protease inhibitor (60% exists intercellularly, normal plasma concentration 1.35 g/liter, molecular weight about 53,000). α_2 M is a bivalent inhibitor which occurs mainly intravascularly (about 70%), with a large molecular weight of 725,000 and plasma concentration of 2.5 g/liter. Thus the intercellular molar ratio of α_1 AT to α_2 M is normally at least 10:1. In α_1 ATD PiZ, the ratio is decreased to about 2:1 in adults and 1:2 in 8-yr-old children, indicating a relatively important role of α_2 M in α_1 ATD during childhood. The wide α_2 M range, 230–440% in healthy children, may also be an endogenous factor explaining the wide clinical variation of lung disease in adult α_1 ATD subjects, although, no significant difference of α_2 M was found between α_1 ATD adults with and without chronic lung disease (6). In that study the α_2 M concentration of α_1 ATD adults was 134% of the normal concentration (6).

Significant changes were found in the α_2 AP, AT III, C α IA, and PG concentrations. The differences are small and the concentrations found are not generally considered abnormal. Since the regulation of the inhibitor concentrations has not been elucidated, the differences are not easily interpreted. The decreased α_2 AP and PG concentration, however, may suggest a slightly increased fibrinolysis. The C α IA level may indicate a tendency toward complement activation. The increased ATIII concentrations are difficult to explain.

The present study shows that several protease inhibitors are altered both in the PiZ and PiSZ α_1 ATD states. α_1 ATD children may benefit from their higher α_2 M levels. The small but significant changes of α_2 AP, C α IA, and ATIII may be worth further investigation.

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