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Alpha-L-iduronidase deficiency: a spectrum of clinical disorders.

Hurler and Scheie diseases (mucopolysaccharidosis I-H and I-S) are both manifestations of the defective action of alpha-L-iduronidase. Fourteen and nine year old sisters are presented showing excessive ^{35}S-mucopolysaccharide storage and deficient activity of alpha-L-iduronidase in their cultured fibroblasts.Their pattern of clinical and radiographic findings differed from that of both Hurler and Scheie diseases. The intelligence was only moderately impaired. Microscopic and ultrastructural studies demonstrated excessive mucopolysaccharide storage in leucocytes, bone marrow cells and liver cells. Increased amounts of mucopolysaccharides with characteristics of dermatan sulfate and chondroitin sulfate were found in the urine. The condition may be caused by a state of double heterozygosity for the Hurler and Scheie gene (so-called Hurler-Scheie compound).

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Loss of lysosomal enzymes, inhibition of enzyme pinocytosis and decreased activity of lysosomal enzymes in chloroquine treated fibroblasts.

In mucolipidasis (I-cell disease) the genetic disorder is characterized by selective loss of lysosomal enzymes, that cannot reenter the cells through pinocytosis, and by depletion of lysosomal enzymes in the cells, leading to disturbance of lysosomal function. Selective loss of lysosomal enzymes, inhibition of uptake of normal lysosomal arylsulfatase A and decrease of intracellular enzyme activity can also be provoked in normal cells after treatment with the antimalaria drug chloroquine in concentrations between 5×10^{-6} and 1×10^{-6} M. Pinocytosis of ^{14}C-Dextran (80'000 MW) however is inaffected. The morphological and the biochemichal changes in the cells are slowly reversible within 3-4 days. We speculate, that the treatment of cultured cells with chloroquine produces effects similar to the ones observed in I-cell disease. But unlike in I-cell disease, where these phenomena are the result of abnormal enzyme proteins, the changes after chloroquine application are brought about by alteration of the cell membranes.

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Aminoadipaturia - a new defect of lysine metabolism.

In an infant with seizures in the neonatal period, ichthyosis congenita, and a muscular weakness a markedly increased urinary excretion of α-aminoadipic acid has been found (53-640 µmoles/day). In plasma the aminoadipate conc. was 0.059 - 0.083 µmoles/ml. After an oral lysine load the urinary aminoadipate increased markedly. Fibroblasts showed a decreased degradation of ^{14}C-1-DL-α-aminoadipate to $^{14}CO_2$ (10 per cent normal). The mother of the infant also showed constantly some aminoadipate in the urine.

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Transport of homoarginine into liver slices of patients with lysinuric protein intolerance (LPI).

LPI is chemically characterized by diaminoaciduria, especially lysinuria, and hyperammonemia after amino nitrogen intake. The hyperammonemia is preventable by arginine or ornithine. The plasma concentration of diaminoacids was decreased to 20-50% of the normal mean, presumably because of defective tubular and intestinal absorption. We have suggested that a similar defect in the uptake of diaminoacids by hepatocytes results in hepatic ornithine deficiency. This incapacitates the urea cycle, as urea is formed on the ornithine molecule. We have studied the transport of the nonmetabolized diaminoacid analoque homoarginine into liver slices of 2 patients and 3 controls. The patients had 2 apparent transport systems. One of these, the "low concentration system", differed clearly from that of the controls. At large substrate concentrations the kinetic constants were similar in both groups of subjects. These findings are in accordance with our hypothesis.