Case 3
Carbonic Anhydrase II Deficiency

Focus concept

The role of the carbonic anhydrase enzyme in normal bone tissue formation is examined.

Prerequisites

- The carbonic acid/bicarbonate blood buffering system.
- Membrane transport proteins.
- Basic genetics.
- Amino acid structure.

Background

In this case, we will consider our patients: three sisters, aged 21, 24, and 29 years of age who are short of stature and obese. (There is a fourth sister in the family who appears to be normal, as she is taller than the other three sisters. The parents also appear to be normal.) As children, the symptoms of the three sisters were similar—delayed mental and physical development, muscle weakness, and renal tubular acidosis. They frequently suffered bone fractures as children. X-rays showed cerebral calcification and other skeletal abnormalities. After reviewing the sisters’ medical histories, you draw samples of blood and send it to the laboratory for analysis. The laboratory reports to you that your patients all have a carbonic anhydrase II deficiency.

There are seven isozymes of carbonic anhydrase (CA), three of which occur in humans and are designated CA I, II and III. They are all monomeric zinc metalloenzymes and have molecular weights of 29 kilodaltons. X-ray crystallographic data shows that the enzyme is roughly spherical with the active site located in a conical cleft. One side of this cleft is lined with hydrophobic amino acid residues while the other side is lined with hydrophilic residues. The zinc ion is located at the bottom of the cleft and is coordinately covalently bound to the imidazole rings of three histidine residues.

The carbonic anhydrase II isozyme is found in bone, kidney, and brain, which is why the defects occur in these tissues when the enzyme is deficient or non-functional. The carbonic anhydrase II enzyme is highly active, with one of the highest turnover rates of any known enzyme, and is critical in maintaining proper acid-base balance.
Questions

1. Carbonic anhydride catalyzes the reaction between water and carbon dioxide to yield carbonic acid. The carbonic acid then undergoes dissociation. Write the two equations that describe these processes. What products form when carbonic acid is dissociated?

2. Each of the three sisters with the symptoms described above showed a carbonic anhydrase II deficiency. In contrast, the fourth sister and both parents showed half-normal levels of the enzyme. Construct a chart which describes how the carbonic anhydrase deficiency syndrome is inherited. Note that the defective carbonic anhydrase gene is inherited as an autosomal recessive gene.

3. A genetic analysis of one of the sister’s genes indicates that a (His → Tyr) mutation at amino acid 107 is responsible for the carbonic anhydrase deficiency. Using what you know about amino acid structure, propose a hypothesis that might explain why such a mutation would result in an inactive enzyme.

4. Osteoclasts in bone tissue are particularly rich in carbonic anhydrase II, and a proper functioning enzyme is critical to the development of healthy tissue. In order for proper bone development to occur, the osteoclast must acidify the bone-resorbing compartment. Also involved in this acidification are several transporters: a Na⁺/H⁺ exchanger, a Cl⁻/HCO₃⁻ exchanger and the Na⁺K⁺ATPase, which exchanges Na⁺ and K⁺ ions. (An exchanger is a protein or protein complex located in the cell membrane which transports one ion in one direction and the second ion in the other direction simultaneously.)

A partial diagram of the osteoclast is shown in Figure 3.1. Fill in the blanks in the diagram indicating the roles of carbonic anhydrase II and the exchangers in the acidification of the bone-resorbing compartment. Include the reactants and products of the appropriate intracellular reaction(s) and note in which direction each ion is transported in the osteoclast.

References
