Zn(II) Metalloenzymes: CO_2 transport and management in Human Body

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CO_2 transport and management:

In general CO_2 is produced in the cells during respiration and it gets accumulated in cells during Krebs cycle, which gets dissolved in water of blood serum producing carbonic acid.

$$CO_2 + H_2O = H_2CO_3$$

The conjugate base of the deoxygenated Hb present in the large excess in the tissues, since the partial pressure of O_2 is low in this region, act as a proton acceptor and H_2CO_3 proton donor (Fig 1).

$$H_2CO_3 + \text{deoxy-Hb} = HCO_3^- + \text{deoxy-Hb}\bullet H^+$$

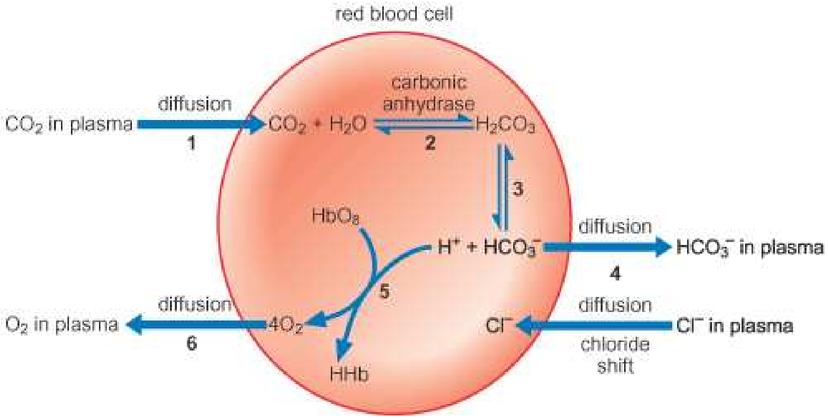


Fig 1

Now the **HCO_3^-** is transported to lungs through blood plasma. In the lungs due to presence of fresh **O_2**, **HCO_3^-** is converted to **H_2CO_3** and due to high partial pressure of O_2 deoxygenated Hb converted to oxy-hemoglobin**.**

$$\text{deoxy-Hb}\bullet H^+ + HCO_3^- = \text{oxy-Hb} + H_2CO_3$$

The produced **H_2CO_3** get immediately converted to **CO_2** & **H_2O.**

$$H_2CO_3 = CO_2 + H_2O$$

And this process may function spontaneously or bio catalysed by some enzyme Carbonic Anhydrase [CA].

And the CO_2 released through lung from the body (Fig 2).

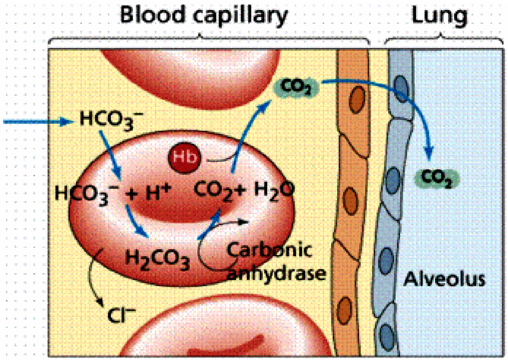


Fig 2

Carbonic Anhydrase (CA)

Carbonic Anhydrase was the first discovered Zn–metalloenzyme [1940]. It is found in animals, plants and some microorganisms. Interestingly in plants CA do not contain in metal atom in the active site.

It catalyzes the reversible hydration of CO_2 during respiration in human body,

$$CO_2 + H_2O = HCO_3^- + H^+ \text{ presence of CA}$$

Without the catalyst the reaction proceeds very slowly at body temperature [35-38 ºC].

$$CO_2 + H_2O = HCO_3^- + H^+ \ (p\ CO_2 = 1atm,\ k = 10^{-1}/sec)$$

The human CA (HCA) enhances the rate of hydration of CO_2 about 10^7 times ($K= 10^6$ / sec) which is the highest known Biological rate.
The enzyme also can catalyzes the hydrolysis of esters as well as aldehydes

$$CH_3CHO + H_2O = CH_3CH(OH)_2$$

In the RBC, this enzyme performs the important role of receiving CO_2 from tissue in the active muscle and releasing it in the lungs. Each molecule of HCA can hydrate about 1 million molecules of CO_2 /sec at body temperature.

Active Site Structure of HCA

A number of closely related forms of CA are found in mammals, its m.w. ~ 30,000 d.

The Zn(II) ion is coordinated by 4 ligands, three N atoms of 3 Histidine (His119, His94 & His-96) residue & the fourth coordination is satisfied by a water molecule. The geometry of the enzyme becomes a distorted tetrahedral molecule (Fig 3).

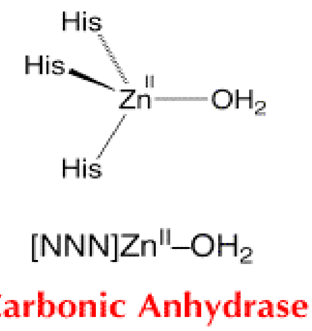


Fig 3

The molecule roughly looks like a ellipsoidal with Zn^{II} ion lies 12Å deep cleft. The active site structure contain other amino acids may function as H-bond formation, proton transfer etc (Fig 4).

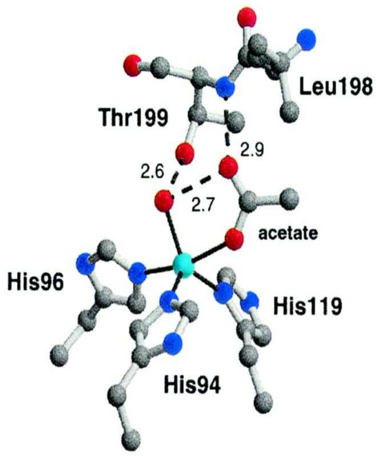


Fig 4

Essential Role of Zn

Now the question is why nature has select Zn^{II} to design such type of important metalloenzymes? And the answer is,

- The Zn(II) ion induces tetrahedrally coordinated geometry, as required in this metalloenzymes
- Very good interactive chemistry and bonding relation with water.
- Zn(II) ion highly stable and acts as a Lewis Acid.
- It shows important catalytic activity as many metalloenzymes.
- It is observed that Zn^{+2} ion performs as a stabilizing the structure of many metalloenzymes.

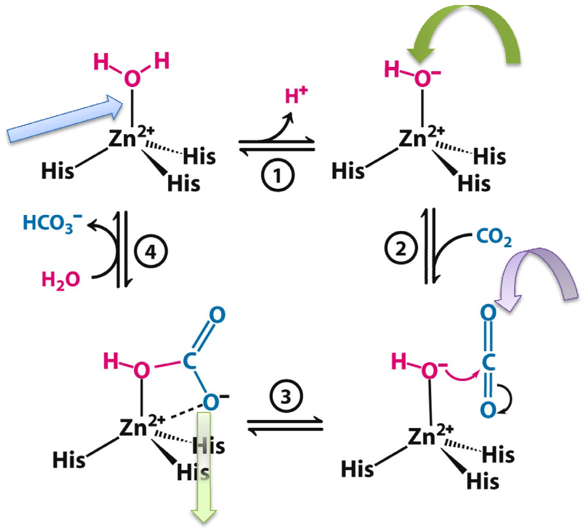
Zn^{+2} ion is essential for all form of life. Deficiency of Zn a large no. of diseases and disorders have been traced –

- retarded growth,
- anemia,
- loss of appetite,
- taste sensitivity
- lots of metabolic disorders

For an adult Human about 15-20 mg of Zn is required per day. It is found in Meat, Egg, Fish, beans and nuts.

Catalytic action of CA

The Zn^{II} ion is more acidic centre in CA : the three Histidine-Ns are pull back the electrons making the Zn centre more electronegative and more acidic towards the fourth position, where the water molecule is binded. The mechanistic cycle of the conversion of CO_2 to HCO_3^- catalysed by HCA is shown below (Scheme 1).



Scheme 1

Step 1. Three N-Histidines polarises the attached water molecule and it will lose a proton forming Zn-co-ordinated hydroxo group producing the Active site of the enzyme.
Step 2. Now the CO_2 molecule bind to this active site by nucleophillic attack of the OH group of the CA.
Step 3. The OH group holding the CO_2^- attached with the Zn, orient itself in such a way that the above attack [$CO_2^- \rightarrow Zn^{II}$] may be possible with the construction of a 4-membered ring.
Step 4. After that a conformational change at the Zn active site followed by nucleophillic attack of water generates HCO_3^- and the initial Zn-metalloenzyme.

This Zn^{II} – metalloenzymes is ready to perform another catalytic cycle as above and so on.

Catalytic action of CA- Model Study

Draw backs: The compounds of Zn(II) are maximum colorless, hence they show very poor photo physical and photo chemical property. They are also non magnetic- hence EPR, Mössbauer silent. Hence compounds of Zn^{+2} ion are not identified easily. Molecular modelling in vitro is the only way to study the mechanism (Fig 4).

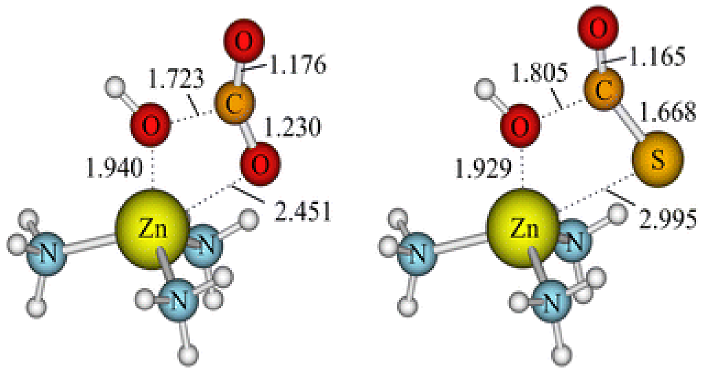


Fig 5

To study the structural feature and the reactivity order of CA as catalytic action, the Zn^{+2} ion [d^{10}] is replaced by the corresponding Co^{+2} ion [d^7], Ni^{+2} [d^8] and Cu^{+2} [d^9], which is spectroscopyally active and we may perform a variety of analysis as absorption, emission, CD, magnetic CD and the X-Ray analysis.

Reference:

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