The element copper

Introduction

Copper, elemental symbol Cu, is a transition d-block metal, and is the least reactive of the first row metals. Copper can have the oxidation states +1 and +2 and can form many complexes with various ligands.

The Cu 2+ ion, at low concentrations, is an essential element to plant and animal life, and a human adult has a required daily intake of 3-5mg. [1] The richest nutritional sources of copper are; animal livers, shellfish, dried fruit, nuts and chocolate. [2] A human who lacks copper can develop a deficiency and in some cases this can result in anaemia, and Wilson's disease (copper accumulates in tissues which leads to neurological symptoms and liver disease). [1]

A human adult contains roughly 100mg of copper, [1] most of which are attached to proteins and found in tissues, with high concentrations found in the liver and muscles.

Eventhough copper is very useful, and required for a variety of process', for example; formation of haemocyanin (oxygen carrying proteins in molluscs), at high concentrations copper ions can be toxic and harmful.

To avoid copper-induced toxicity most organisms use a combination of copper-regulated import inhibition and extraction of copper through specific export mechanisms. In mammals, copper is partially detoxified by sequestration in the metal- binding metallothioneins or export via the copper-translocating ATPases. [3]

Use of copper in the human body and cells

Copper has many roles in the human body and it plays a vital role in a range of chemical reactions that are essential to human health and development. Copper is distributed to several areas in the body so it can be used in various ways. Copper plays a major part in the conversion of iron to its useable Fe (III) form and also helps transport iron around the body. Copper is needed for the synthesis of collagen, a protein found in human skin, which maintains elasticity. [4] As a cofactor for the enzyme tyrosinase; copper is involved in the synthesis of the skin pigment melanin. Copper is also key for the development of the brain and nervous system as it plays a role in the production and maintenance of myelin, which insulates nerve cells thus ensuring the transmission of nerve impulses. Copper is also involved in the synthesis of neurotransmitters, chemicals that allow communication between nerve cells. [5] Within cells the generation of energy (ATP), inside the mitochondria, depends on the involvement of a copper-containing enzyme. [4] Another vital function for the copper as a cofactor is the neutralisation of free radicals that would otherwise oxidise and destroy healthy cells. [6]

More specific examples;

Cytochrome c oxidase

The enzyme cytochrome c oxidase, a large transmembrane protein complex found in the mitochondrion, is the last enzyme in the respiratory electron transport chain. It contains two heme centres called cytochromes a and a3, as well as two copper atoms. The copper sites, CuA and CuB, are associated with cytochromes a and a3, respectively. CuA is liganded by two cysteines and two histidines (Fig 1. 0). The heme of cytochrome a is liganded by imidazole rings of histidine residues. CuB and the iron atom of cytochrome

a3 are located close to each other and this closely coupled pair of metal ions is referred to as a binuclear centre (Fig 1. 1). [7] [8]

The copper sites play a part in electron transfer by switching between the Cu- state and the Cu2+ state. Reduction of one oxygen molecule requires passage of four electrons through carriers. Electrons from cytochrome c are transferred to CuA sites and then passed to the heme iron of cytochrome a. The electron pathway continues as CuB accepts a single electron from cytochrome a. A second electron then reduces the iron centre to Fe2+, leading to the binding of O2 and the formation of a peroxy bridge between heme a3 and CuB. This amounts to the transfer of two electrons from the binuclear centre to the bound O2. The next step involves uptake of two H+ and a third electron, which leads to cleavage of the O-O bond and generation of Fe4+ at the heme. Uptake of a fourth e- facilitates formation of ferric hydroxide at the heme centre. In the final step of the cycle, protons from the mitochondrial matrix are accepted by the coordinated hydroxyl groups, and the resulting water molecules dissociate from the binuclear centre. [9]

Summary reaction:

4 Fe2+ -cytochrome c + 8 H+ + O2 ? 4 Fe3+ -cytochrome c + 2 H2O + 4 H+ [7]

Haemocyanin

Hemocyanins are a type of respiratory protein in the form of metalloproteins containing two copper atoms. The deoxy-form of a haemocynin is colourless and contains Cu (I), while O2 binding results in the blue Cu (II) form. [10] Hemocyanins carry oxygen in the blood of some molluscs (e. g. snails, whelks) and some arthropods including crabs and lobsters. They are second

only to haemoglobin in biological popularity of use in oxygen transport. Hemocyanins are found suspended in the hemolymph, and aren't bound to blood cells like haemoglobin. [11] Contained within the metalloprotein are two neighbouring non-bonded Cu (I) centres, each of which is bound by three histidine residues. [11] Fig 1. 2 shows the binding of oxygen in relation to the copper sites.

Tyrosinase

Tyrosinase is an enzyme, which contains copper, and is present in plant and animal tissues that catalyzes the production of melanin and other pigments from tyrosine. [12] The reaction includes the reduction of the copper by an o-dipfenol. This reaction is followed by reaction of the intermediate with dioxygen to yield a highly reactive intermediate complex that is broken down by the substrate to form water and the required product. [2]

Catechol oxidase

Catechol oxidase is a copper-containing enzyme whose activity is like that of tyrosinase. Catechol oxidase carries out the oxidation of phenols such as catechol, using dioxygen. In the presence of catechol, benzoquinone is formed (reaction below). [14] In this reaction hydrogens are removed from catechol and combine with oxygen to form a molecule of water.

Superoxide Dismutase

One of the most important enzymes involved in removing free radicals from the human body is superoxide dismutase (SOD). Its function is to defend and protect cells against molecular damage from oxygen. SOD is located in two places within the cells, the mitochondria and the cytoplasm. The SOD that is found in the mitochondria contains manganese, and the SOD found in the

cytoplasm contains copper and zinc. [15] This enzyme catalyzes the dismutation, (a reaction involving a single substance but producing two products), [16] of superoxide into oxygen and hydrogen peroxide. For each two superoxides that are encountered by the SOD, one hydrogen peroxide is formed. One molecule of super oxide has their extra electron removed by SOD, and places it on the other super oxide molecule. [17] Therefore one ends up with one less electron, forming normal oxygen, and the other ends up with an extra electron. [15] The superoxide molecule, with the extra electron, then quickly picks up two hydrogen ions to form hydrogen peroxide. Hydrogen peroxide is a dangerous compound, as it transforms easily into the reactive hydroxyl radical, so the cell uses the enzyme catalase to detoxify it, producing water and oxygen. [15]

An example of a reaction of an SOD protein containing copper;

$Cu2 + SOD- + O2- \rightarrow Cu1 + SOD- + O2$

$Cu1 + SOD- + O2- + 2H+ \rightarrow Cu2 + SOD + H202.$

In this reaction the oxidation state of the copper changes between +1 and +2. [15]

Toxicity of copper

At high concentrations copper can be toxic to the human body and to cells. Problems can also develop if the body doesn’t have enough copper or the copper can’t be efficiently used within the human body. [18] People can have three different copper imbalances, which can make a person; copper-toxic, copper-deficient, or develop a condition called biounavailable copper. People

who are fast oxidisers need more copper in theirs bodies. Slow oxidisers often have excessive copper in their bodies, therefore more prone to copper imbalance. [18] Biounavailable copper refers to when copper is in excess in the body, but it cannot be utilized well. Biounavailability often occurs due to a deficiency of the copper-binding proteins, metallothionein. Without sufficient binding proteins, copper ions may flow around the body, where it may gather in the liver and brain. [18] Copper has certain places where it accumulates in the body referred to as ‘ target organs’, these are, the liver first, then the brain. Copper may affect any organ or system of the body. However, it usually affects major systems and organs like; the nervous system, connective tissues such as hair, skin and nails and organs like the liver. [18]

How do cells protect themselves against copper toxicity?

Metallothioneins

Figure 1Cells control the movement of copper across its membranes, maintaining the amount needed for biological functions while avoiding excess toxic levels. [19] Among the many factors required to achieve this equilibrium of highly toxic levels and the amount needed, are the metallochaperones, a family of proteins that transfers metal ions to specific intracellular locations where metalloenzymes bind to the metal ions and use them as cofactors to carry out essential biochemical reactions. [9]

Knowledge of the transportation of copper to its final destination has increased with the identification of two proteins involved in Cu trafficking in yeast: Atx1 and Cox17. [20] The uptake of Cu in yeast starts with reduction by a plasma membrane reductase. The reduced copper is then transported

across the membrane by the Cu transporter Ctrl. “ Three different proteins transport Cu from Ctrl to three different locations within the cell: Cox17, takes Cu to the mitochondria for incorporation into the cytochrome c oxidase (Sco); Ccs targets Cu to CuZnSOD, a primary antioxidant enzyme; and Atx1 directs Cu to a post-Golgi compartment, by way of Ccc2, a P-type ATPase transmembrane Cu transporter, for final insertion into Fet3, a multicopper oxidase.” [20] The Cu transport mechanisms described, in figure 1. 4, are active when concentrations of copper are low, and some aren’t used/ needed when the concentration of copper is very high in the medium. “ Therefore, yeast strains missing the gene for Cox17 cannot respire in normal growth media because CCO is Cu deficient, but are rescued when the medium is made 0. 4% CuSO4.” [20] Increasing the Cu concentration in the medium means Cu can be delivered to the Fet3 oxidase in yeast strains missing the gene for Atx1. These results show that Cox17 or Atx1 is required for proper Cu trafficking when Cu levels are high and that their presence is not required to detoxify Cu. [9]

Cu-ATPases

ATPase pumps are involved in the movement and translocation of ions (Na+, K+), and a variety of metal ions such as copper. The pumps that translocate metal ions are referred to as P-type ATPases. These Ptype ATPases, including the copper ATPases, are highly conserved from bacteria to humans. The Menkes ATPase translocase (MNK) is largely involved in the transfer and detoxification, of copper ions. Defects in this P-type pump lead to a fatal copper-deficiency disease in humans called Menkes syndrome. MNK’s activity appears to be regulated by the metal it exports, copper. The

composition and sequence of the metal binding domain of the Menkes ATPase (MNKr) is distinct from metallothioneins, which have major folds organized or stabilized by Cu (I) ions. The Menkes protein functions to export excess copper and is reversibly metalloregulated through the specialized copper-binding sites in the amino end of the protein. The metalloregulation couples the cellular export of copper to the intracellular concentration of copper ions. [3]

Conclusion

As seen in this report copper is very useful and needed in the body for a variety of different reactions and functions. It’s a key part of many enzymes such as; cytochrome c oxidase, Tyrosinase, Catechol oxidase and superoxide dismutase. Therefore copper is a key role in the formation of cellular energy (ATP), using cytochrome c oxidase in the electron transport chain. Copper also plays a key role in the production of myelin and neurotransmitters and therefore is essential in the development of the nervous system. Another way in which copper has been proven to be important in the human body is in the production of melanin and collagen, essential proteins in the skin.

However this report has shown that at high levels copper can be toxic and can cause problems within the human body. Copper can accumulate within vital organs and affect and damage major systems. To tackle this problem of accumulation cells contain unique proteins within their membranes that help regulate and remove copper, from inside the cell, if the levels are becoming excessive. These proteins are called metallothioneins and have specific binding sites for copper atoms (and other mineral/metals) to attach to. The mechanism, of the uptake and removal, is complicated and involves the

transfer of copper ions between certain proteins along three different pathways. These methods are outlined in this report.

References

1. Chemistry of the Elements 2nd Edition, N N Greenwood and A Earnshaw, Butterworth Heinemann
2. Biological Roles of Copper, Ciba Foundation Symposium 79 (new series) 1980
3. www. ajcn. org
4. http://resources. schoolscience. co. uk
5. www. anyvitamins. com/copper
6. www. vitamins-nutrution. org
7. http://en. wikipedia. org/wiki/Cytochrome_c_oxidase
8. http://metallo. scripps. edu
9. www. jbc. org
10. www. hull. ac. uk/chemistry/bioinorganic
11. http://en. wikipedia. org/wiki/Hemocyanin
12. http://en. wikipedia. org/wiki/Tyrosinase
13. www. science-projects. com/Tyrosinase. htm
14. http://en. wikipedia. org/wiki/Catechol_oxidase
15. www. whyweage. com
16. www. mondofacto. com
17. www. rcsb. org
18. www. drlwilson. com/articles/copper_toxicity_syndrome. htm
19. Science Magazine 1999, Volume 284, pages 748-749
20. Science Magazine 1997, volume 278, pages 817-818