COPPER METABOLISM AND CHARACTERISTIC OF INHERITED METABOLIC SYNDROMES CAUSED BY COPPER DEFICIENCY AND LACK OF ATP7A PROTEIN ACTIVITY

Summary

Copper due to its oxyreductive properties plays a role as a catalytic cofactor in a variety of enzymes. On the other hand excess of copper can be cytotoxic because copper can participate in reactions that result in the production of highly reactive free radicals. Thus, living organisms developed precise regulatory mechanisms to keep accurate copper homeostasis. In cells copper ions are bound by several proteins such as: membrane transporters (CTR1 and DMT1) responsible for influx of Cu ions into cytoplasm; copper chaperones (CCS, ATOX1, COX and SCO) necessary for copper delivery to specific subcellular compartments and thereby to cuproenzymes; Cu-transporting P-type ATPases (ATP7A and ATP7B) involved in copper transport into the secretory pathway and its export from the cell. Mutations of these proteins result in disturbance of copper homeostasis and lead to severe metabolic diseases. For example mutations of critical copper-transport protein- ATP7A are implicated in distinctive phenotypes of Menkes disease or the milder Occipital Horn Syndrome. Severe form of Menkes disease characterized by growth failure and deterioration of the nervous system developed when mutation lead to lack of activity of ATP7A protein. When mutated ATP7A protein preserves partial activity, milder form of disease is developed. Recently it was reported that missense mutations in *ATP7A* gene can lead to isolated adult-onset distal motor neuropathy. Such mutations appear to selectively disturb normal motor neuron function and it is distinctively different from Menkes disease, however. Additionally, two other syndromes induced by autosomal recessive mutations which indirectly affected the function of ATP7A have been discovered. Huppke–Brendel syndrome is caused by mutations in *SLC33A1* which encodes an acetyl CoA transporter needed for acetylation proteins. MEDNIK syndrome is developed in the presence of mutations in the s1A subunit of adaptor protein complex 1 (*AP1S1* gene), which mediates intracellular trafficking linking clathrin to receptors in coated vesicle. Both proteins are probably involved in ATP7A modification or trafficking, respectively. Unfortunately, therapeutic strategies against inherited copper deficiency disorders are still unsuccessful.